TRENDS IN CARE FOR HIV POSITIVE PREGNANT WOMEN IN BRITISH COLUMBIA, 1994-1999

by

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ABSTRACT

Background: With the increasing prevalence of HIV in Canadian women of childbearing age, there is an attendant risk for increased perinatal HIV transmission. Use of combination antiretroviral therapy in the HIV positive pregnancy, coupled with AZT during labour and for the infant can significantly decrease risk of perinatal HIV transmission to less than five percent. There is a need to establish if Canadian HIV positive pregnant women are receiving this intervention, and if this has lead to a decrease in perinatal HIV transmission in the Canadian setting. It is also important to establish if use of these medications in the antepartum period has any negative consequences on the developing fetus.

Methods: This study used data gathered both retrospectively and prospectively from the Oak Tree Clinic, the provincial centre providing clinical care for HIV positive pregnant women in British Columbia. Care that HIV positive maternal infant pairs received between January 1994 and December 1999 was evaluated. Chi square tests were conducted to compare event rates between cohorts, and odds ratios with confidence intervals were conducted to provide a measure of the strength of association between two variables. A p value of 0.05 was considered statistically significant, and all reported p values are two sided.

Results: One hundred and forty five HIV positive pregnancies were evaluated at Oak Tree Clinic. Ninety-nine HIV positive women gave birth to 116 infants. Sixty five maternal infant pairs received some type of antiretroviral treatment during pregnancy. Twenty four pairs received combination antiretroviral therapy, twelve received dual
therapy and twenty nine received AZT monotherapy. Eighteen infants contracted HIV, for an overall transmission rate of 15.5%. There has been a significant increase in the use of combination treatment in pregnancy since 1996 (38.3% vs 75%; OR 6.37; 95% CI 2.4–17.1) and a reduction in the perinatal transmission rate in the same time period (25% vs 5.4%, OR 5.9; 95% CI 1.6–21.6). In this study, no specific treatment regimen was linked consistently with any adverse effects in the pregnancy or in the infant.

Conclusion: In one Canadian province, there has been a significant increase in the use of combination antiretroviral treatment for HIV positive maternal infant pairs. This has lead to a reduction in the perinatal transmission of HIV.
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Science is not a mechanism but human progress, and not a set of findings but a search for them. Human search and research is a learning by steps of which none is final, and the mistakes of one generation are rungs in the ladder, no less than their correction by the next.

Jacob Bronowski
Science and Human Values, 1956
BACKGROUND

HIV and AIDS Epidemiology

The human immunodeficiency virus (HIV) is estimated to have infected between thirty five and forty million people by the end of the year 2000, and has touched the lives of millions of others since its arrival on the world stage in 1981. This infectious disease has had devastating consequences world wide - over 21.8 million people have died from AIDS in the past 20 years (1). The world wide epidemic continues to spread at a rate of over 16 000 new infections per day, with women representing 40% of newly diagnosed HIV cases (2).

In North America, women represent an increasingly large proportion of the population with HIV. Twenty percent of those newly diagnosed with HIV are women, the majority of whom are of childbearing age. In Canada by December 1999, 1 345 of the 16 913 Canadians who had been diagnosed with AIDS since the beginning of the epidemic were female (3,4). An evaluation of HIV testing shows that before 1995, adult women represented less than 10% of all newly HIV positive individuals, but in 1999, 23.9% of positive HIV tests are in females. Sixty three percent of Canadian women who have been diagnosed with AIDS name heterosexual sexual contact as their risk behaviour for contracting HIV. However, in the AIDS cases in women reported in 1999, 36.6% attributed their HIV to heterosexual contact while 46.1% identified intravenous drug use as their risk behaviour. This indicates a continuing shift in the risk behaviour responsible for HIV contraction in Canadian women, with an increasing number of women
acknowledging intravenous drug use as their risk behaviour for viral contraction. Most HIV and AIDS cases in Canadian women were among adult women of child-bearing age (between 15-49), an experience mirrored worldwide. Presently in Canada, of the estimated 40,000 Canadians who are HIV positive, approximately 4 600 are women (4).

British Columbia reports that there have been a cumulative total of 166 women with AIDS in the province since 1983, and 1272 women have tested positive for HIV since 1985 (5). In 2000, 88 women in British Columbia tested positive for HIV, and 92.0% (81/88) were of child-bearing age. In 2000, 26 women identified intravenous drug use as their risk behaviour for contracting the virus (26/88=29.5%), and 25 contracted the virus from contact with a heterosexual partner. Forty women identified themselves as Caucasian, twenty-two were First Nation women, eight were Black women, six were Asian and two were from South Asia. Overall in British Columbia, in the year 2000, women comprised twenty one percent of the 419 individuals who were newly diagnosed with HIV (88/419).

As HIV can be transmitted from mother to infant, there is an increasing concern about the risk of perinatal transmission, as the number of women in Canada contracting HIV increases. Anonymous unlinked seroprevalence surveys of HIV infection among pregnant women in different provinces were conducted in the 1990s in most provinces, to establish the risk of perinatal HIV transmission in Canada(6,7). The British Columbia and the Yukon Territory study conducted in 1989 found a crude overall seroprevalence rate of 2.7 per 10 000 pregnant women (95% CI 1.0 to 5.8). Follow up studies were
reported until 1994, when seroprevalence rates were found to be 3.4 per 10 0000 (95% CI 1.5-7.3) (7).

UNAIDS and WHO estimate that 90% of the over 1.4 million children currently living with HIV/AIDS acquired the virus through perinatal transmission (2). By December 2000, 203 children in Canada had been diagnosed with AIDS since the start of the epidemic (4). Sixty nine percent reported contraction of HIV through perinatal transmission. However, prior to 1994, 53% of pediatric HIV was contracted perinatally, while after 1995, perinatal transmission has lead to over 90% of HIV contraction in infants and children. Perinatal HIV transmission is now the single largest reason for pediatric HIV cases in Canada. Since 1985, 626 children under the age of 15 have been diagnosed with HIV. With the increasing world-wide and Canadian population of HIV positive women, action to decrease the number of children infected with AIDS is a pressing priority.

Biology of HIV/AIDS

HIV is an RNA retrovirus that is transmitted across the mucocutaneous barrier into regional lymph tissue. Massive viremia follows a few weeks after, leading to widespread dissemination of the virus, with extensive lymph tissue involvement. Persistent viral replication then leads to an HIV RNA set point, which is usually established approximately four months after transmission in the HIV positive adult. Viral replication continues with an average of $10^{10}$ new virions/day. Cells with CD4 receptors are the
targets for the virus, and there is gradual depletion in the CD4 cell count over several years. It is this destruction of CD4 cells, which are key players in coordinating host defence systems, that leads to susceptibility to opportunistic pathogens and tumours (8).

Perinatal Transmission

HIV, the RNA retrovirus that causes AIDS, may be transmitted from mother to infant during pregnancy and delivery. The actual timing of the transmission remains unclear, but natural history and observational data appears to demonstrate that the majority (50-80%) of perinatal HIV transmission occurs at the time of labour and delivery (9,10). Newell’s review highlights that a relatively small number of infants who are born to HIV positive mothers have early evidence (within two days of birth) of virus detectable in their blood. Most children who eventually become positive demonstrate evidence of the virus within 4 to 6 weeks of birth, either by polymerase chain reaction (PCR) testing or viral culture(11). This phenomenon indicates that viral contraction probably occurred at the time of labour and birth.

Available research indicates that intrapartum HIV transmission appears to be responsible for the majority of perinatal HIV transmission, particularly in non-breastfeeding populations(12,13). Infant viral contraction could be as a result of a number of pathological processes, including direct contact with infected maternal blood and genital secretions in the birth canal, ascending infections from the vagina and cervix to the amniotic sac and fluid, microtransfusions during uterine contractions and fetal
consumption of maternal fluids leading to gastrointestinal absorption of infected fluids. There is indirect evidence supporting all of these potential modes of viral contraction, including decreased transmission rates for the second twin in the birth canal (reduced exposure time to infected fluids), increased transmission with long labours (9,14,15), and in women not treated with antiretrovirals, a reduction in transmission when infants are delivered by cesarean section as opposed to a vaginal delivery (16). One small study also linked bloody neonatal gastric aspirate with HIV infection in the infant (17).

There remain a small percentage of infants who become HIV positive in utero (12). Research has shown that HIV can infect the placenta at all stages of pregnancy, and that infected placental cells can be passed on to the fetus during birth (18). With intact amniotic sacs, the methods of transmission appear to be via placental tears (leading to inoculation of fetal circulation with infected blood) or by infection of the placental layers, until the infection reaches the fetoplacental circulation. Evidence for the phenomenon of intrauterine HIV transmission has been reported: including HIV positive fetal tissue of 12 weeks gestational age (19), intrauterine onset of symptomatic HIV disease (20) and viral isolation in the amniotic fluid (21). However, intrauterine infection appears to be a rare event – one study found that only two out of 100 first and second trimester fetus had evidence of HIV infection (22).

Although less of a concern in developed countries, viral transmission as a result of breastfeeding is a common event in developing nations. It has been proposed that infected breast milk could transmit HIV either because of penetration of the
gastrointestinal lining by cell-free virus, or by direct entry into infant bloodstream via mucosal breaches. Early introduction of solids to an infant may exacerbate the chances of viral contraction, due to increasing the permeability of the gastrointestinal tract. Also, the immature neonatal gastrointestinal tract may also facilitate viral transmission from breast milk to the infant(12). Regardless of whether due to intrauterine, intrapartum or breastfeeding, it is estimated that without treatment or intervention, fifteen to forty five percent of infants born to HIV positive mothers will themselves be HIV positive (23).

Pediatric Natural History of HIV

Perinatal HIV infection, which leads to pediatric HIV infection and potentially pediatric AIDS is a significant and often life ending illness. The age of onset for AIDS in children and infants with perinatally acquired HIV is described as bimodal, with some infants developing AIDS very early in the first year of life, and others surviving for several years without any symptoms or signs of AIDS(24). Prior to the use of combination therapies, 23% (95% CI; 15%-31%) of infants who contracted HIV in utero developed AIDS before the age of one year. By four years old, 39% (95% CI 27% - 50%) had developed AIDS. An estimated 10% of infants die before one year of age, and 28% die before their fifth birthday. This rate of progression to AIDS is faster in children and infants than is seen in adults. Recent advances in treatments have been evaluated in population based longitudinal studies and have shown a significant increase in survival for the cohort born in 1996-7 compared to those born between 1980-95 (25). Despite these treatment improvements, these infants still have a median survival time of 3.3 years.
Predictors of Maternal to Infant HIV transmission

Certain factors appear to be associated with viral transmission from mother to infant. These include specific maternal clinical factors (viral load, CD4 count) (26,27) type of delivery(28), mode of infant feeding (breast-feeding or bottle-feeding) (29-31) and use of combination antiretroviral medications during pregnancy, labour and to the infant for six weeks after birth (32). Use of appropriate HIV medication in the antepartum, intrapartum and post-partum periods has emerged as the most important factor determining HIV perinatal transmission in most evaluations (32). However, the potential role of all factors will be presented in this discussion.

Maternal Clinical Factors

Studies have reviewed numerous factors, such as gestational age, birth weight, type of delivery (cesarean section, vaginal delivery, instrumental delivery), duration of rupture of membranes, presence of chorioamnionitis, CD4 count at delivery, viral load at delivery and evaluated their link with HIV transmission both by univariate and multivariate analysis (9,26,33). Although earlier reports listed a wider variety of factors that were associated with HIV transmission, such as duration of rupture of membranes, prematurity, low birth weight and chorioamnionitis (9), these evaluations were conducted prior to the availability of plasma viral load measurements. When plasma viral load was introduced into models evaluating risk factors for transmission, this appeared to emerge as the single most predictive factor in viral transmission from mother to infant (26).
Garcia evaluated 552 women who delivered between 1990 and 1995, and who had had their plasma viral loads measured during their pregnancies and at delivery (26). After adjustment for other factors, logistic regression analysis demonstrated that maternal plasma HIV-1 RNA levels were strongly associated with the risk of transmission, with a progressively higher risk of transmission linked with higher plasma HIV-1 RNA levels. In this study, women with viral loads below 1000 copies/ml had a transmission rate of zero. Duration of rupture of membranes, low birth weight (<2500gm) and absence of treatment with AZT during pregnancy were also independently associated with transmission of HIV from mother to infant in this evaluation.

In another study conducted in 1999, Mofenson and colleagues evaluated 480 women who had delivered between 1993 and 1997 (34). Risk factors were included in both univariate and then subsequent logistic regression analysis. After including significant variables from the univariate analysis into the logistic regression, the only variable significantly associated with viral transmission from mother to infant was HIV-1 RNA levels at delivery (OR 2.5; 95% CI 1.1-5.8). In both reviews in the univariate analyses, CD4 count at delivery was associated with transmission, but because the CD4 count was correlated with HIV-1 RNA levels, this association did not remain in the multivariate analyses.

A recent nested case-control study published by Leroy evaluated the role of maternal viral load in HIV transmission in an international study (27). This study used participants from the DIATRAME ANRS 049 study, which was a randomized control trial evaluating the use of short course AZT monotherapy for reducing perinatal transmission. Fifty-five
women who had transmitted were considered cases and 117 women who did not transmit were named as controls. Women who transmitted HIV had mean log_{10} viral load of 4.6 at inclusion into the trial (36-38 weeks gestational age) compared to 3.7 in non-transmitters (p=0.0001). Viral loads were also measured at one week post partum, and transmitting mothers once again demonstrated a higher mean log_{10} viral load (4.73 vs 3.73, OR 5.99; 95% CI 3.1-11.5, p=0.0001).

The likely mechanism behind the level of plasma viral load and risk of transmission is based on the amount of virus to which the infant is exposed. With a higher maternal plasma burden, there is a corresponding increase in the level of circulating virus in the cervical and vaginal secretions (35). During delivery, there is a tremendous potential for infant exposure to maternal blood, and maternal cervical and vaginal secretions. As the viral inoculum to the child increases, due to increased amount of viral exposure, the chance of contracting the virus increases. As a result, transmission rates vary with maternal plasma viral load levels. For instance, in Garcia’s study, the risk for contracting HIV was 20% when maternal viral load ranged between 1000 and 10 000 copies/mL, while the rate of transmission increased to 63% when maternal viral load was greater than 100,000 copies/mL (26).

Regardless, reports do exist describing perinatal HIV transmission in mothers with undetectable viral loads at delivery (36). Forty four cases of transmission occurred in 1202 mothers with maternal viral loads at <1000 copies/ml. This highlights the fact that the absence of detectable virus in circulation does not equal the absence of virus – HIV
seropositivity does put infants at risk for viral contraction, even in the face of undetectable viral loads.

Any elements at birth that will increase the time or amount of blood or body fluids to which an infant is exposed has also been associated with viral transmission, in various different analyses. A meta-analysis of 4721 deliveries of HIV positive mothers who had ruptured membranes for less than 24 hours was conducted by the International Perinatal HIV Group. After adjusting for other factors, these authors concluded that the risk of transmission from mother to infant increased approximately 2% with each one hour increase in the duration of rupture of membranes (adjusted OR 1.02; 95% CI 1.01-1.04 for each 1 hr increment) (37). Instrumental deliveries or operative vaginal deliveries, such as forceps and vacuums (which increase exposure to maternal blood), use of obstetrical devices and procedures, such as amniocentesis, scalp electrodes, and the presence of ulcerative diseases of the vagina or cervix such as herpes and chancroid (which increase exposure to maternal cervical, vaginal fluids and blood) all increase the likelihood of perinatal HIV transmission (9).

Of interest, however, is the fact that interventions geared to remove the birth canal of infected cells by disinfecting the vagina with chlorhexidine during labour have not impacted significantly on maternal-infant viral transmission. One prospective study in Kenya enrolled over 600 women, with half receiving a vaginal lavage with 0.2% chlorhexidine every 3 hours during labour and the other half receiving no intervention. This trial failed to demonstrate any difference in transmission (17.2% vs 15.9%, OR 0.9
95% CI; 0.6-1.4) between the non-lavage and the lavage group(37). Another study conducted in Malawi used 0.25% chlorhexidine solution every four hours in labour, and with a wash of the baby in chlorhexidine after birth. Again this did not demonstrate an overall reduction in maternal to child HIV transmission, but there was a significantly lower rate of transmission in the subgroup of women who received chlorhexidine compared to those who did not with ruptured membranes for more than four hours (38).

Breastfeeding and HIV Transmission

Breastfeeding has been an area of important research in transmission of HIV, due to the risk infants of positive mothers face in contracting the virus from breast milk versus the significant nutritional, immunologic and developmental benefits afforded to infants that breast feed. In developing countries, the question is particularly complex, as few mothers have the resources required to purchase formula and access to safe water to mix formula. In the developing world, breast feeding is central to most infants' nutrition and infants in these settings are particularly in need of the benefits of breast feeding in their first years of life. However, the risk of HIV transmission with breast feeding has been estimated to be 14% (95% CI 7-22%) in women with established HIV infections (39). In a randomized trial conducted in Kenya, 401 maternal infant pairs were evaluated (31). These mothers lived in an urban setting and had running water in their homes and were provided with free formula. The rate of HIV transmission in breast fed infants was 16.2% (95% CI 6.5%-25.9%), with a cumulative risk of HIV-1 infection at 24 months of 36.7% (95% CI; 29.4%-44.0%) vs 20.5% (95% CI; 14.4% -25.6%) in the breast fed vs formula fed arm respectively. Of note, is that a substantial proportion of transmission
occurs early during breast-feeding – by 6 months, approximately 75% of transmissions had occurred, although exposure to breast milk continued for an average of another year. Numerous reasons for this phenomenon exist. Studies have shown a variation in the prevalence of HIV-1 DNA in breast milk, with the greatest prevalence between 1 week and 3 months. However, as additional foods are included in the diet, as the infant gets older, milk intake declines. As well, infants may vary in their susceptibility over time, and infants who do not contract the virus early on may be relatively more resistant to the virus than others.

The other significant finding in this study was that, despite HIV contraction, at two years both the breast fed and formula fed group had similar mortality rates (24.4% vs 20.0%, p=0.3). This speaks to the protective effects afforded by breast feeding not available in commercial formulas. However, despite this short term similarity in mortality rates, this study demonstrated that HIV-1 free survival rates at 2 years were significantly lower in breastfeeding arm. Less than 60% of women in the breastfeeding arm had an infant that was alive and HIV negative. The findings of this study highlight the tremendous dilemma facing the developing world regarding breastfeeding in HIV positive mothers. Breastmilk avoidance could decrease overall maternal to child transmission (MTCT) by 44%, but formula is not affordable for most women in sub-Saharan Africa. Appropriate formula feeding requires identification of positive mothers, and a health care system ready to provide timely and accurate health education regarding formula feeding. The findings of this study were in women with access to clean water and free formula – an often uncommon if not rare setting in sub-Saharan Africa.
In the case of the developed world, in nations such as Canada, the issue of breastfeeding in HIV positive mothers is less pressing. Given that most North American women have access to clean water, and if not able to afford infant formula, they can often receive social assistance subsidies, all HIV positive women in developed countries are strongly advised not to breastfeed. Infants born to HIV positive mothers are expected to use formula for their infants from birth.

Cesarean Section and HIV Transmission

The type of delivery has been a major interest for those evaluating HIV transmission, and elective cesarean sections have been proposed as another option to decrease the transmission of HIV from mother to infant. The benefit of cesarean section is once again thought to be diminished exposure to infected vaginal and cervical fluids, and decreased exposure time to maternal blood in the birth canal. This benefit is maximized in the case of the elective or planned cesarean section, as the onset of labour will likely increase transplacental transfer of cellular material(12). Initially, in order to make recommendations to patients and their families, clinicians had to rely on data from small prospective reviews of data bases, but in 1999, three important studies were published; one large prospective study (40), one randomized trial (28) and one meta analysis of 15 prospective studies (41) each provided more information on this topic. In the randomized trial (28), women were assigned to elective cesarean sections or vaginal deliveries at 38 weeks gestational age. Most women received AZT monotherapy during their pregnancy. Women who had cesarean sections who received AZT therapy transmitted the virus 2.1%
of the time, while women who were on AZT therapy but did not have an elective section had a transmission rate of 3.3% (OR 0.6; 95% CI 0.1-3.2). However, there did appear to be a much more significant benefit from elective sections in this trial in women who did not receive AZT monotherapy. The difference in transmission in the untreated group was 18.9% in the vaginal delivery group compared to 6.8% in the cesarean section group (OR 0.3; 95% CI 0.1-1.0). This study also reported a “low” post partum complication rate; women who had cesarean sections were significantly more likely to report post partum fevers (1.1% vs 6.7%, p =0.002) but rates of postpartum bleeding, and anemia were similar in both groups.

The Swiss prospective study evaluated 414 deliveries from Swiss centres where routine use of elective cesarean sections for HIV positive pregnant women has been standard of care since 1985 (40). Transmission rate was 6% (95% CI 2-12) in elective section deliveries, compared to 20% (95% CI 16-23, p<0.0001) in all other delivery modes. Transmission rates were 0% (0-11%) for women who had both elective sections and used zidovudine therapy during their pregnancies, compared to 8% (3-16%) in women who had elective sections but no zidovudine. Women who received AZT but had vaginal deliveries had a 7% transmission rate, compared with a 17% transmission rate in the absence of AZT therapy (OR 0.37; 95% CI 0.13-0.17).

Finally, in the meta-analysis conducted in 1999 (42), 15 prospective studies with more than 100 maternal infant pairs evaluating the relation between elective cesarean sections and HIV-1 transmission were included. Data analysis included 8533 maternal-infant
pairs. This study also found that the risk of vertical transmission was significantly decreased in women who underwent elective sections prior to the onset of labour and rupture of membranes, compared to those who did not. Transmission rate in elective sections was 8.2%, while other modes of delivery had a transmission rate of 16.7%. After adjusting for receipt of ART, maternal stage of disease and infant birth weight, elective sections were strongly associated with a decreased risk of vertical transmission (OR 0.43; 95% CI 0.33-0.56). Use of ART and elective section decreased the risk of transmission even further (adjusted OR 0.13; 95% CI 0.09-0.19).

Of note in all mode of delivery studies is the critical role that AZT monotherapy played in additionally reducing the risk of transmission of the virus from mother to infant. These reports appear to confirm that antiretroviral therapy still plays a critical part in diminishing the transmission rate of HIV to infants, and it is not clear if cesarean sections would truly offer women any further benefit above combination antiretroviral therapy use. This is particularly relevant in the current context, where most positive women are no longer simply offered AZT monotherapy, but most receive combination therapies throughout their pregnancies(43-45). With combination therapies, in most centres vaginal deliveries have transmission rates that are approaching 0%, and ranging between 0% and 2%, when women have good viral suppression, avoid instrumental deliveries and minimize the duration of the rupture of membranes (43). (32) The relative contribution of an elective operative in this situation is unclear, and the benefits may be imperceptible.
The other concern for HIV positive women is the risk of complications following an operative delivery. Sections are associated with greater postpartum morbidity, and particularly in the case of the HIV positive women, there is concern that their risk may be greater. One study showed that elective sections were associated with an increased risk of postpartum morbidity, including postpartum fever and urinary tract infections(46).

Clinical guidelines do not currently recommend routine cesarean sections for pregnant HIV positive women, in the setting of optimal antiretroviral therapy and viral suppression (47,48). Elective cesarean sections are recommended in the setting of ART monotherapy, poor viral suppression (> 1000 copies/ml), unknown viral load and unknown prenatal care. Women who have achieved good viral suppression should have decisions regarding mode of delivery based on the conduct of their labour, pregnancy risks and other pertinent factors, and not based on their HIV status.

Combination ART in Pregnancy

In 1994, the AIDS Clinical Trial Group (ACTG) published the results of Study 076, a seminal paper that established the efficacy of antiretroviral therapy in pregnancy and for the infant in reducing transmission of HIV from mother to infant (49). This trial, which was halted after an interim analysis, demonstrated that AZT given during the antepartum, intrapartum and postpartum period reduced transmission of HIV from mother to infant from 25.5% to 8.3%. The protocol started AZT monotherapy at 14 weeks gestational age at 100 mg five times per day. Women then received IV AZT at 2mg/kg in 100ml D5W over one hour. Then, a continuous infusion of IV AZT at 1mg/kg was continued until the
cord was clamped. The infant then received 2.0 mg of AZT q8h for the first six weeks of life. This regimen was not associated with any significant congenital abnormalities, and worldwide, clinicians were strongly advised to offer AZT therapy to all pregnant HIV positive mothers.

Since the publication of ACTG 076 results, and the subsequent evidence for this intervention in the community(50), there has been a revolution in HIV care due to our increased understanding of the pathogenesis of the disease. Monotherapy with AZT is no longer acceptable in the care of HIV infected individuals, given its poorer efficacy and the increased likelihood of resistance (51). Viral turnover during all stages of HIV-1 infection is enormous, as plasma virions are estimated to have a mean half life of 6 hours (52). This significant shift in the care of HIV positive adults has forced a re-evaluation of the care offered to HIV positive pregnant women, and mandates that pregnant women not be disadvantaged in the care they receive, simply because they are pregnant(53).

Combination antiretroviral therapy, which is also known as highly active antiretroviral therapy (HAART) usually consists of two nucleoside analogue reverse transcriptase inhibitors (NRTI) combined with either one protease inhibitor or non nucleoside reverse transcriptase inhibitor and is the current recommended standard of care in HIV positive patients in the developed world (54-57). The benefits of the combination regimens in decreasing plasma viral loads, decreasing short term mortality and increasing AIDS free survival have been confirmed both in randomized trials and in population-based studies.
Studies have highlighted that either a PI or NNRTI is an essential component of any combination therapy regimen.

Current guidelines, including those of the US Public Health service and the International AIDS Society, recommend that treatment regimens for antiretroviral therapy in pregnant women essentially follow those for the non-pregnant individual. These guidelines focus on early initiation of combination antiretroviral therapy to maximally suppress viral replication to below 500 copies/ml to preserve immune function and reduce the development of resistance. In the non-pregnant HIV positive individual, these combination regimens are associated with improved clinical outcomes and survival. Such approach to therapy is believed to be optimal for long term maternal and fetal well being, in terms of providing the mother with optimal care for her own HIV disease, and in terms of reducing transmission to the infant and diminishing opportunities for developing therapeutic resistance. By reducing circulating virus in the blood, it is expected that in utero and at birth transmission is less likely to happen, as the infant will have less exposure to the virus.

Recent studies in the US have confirmed that since 1997 there has been a significant change in the treatment of HIV positive pregnant women. Minkoff reviewed treatment received by HIV positive pregnant women in the Women’s Interagency HIV Study. After October 1996, there was a significant decline in the use of AZT monotherapy, with a concomitant increase in the use of HAART in pregnant women. However, this use of combination treatment in pregnancy raises a number of questions. We know combination
therapy can effectively treat HIV in the female patient. However, does combination therapy impact on HIV perinatal transmission rates? Is combination therapy safe for the developing fetus? Is it safe for the pregnancy? Although these questions have yet to be answered in a randomized controlled trial, there are numerous reports and abstracts that evaluate a relatively small number of pregnant seropositive women who have received HAART during their pregnancies, both retrospectively and prospectively. These reports describe transmission rates and any fetal and pregnancy side effects. As well, animal model studies have been conducted to evaluate the safety of these medications for the developing fetus.

Combination ART in Pregnancy: Teratogenic, Placental and Fetal Effects

Nucleoside reverse transcriptase inhibitors act by inhibiting reverse transcriptase, the enzyme that converts the ribonucleic acid (RNA) into deoxyribonucleic acid (DNA), thus preventing HIV incorporation into the host genome. Included in this family are AZT (zidovudine), zalcitabine (ddC), didanosine (ddl), stavudine (d4T) and lamivudine (3TC) and abacavir (ABC). Clinicians have the most experience with AZT in the clinical setting with pregnant women, and also have evidence that AZT effectively decreases HIV transmission (65,66). It is actively transported across the placenta, and has an equivalent concentration in both maternal and fetal circulation (62,67). Although there was no increased incidence in fetal abnormalities in infants born to mothers who had taken AZT in ACTG 076, there have been reports of possible carcinogenicity in animal studies. A study by the National Cancer Institute found an increase in liver, lung and genito-urinary tract tumours in offspring of mice given very high doses of zidovudine in the last
trimester (68). However, a further trial with lower doses, which more accurately reflect the doses given to mothers in pregnancy, failed to confirm this earlier finding (44). As well, of the over 1000 children exposed to AZT in utero who were followed for 3 years, no tumours have been found (69).

Lamivudine (3TC) is being evaluated in Phase III studies in the third trimester of pregnancy, as previous studies established that 3TC had excellent placental transfer rates, good maternal and neonatal blood levels and no documented human malformations (70). Animal models used doses more than 100 times that administered in humans and failed to demonstrate any evidence of harm to the fetus.

Animal studies completed by the manufacturer of didanosine (ddI) did not produce any adverse fetal effects, despite using doses of 12 times that used in humans. Lifetime rodent studies have not found an increased rate of tumours (62). Placental passage has been confirmed in humans with a newborn to mother drug ratio of 0.5 (70). Despite its substantially less placental transfer, didanosine is a potential option for pregnancy, as it is the only NRTI that is classified as Food and Drug Administration (FDA) Pregnancy Category B (Appendix 1).

Zalcitabine (ddC) studies in pregnancy demonstrated placental transfer rates of 0.3 to 0.5, and tetratology studies have shown skeletal defects and embryo lethality at extremely high dosages (70). Hydrocephalus was also seen in in utero exposed rats given doses that were 1000 times the recommended human dose. Studies with zalcitabine have appeared
to demonstrate cytotoxic effects on the thymocytes, creating concern about its potential
effect on a newborn's developing immune system (70).

Stavudine (d4T) is transferred across the placenta, and demonstrates a newborn to mother
drug ratio of 0.76(70). Progression to the blastocyst stage was inhibited by exposure of
embryos to stavudine concentration of 10umol/L. Studies have failed to establish any
increase in birth defects when the drug was administered at more than 150 times then
normal dose(68).

The protease inhibitors, saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and
lopinavir/ritonavir act by preventing cleavage of protein precursors in of HIV-1 in
infected cells (71). Although they have contributed significantly to the decrease in AIDS
related deaths in the past few years, and are a central component of HAART (54,56),
information about their use in pregnancy remains limited(44). Developmental studies
have revealed no increased teratogenicity with indinavir (70), but there have been
treatment-related increases in the incidence of supernumerary and cervical ribs in
offspring of rodents receiving indinavir at doses similar to those administered in humans.
Long term animal carcinogenicity studies are not yet completed with indinavir. Although
significant placental passage was seen in rats and dogs, there was limited passage in rats.
Unlike the other protease inhibitors which are classified Pregnancy risk B by the FDA,
indinavir is classed as Pregnancy Risk C (62).
Saquinavir has very poor bioavailability, which has considerably limited its usefulness in adults. It has demonstrated poor placental transfer in pregnant rats and rabbits (62). There have been no studies demonstrating teratogenic effects of saquinavir. Ritonavir studies in rodents and rabbits produced no increase in congenital malformations. However, developmental toxicity studies found that offspring of mothers who had received ritonavir in pregnancy had decreased body weight, and in rabbits, decreased litter sizes (70). Given this data, clinicians who prescribe the medication to pregnant women are advised to do so with caution in the first trimester, and carefully monitor women for the duration of their pregnancy. Nelfinavir exposure in rats showed no maternal or developmental toxicities in studies that used up to 1000 mg/kg per day. Rabbit studies also confirmed no developmental toxicity and found a small body weight to food consumption reduction (44). Data on placental passage is unknown.

Nevirapine is a benzodiazepine derivative, and is a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase that is currently available for use in HIV positive individuals. Although the NNRTIs are a relatively new family of antiretroviral medications, their ability to significantly decrease plasma HIV-1 RNA levels to below 20 copies/ml compared to other regimens has been established in clinical trials(59). This decrease in viral load was sustained for a longer period of time, in comparison to the other regimens. Viral load is a strong, independent predictor of outcome (72), and future studies will likely confirm the beneficial influence of nevirapine on AIDS progression and mortality.
The pharmacokinetics of nevirapine at term have been evaluated. No adverse events were noted in either the mother or the infant. The medication was well tolerated, and had excellent placental transfer, with neonatal blood concentrations equivalent to those in the mother\(^{(73)}\). No teratogenic effects have been observed. However, in rats a significant decrease in fetal weight has occurred at doses when the systemic concentration is approximately 50 percent higher than in human exposure. Long term carcinogenicity studies are not yet available.

Other medications in this family include delavirdine and efavirenz. Efavirenz was given to sixty pregnant monkeys starting in the first trimester of their pregnancies, and major malformations were associated with its use, including cleft palate, microphthalmia and anencephaly\(^{(44)}\). Delavirdine was associated with significant maternal toxicities, delayed fetal development and reduced survival in offspring when pregnant rats had drug concentration five times higher than would be routinely given to humans\(^{(44)}\).

Combination Therapy Use in Pregnancy – Clinical Experience

Since the introduction of combination therapy, several abstracts and reviews have been published which describe the clinical experience of combination therapy use in pregnancy. Clinical studies at the International Conference in Geneva reported on 3TC use in the second and third trimester of pregnancy. Blanche\(^{(74)}\) evaluated over 200 women who had received AZT and 3TC in their third trimester of pregnancy, and reported an HIV transmission rate of 2.6%, satisfactory maternal tolerance and slight
elevation in liver functions and renal function. Scott reviewed a small study of women who received 3TC in their second and third trimester(75). One woman developed oligohydramnios, and required preterm delivery. This infant subsequently died due to infection. Two infants had hypoglycemia events post delivery requiring glucose therapy. Other infant complications included hyperbilirubinemia, neutropenia and anemia.

Stek (76) reviewed 42 pregnancies where protease inhibitors were used for an average of 19 weeks during pregnancy. Drug related complications during pregnancy were vomiting and ureteral obstruction. Four women delivered preterm due to pre eclampsia (28 weeks), one due to oligohydramnios and Down's syndrome at 31 weeks and two because of preterm labour. Mean gestational age at delivery was 38 weeks. Eight months after delivery, all of the children remained HIV negative.

A study in Thailand evaluated the impact of short term ritonavir therapy in 86 pregnant women. Treatment naïve women were given ritonavir for an average of twenty days, and at the time of labour 47% had viral loads of <400 copies/ml. HIV transmission rates to infants was 9.46%. Ritonavir treatment was discontinued in 14% of women due to side effects but there is no description of infant side effects.(77).

Indinavir is associated with renal stones and hyperbilirubinemia in the adult, both of which would be significant consequences for a newborn. Given the immature hepatic metabolism in neonates, indinavir would probably experience a prolonged half life in the newborn infant, potentially increasing and prolonging the hyperbilirubinemia often seen
in newborns. As well, renal stones remain a considerable concern, because of the difficulty of ensuring adequate hydration in newborns (62).

In a review of 89 pregnancies in which mothers took protease inhibitors (which included nelfinavir, saquinavir, indinavir and ritonavir) Morris (78) found that 20% of the births were preterm, but 60% of these mothers had other recognized risks for preterm delivery. None of the infants in this evaluation contracted HIV perinatally. He concluded that protease inhibitor use in pregnancy did not increase the rate of obstetrical complications or fetal abnormalities, and that protease inhibitors were generally safe for mothers and infants.

Studies presented at the International AIDS Conference in Geneva in 1998 reviewed the experience of 37 women who took nevirapine for a mean of 16 weeks during their pregnancies. Between 78% to 91% of mothers taking nevirapine had HIV RNA levels of less than 400 copies/ml at delivery. Three mothers who took nevirapine had a rash, and one experienced hepatitis. Two mothers delivered prematurely, due to placenta previa and pre eclampsia. Mean age at delivery was 38 weeks, and the average birth weight for these infants who had been exposed nevirapine in utero was 3288 g. All infants who had been exposed to nevirapine were HIV negative at 8 months (76).

A retrospective study was published in 1999, which evaluated 30 women who received combination therapy during their pregnancies(43). Thirty seven percent in this cohort used intravenous drugs, and fourteen received combination therapy during their first
trimester. Median time for HAART use in pregnancy was 26 weeks and eighty percent had a “successful” response. Fourteen women received combination therapy that included a protease inhibitor, while four had dual therapy and two women received NNRTIs in combination. Median time for starting ART was 14 weeks. Four women experienced gestational hypertension, one woman developed gestational diabetes, and one woman had an exacerbation of her hepatitis C. Nineteen infants were delivered by a normal spontaneous vaginal delivery. Seven percent of the infants were born preterm, and five were born with a low birth weight. The two preterm deliveries were exposed to protease inhibitors. None of the infants contracted HIV, despite reported adherence difficulties in at least nine of the thirty cases. One pregnancy where the mother took AZT and 3TC resulted in an unexplained stillbirth, and one infant who was exposed to methadone, heroin, AZT and 3TC in utero was born with microcephaly at 39 weeks. None of the live infants had major birth defects.

The European collaborative study recently reported on vertical HIV transmission since 1986 (32). This prospective study evaluated 2876 women and their 3076 infants. Eighty two percent of these women were white, fourteen percent were black, two percent were Asian and the remaining two percent were undefined. Forty one percent of the mothers attained undetectable viral loads at delivery and by 1999, 44% were receiving triple therapy. The most common combination regimens used were AZT/3TC/nelfinavir (24) and AZT/3TC/nevirapine (16). In this cohort, 71% of infants were delivered by cesarean section, although there was a wide range in rates between centres. Infants exposed to either AZT monotherapy or combination therapy had a significantly lower incidence of
neonatal anemia. There was a similar rate of congenital abnormalities in both the
treatment exposed and unexposed infants (1.25% vs 1.4%). Perinatal HIV transmission
decreased from 15.5% in 1994 to 2.6% after 1998. In women receiving combination
therapy, the HIV transmission rate was 1.7%. Both cases of transmission that occurred
despite maternal combination therapy use had insufficient treatment.

Lorenzi reported from several Swiss cohorts on the safety of HAART in both pregnant
HIV positive women and their newborns(79). This study evaluated 37 pregnancies that
received both dual and triple therapy regimens. Side effects of concern included anemia
(15), hepatitis (2), nausea (4), thrombocytopenia (1), gestational diabetes (1), gestational
hypertension (1) and nephrolithiasis (2). Thirty infants were followed, and they reported
that ten infants (33%) were born preterm, and four newborns were low birth weight.
Eight infants had mild cases of anemia, two infants had cryptorchidisms, two had
cutaneous angiomas, and two infants had non-life-threatening intracranial hemorrhages.
Of note in this cohort was the significantly increased rate of prematurity (OR 2.73;95%
CI 1.37-6.86) which remained significant after controlling for opiate use, clinical stage
and cesarean section (OR 2.3; 95% CI 1.17-7.1). Only one case of HIV transmission
was documented, and this occurred in a maternal-infant pair with poor compliance with
medications during pregnancy.

International Perinatal Trials

A number of international trials have continued to evaluate the use of monotherapy
regimens in the context of perinatal transmission, despite the proven effectiveness of
combination therapies in both the treatment of the mother and in the reduction in HIV transmission. Although the ethics of such trials have been questioned by individuals and institutions in the developed world (80,81), the intent of these trials has been to try to evaluate the most sustainable intervention to reduce perinatal HIV transmission that is both effective but also mindful of the relatively limited financial resources and settings that are the reality in many developing countries.

In 1999, Shaffer published the results of the Bangkok study, a collaborative study between the CDC in Atlanta and the Ministry of Public Health in Thailand (82). This trial evaluated the use of oral zidovudine from 36 weeks gestational age twice daily until delivery, and then oral zidovudine every three hours in labour until delivery. In this protocol, intravenous zidovudine was not used in labour, and the infant did not receive any treatment after birth. This trial was placebo controlled, and demonstrated a significant reduction in transmission from 18.9% in the untreated group to 9.4% in the treated group (Kaplan Meier estimate at 6 months; p=0.006).

The RETROCI study in the Ivory Coast trial used a similar regimen to the Bangkok trial, although the women in the Ivory Coast trial were allowed to breast-feed postpartum. This evaluation found a transmission rate of 24.9% in the AZT group compared to a rate of 15.7% in the placebo group (Kaplan Meier estimate at age 3 months, p=0.07)(83). The DITRAME study used similar protocol as well, and permitted breast-feeding. Combined with the results from the RETROCI study, these two studies found a transmission risk of 30.1% in the placebo arms and 22.1% in the AZT arms at 24 months post delivery.
Breast-feeding appeared to account for approximately 9% of the transmission in both arms (84).

The PHPT trial had preliminary results published in October 2000 (85). This trial has four arms, with similar dosages of AZT (300 mg po BID) given at varying durations of either the antepartum or infant period (long/long, long/short, short/long, short/short). Oral zidovudine was provided uniformly for labour. The short/short arm was discontinued after interim analysis as it demonstrated a significantly higher rate of transmission compared to the long/long arm (10.6% vs 4.1%, p=0.004). In the long/long arm, a transmission rate of 6.7% was reported, compared to 5.7% in the long/short arm. This finding implies that shortening the duration of treatment for the infant is acceptable when the mother has received an appropriate amount of treatment in pregnancy. The short/long arm had a transmission rate of 8.4%, indicating that decreased maternal treatment was linked with higher transmission rates.

The South African study AI455-094 evaluated oral regimens of stavudine (d4T) 40 mg BID, ddI 200mg BID, combined d4T/ddI and AZT 300 mg BID all starting at 34 weeks gestational age. The medication the mother received in pregnancy was also given to the infant at appropriate dosages for weight for 6 weeks after birth. The overall transmission rate in this study was 3.6%, and there was no difference in between the different arms, with no significant differences in treatment toxicities.
The HIVNET 012 trial was conducted in Uganda and was a collaboration between Makere University and Johns Hopkins University (86). This evaluation compared nevirapine 200mg orally in labour and a single dose to the infant with AZT 600mg orally and then infant treatment for 7 days. Mothers enrolled in this trial were permitted to breastfeed. By one year the transmission rate in the nevirapine arm was 15.7% compared to 24.1% in the AZT arm. This trial was significant not only because of the differences in transmission, but also because the nevirapine arm required only one dose for the infant and was less expensive. However, there was evidence that several women who received single doses of nevirapine during labour had the K103N nevirapine resistance mutation at 6 weeks postpartum (87). The clinical consequences and implications of this finding for the mother is uncertain and requires continued evaluation.

The PETRA trial was conducted in South Africa, Uganda and Tanzania, and was a placebo controlled trial comparing 3 part (antepartum/intrapartum/postpartum) to 2 part (intrapartum/postpartum) to 1 part (intrapartum) regimens of AZT 300 mg BID and 3TC 150 mg BID(88). This cohort was permitted to breastfeed. The antepartum protocol started at 36 weeks, intrapartum medication was provided orally every 12 hours and postpartum medication was given for one week. This trial found that the three part regimen was the most effective in decreasing transmission (8.6%) compared to the placebo arm (17.2%), but the two part regimens was also effective in decreasing transmission (10.8%). The intrapartum alone arm was not significantly different from placebo.
Prenatal Testing

In order to ensure that women access treatment for HIV in pregnancy, they need to be aware of their HIV status in the antepartum period. This had lead to HIV prenatal testing programs in both the developed and developing world. A voluntary prenatal HIV testing program was initiated in British Columbia in 1994 to ensure that all women were aware of their HIV status during their pregnancy and prior to delivery (53,89,89). Between 1995 and 1996, HIV testing in pregnancy increased from 55% to 76%. In this time frame, 42 HIV positive maternal infant pairs were identified, and 25 (60.0%) were identified only through the screening program.

HIV Positive Pregnant Women and Pregnancy Termination

For many HIV positive women, the concept of child bearing and the risk of HIV transmission to their infant remains too great a risk to undertake. For these women, pregnancy termination is their option. Data on reproductive choice in HIV positive pregnant women is relatively limited, in large part because many women may not disclose their HIV status to abortion providers, or may not disclose a decision to terminate to HIV providers. Prior to the routine use of monotherapy in pregnancy, termination rates were reported from 30% to 93% for HIV positive pregnancies. Of note, these rates were comparable with demographically similar HIV-negative cohorts – and when women were asked about their reasons for termination, few identified their HIV status as the catalyst for their decision (90). However, as treatment for HIV has improved and dramatic reductions in perinatal transmissions have been reported, studies
have found a decrease in the abortion rate in HIV positive women. In fact, a Swiss study noted that 43% of the HIV positive pregnancies were actively planned, and 66% of HIV positive pregnant women were choosing not to terminate, because they in fact wanted to have a child (91). However, risk of transmission and the health of the infant (as opposed to the health of the mother) remains a central concern for HIV positive pregnant women who are evaluating their reproductive options.

Rationale for This Study and Hypothesis

Transmission of HIV perinatally is one outcome in HIV care that can be prevented on most occasions. In order to do so, pregnant women need to be informed of their HIV status prior to or during their pregnancies. Subsequently, these women need access to care in a setting that is mindful of the realities that many HIV positive women face – substance abuse, poverty and limited resources. They then need access to safe and effective treatment, both for their own HIV disease and to prevent viral transmission to their developing fetus. Although there have been a variety of reports world wide examining the issue of perinatal HIV transmission, virtually no in depth studies have been conducted in the Canadian setting. With universal health care and free antiretroviral medications, combined with a vastly different cultural makeup in our HIV positive pregnant population, there is a unique opportunity in British Columbia to evaluate the care provided to HIV positive pregnant women and their infants. There is a need to establish the trends in use of combination therapy in pregnancy, and the outcomes of this use. It is particularly ideal to evaluate the situation for expecting seropositive women in British Columbia, given the centralized system for providing care to HIV positive
pregnant women and their infants at the Oak Tree Clinic at Children’s and Women’s Health Centre of British Columbia. In essence, the structure for ideal care exists in British Columbia, and it will be important to examine the trends in use of combination therapy and the outcomes of this use, to determine if there are areas which require further support and if there are any particular issues that emerge requiring immediate attention.

Hypothesis

There has been an increase in the use of combination antiretroviral therapy in the care of pregnant HIV positive women in BC between 1994-6 and 1997-9. This has resulted in a decrease in perinatal HIV transmission in the same time period.

Sample Size Calculation

The priority evaluation for this descriptive analysis is the rate of use of combination therapy in HIV positive pregnant women between 1994-6 and 1997-99. Previously published national reviews estimate that ART use in pregnancy has been increasing(92). In 1994, 37% of pregnant HIV positive women in Canada received ART in pregnancy. In subsequent years, the rates increased to 53%, 58%, 72% and 84% respectively. Thus, nationally, between 1994 and 1996, 49.3% of pregnant HIV positive women received ART antenatally, and in 1997 and 1998, 78% received ART. Thus, to establish a difference of 25% (75% vs 50% receiving therapy in pregnancy), using an α of 0.05 and β of 0.2 and a two sided test, 58 patients are needed per arm (Appendix II). Thus, 116 pregnant HIV positive women need to be evaluated.
METHODS

Study Design
This evaluation examined the trends and outcomes of treatment of HIV positive pregnant women and their infants in British Columbia between January 1994 and December 1999. This study used an established longitudinal data set from the Oak Tree Clinic, which has been collecting data regarding perinatal care for HIV positive women and HIV exposed and positive infants since January 1994.

Setting
Data for this evaluation was gathered from the Oak Tree Clinic (OTC), Women and Family HIV Centre at Children’s and Women’s Health Centre of British Columbia. This program provides consultative outpatient HIV Care to HIV positive women, their children and partners utilizing a multidisciplinary team approach. Clinical team members include: adult infectious disease specialists, pediatric infectious disease specialists, obstetrical and gynecological infectious disease specialists, family physicians, pharmacists, dieticians, nurse clinicians, social workers and research nurses and outreach staff.
Established in 1994, this centre is located in Vancouver, British Columbia, but provides consulting services and expertise about HIV positive women and HIV positive and antiretroviral exposed children to the entire province. A cumulative total of 495 adult patients (73% women) and 143 children (40 infected and 103 uninfected) and over 100 maternal infant pairs have received care through the Oak Tree Clinic (94). The program sees approximately 80 new adults per year, and assists in managing 25-30 pregnancies and 30 new HIV perinatally exposed infants and children annually.

Data Collection

Data for this review was gathered from both a retrospective and prospective chart review. In 1998, uniform chart forms designed to standardize data collection during the clinical interview from patients were introduced after extensive consultation with the clinical team and after comprehensive literature review. These assessment forms review patient demographics, clinical history and interventions, medication history, alcohol and drug use, lab data and physical examination results. These forms are completed as part of each medical assessment at the time of the visit. Any data not completed on the form by the treating clinician (such as recent lab results) is gathered from the chart by the research nurse. The data is then inputted into a Microsoft Excel spreadsheet by Oak Tree clinic research nurses. Prior to 1997, data entered into the data base was obtained by retrospective chart reviews. Data forms were used as the template to guide the data gathering process, and this information (where available) was taken from the chart and
inputted onto the spreadsheet. There is currently no process for continual quality assurance of the perinatal data spreadsheet.

It is important to note that although this database has captured comprehensive data regarding the pregnancy and treatment during the pregnancy of HIV positive mothers who gave birth between January 1994 and December 1999, some of the pregnancies were not identified until after the delivery of the infant. Rather, the infant came into care at Oak Tree Clinic, and data regarding the pregnancy was obtained from prenatal and birth records. In these cases, history of treatment and risk factors in the pregnancy were gathered retrospectively from the mother.

Variable Identification and Selection

Variables included in the overall database were selected after extensive discussion with experienced clinicians at OTC and after review of the HIV medical literature. Variables that were felt to be clinically relevant to care provision and patient outcomes were identified and included in the database. In general for pregnant HIV positive women, they include: maternal and (if available) paternal demographic data, method of HIV acquisition, past obstetrical history, family medical history, HIV history, past medical history, infectious diseases in pregnancy, medical evaluations in pregnancy, access to treatment, antiretroviral use in pregnancy, drug exposures in pregnancy, lab results from pregnancy, antenatal complications, antenatal hospital visits, pregnancy outcome, duration of labour, type of delivery, use of analgesia, use of antiretroviral therapy in delivery, placental pathology, postpartum complications and postpartum lab results. For
infants born to HIV positive mothers, gestational age, birth-weight, APGARS, birth
defects and congenital abnormalities, complications of delivery, medical problems of
infant, feeding status, use of ART after delivery are collected for the database.

Data from External Sources

In order to compare the cohort of women and infants at evaluated at the Oak Tree Clinic
with other women in the province and across the country, external data sources were used
to obtain baseline data. National cultural and ethnic data was obtained from Statistics
Canada, from the 1996 Canadian Census (95). Ethnic origin was defined as the ethnic or
cultural group to which one’s ancestors belonged. Canadians were asked to write down
their ethnic origin (as opposed to selecting from pre-defined choices). For ease of the
respondent, twenty four examples of ethnic origin were provided. Respondents were also
asked to indicate as many ethnic origins as possible which could describe them, as
opposed to paternal ethnic origin. Aboriginal refers to individuals who identify with one
of the following cultural groups; North American Indian, Metis or Inuit, and/or those who
are registered Indians under the Indian Act.

National HIV/AIDS data was gathered from the Health Canada HIV and AIDS in
Canada; Surveillance Report to December 31, 2000(4). This report is compiled annually
by the Division of HIV/AIDS Epidemiology and Surveillance of Health Canada. Data is
gathered on the basis of non-nominal, confidential information regarding positive HIV
test reports and diagnosed AIDS cases provided by all provinces and territories of Canada
to Health Canada. British Columbia HIV/AIDS information was based on the British Columbia Centre for Disease Control Society, Division of STD/AIDS control, Annual HIV/AIDS Update 2000 (5). This report is also based on data from Health Canada’s Division of HIV/AIDS surveillance. Data on health statistics for the aboriginal community of British Columbia was obtained from the “Analysis of Health Statistics for Status Indians in British Columbia, 1991-1999”, which has been produced by the British Columbia Vital Statistics Agency on behalf of the Medical Services Branch of Health Canada(96). Data for this report was extracted from BC Vital Statistics Agency, BC Medical Services Plan and the Indian Status Verification file. This report presents summaries of birth and mortality related statistics of health status for Status Indians who live in British Columbia and compares them to other BC residents. Of note, in this report the only First Nations group used for evaluation was Status Indians.

Provincial birth statistics for British Columbia were obtained from the British Columbia Vital Statistics Agency (97). Data is gathered on events that occurred in the province for British Columbia residents only. All live births must legally be reported within 30 days by both the parent(s) of the infant and by the registered practitioner who conducted the delivery. Other data, such as mode of delivery, birth weight and gestational age are submitted to the agency by the practitioner at the time of delivery. These are then coded for their specific health regions. National abortion data was obtained from the Canadian Perinatal Surveillance System, which compiles abortion and abortion related statistics from Statistics Canada (95).
Study Variables

Variables selected for use with this analysis were generated after a comprehensive review of the literature pertaining to HIV positive pregnant women in particular. Factors that have been demonstrated to impact on medication adherence and compliance, transmission, delivery outcomes, fetal well being, as well as outcomes of interest that were available for study from the database were identified. It was also important, given the relatively low event rate and the large number of variables available, that the data analysis be streamlined to evaluate specific pre-defined questions and describe trends that were biologically plausible and logical. With the relatively small event rate to variable ratio, in a descriptive analysis one risks the possibility of missing important relationships between variables (Type II errors), which are merely a result of the relatively small sample size. Thus, careful and judicious selection of variables for analysis is paramount.

Data base Validation

The other important criteria for variable selection was variable accuracy. As there is no continual quality assurance process for the OTC perinatal dataset, variables which had been inputted into the database were verified by the consulting pediatric physician for each patient after reviewing the patient’s chart and clinical history once they had been put into the database. For purposes of this thesis, a random selection of 5 maternal and 5 infant charts were identified and information available in the chart for all variables was compared to information listed in the database. Each variable in the spreadsheet was reviewed and confirmed in the patient chart.
Variable Definition

*HIV seropositivity* of the expecting women was confirmed through the British Columbia Centre for Disease Control (BCCDC), and a copy of their positive ELISA and Western Blot was retained in their file. This confirmation process is standard practice in most centres caring for HIV positive individuals. All adult blood that is tested for HIV in the province of British Columbia is completed at the British Columbia Centre for Disease Control (BCCDC). All blood is initially evaluated using the Abbott AxSYM micro enzyme linked immunoabsorbent assay (MEIA). Negative MEIAs are reported as negative to clinicians. Any positive or grey MEIAs are repeated twice. If both repeated MEIAs are negative, the test is reported as negative to the requesting clinician. Any weakly positive or positive MEIAs are then evaluated with Bio Rad HIV-1 Western Blot. Negative western blots have the Ortho electrochemiluminescence (ECI) Anti-HIV 1,2 supplemental completed. If this continues to be negative with the Ortho ECI, then the blood is tested with Organon p24 antigen EIA, and negatives are reported as negative to the clinician. Positive Western blots are evaluated with the supplemental Ortho ECI Anti HIV 1,2 supplemental, and if positive, the test is reported as positive to the ordering clinician. Inconsistent results, such as positive Ortho ECIs and negative Organon p24 antigens, are reported to the clinician with a request for followup. These usually indicate the patient is in the seroconversion stage or an HIV-2 infection. The overall sensitivity for an HIV testing procedure including MEIA and western blot is greater than 99.7% and specificity of 99.9%(8).

*Maternal age* at the time of delivery was calculated from recorded maternal date of birth.
Cultural background was self described by each woman. "Aboriginal" and "First Nation" are used interchangeably in this study, and include First Nation, Metis and Inuit women in the cohort. "Black" is used to define women of African, Caribbean, African-American or African Canadian heritage. "Asian" women include women from South Asia (India, Pakistan, Bangladesh etc.) as well as South East Asia (Thailand, Phillipines, Indonesia etc.) and Asia (China, Japan, Korea etc.)

Risk behaviour for HIV contraction was self-reported by patients. Risk behaviours for viral contraction include use of intravenous drugs, unprotected heterosexual intercourse, transfusion, perinatal transmission or unknown. Intravenous drug use both prior to and during the pregnancy was also gathered from patients. As per Health Canada reporting guidelines, cases are assigned a single category according to an established “hierarchy of exposures” (4). If more than one mode is reported, a case is classified by the highest category. Intravenous drug use is accepted as the highest risk activity, followed by heterosexual activity.

Maternal clinical factors analyzed include CD4 counts, viral loads, type of combination therapy used and mode of delivery.

CD4 counts were available from hospital lab departments. To measure CD4 counts at Children’s and Women’s Health Centre of British Columbia, whole blood was incubated with pre-mixed 3-colour monoclonal antibodies, Tri-Chrome CD4-PE/CD8-FITC/CD3-PECy5 Beckman–Coulter. After lysis and fixation, cells were analysed by flow cytometer, Beckman-Coulter EPICS:XL-MCL. By gating on the lymphocyte population, both T-helper (CD3+4+) and T-suppressor (CD3+8+), subpopulations could be measured.
Viral load testing in British Columbia commenced in June 1996, and all viral loads samples are sent and evaluated at the Diagnostic Virology and Reference Laboratory at St. Paul's Hospital in Vancouver. Viral loads are evaluated using the Roche HIV-1 monitor test. Initially, the Roche HIV-1 test could only detect a minimum of 500 viral copies/ml, and if a sample had less than 500 copies of virus/ml, the sample was labelled as having an "undetectable" level of virus. In April 1997, the undetectable level decreased to 400 copies/ml. Between August 1997 and 1998, several new primers were added in order to identify different subtypes of HIV-1. In April 1999, the ultrasensitive method was added on to the process, and the undetectable viral level decreased to 50 copies/ml.

Delivery mode were described in and obtained from birth records. Delivery mode was described as either a vaginal birth or a cesarean section. No distinction was made between urgent, emergent and elective cesarean sections.

Type of combination therapy used was available from the OTC chart. Women who took any combination therapy during their pregnancies, regardless of their compliance or duration of their therapy were defined as having received combination therapy.

HIV Serostatus identified: Some HIV positive mothers were not identified until after delivery of their infants, while others knew their HIV status but did not access care and treatment during their pregnancy. This issue was captured by the time at which the infant came into care at Oak Tree Clinic. If there was a delay between the date of birth and "date of diagnosis", this indicated in virtually all cases that the mother was unaware of her HIV status during pregnancy.
Pediatric factors include gestational age, birth weight, use of combination therapy in the immediate post partum period and HIV status of the infants.

*Gestational age and birth weight* use was available in the delivery record.

*Antiretroviral therapy use* in the infant was gathered from the delivery record and the clinical record at Oak Tree Clinic.

*Infant HIV status* was obtained from the BCCDC. Evaluating the HIV serostatus of infants is somewhat more complex than an adult evaluation. Maternal HIV IgG antibodies passively cross the placenta, and infants carry these antibodies for up to eighteen months after delivery. Thus, the HIV status of neonates exposed to HIV *in utero* can not be assessed accurately using the standard HIV antibody based test. Infants in British Columbia have their HIV serostatus evaluated with Roche HIV-1 DNA PCR assay and HIV cultures. The PCR test has a sensitivity of greater than 99% and a specificity of 98%. Positive HIV-1 DNA PCR and/or positive HIV cultures in HIV exposed infants were repeated. Two positive results on different occasions indicated a positive HIV infection in the infant and then a viral load estimation is performed. Two negative PCRs and/or HIV culture results performed after the age of one month drawn on separate occasions indicate that the infant is not infected. The HIV culture has been discontinued by the BCCDC in January 2001(5).

Study variables not available for analysis include the home address of the patient and whether women first received treatment during pregnancy, or had received treatment prior to their pregnancy. Duration of therapy was also not available on all maternal infant pairs, and was therefore not included in this analysis.
Data Analysis

Unit of Analysis

In perinatal data evaluation, selecting the unit for analysis warrants discussion. There exists no uniform or standard method of reporting perinatal events. Depending on the question and the outcome available for analysis, the mother, the pregnancy, the delivery, or the infant(s) can each be the event. Provincial and national perinatal data such as Statistics Canada, the National Perinatal Surveillance Study (95) and the British Columbia Reproductive Care Program usually select the infant or the live birth as the event, reporting singletons, twins, triplets, quadruplets as one, two, three and four events respectively and so on. Because these are annual reports, and rarely would one mother have two pregnancies in a calendar year, the chance of including two separate pregnancies for one mother is limited. However, in those databases, multiple gestations result in multiple counts of maternal age, demographics, place of birth, obstetrical risk factors and other variables related to the mother and the pregnancy. Other reports use the phrase "maternal-infant pair". Again, in this situation, twins would be two maternal infant pairs. Other evaluations look at the delivery, and will count each peripartum period as one event, regardless of the number of infants produced at that delivery. In this situation, type of delivery is usually, though not always recorded as the delivery mode for Obstetrical and pediatric clinical definitions are appended (Appendix III).
the first infant. Finally, obstetrical literature tends to identify the mother/pregnancy as
the event, and multiple gestation pregnancies are counted only as one event.

Because this data set has been gathered over a period of six years, there are several
women in the cohort who have had more than one pregnancy, and a multiple gestation
has also been reported in the cohort. Failure to identify repeat pregnancies would
certainly threaten the validity of the information reported in this study.

An extensive review of methods in perinatal literature, and discussions with
epidemiologists experienced in perinatal research failed to reveal any accepted standard
of reporting perinatal events in longitudinal databases. The consensus appeared to be that
one should select the event (mother, pregnancy, delivery, infant) which best answers the
question of interest. However, in an effort to provide the most comprehensive analysis,
in this study, where relevant, the mother, the delivery and the infant will all be used as the
event of interest.

Data Analysis

Data analysis was conducted using Microsoft Excel™ and Statistical Solutions program.
Means with standard deviations were calculated and t-tests applied for maternal age,
gestational age, CD4 counts at or near delivery, and viral loads at or near delivery. These
were also calculated for specific subgroups, such as First Nations infants, infants exposed
to medication in utero, and HIV positive infants. Pearson chi squares test were
conducted to compare event rates between patients at OTC to the rest of the province and
country. Fisher's exact test was used when the expected number in a cell was less than five. Yates correction was not employed in the Chi square calculations. Comparisons include percentage of First Nation individuals, rate of preterm labour and delivery, rate of low birth weight infants and rate of caesarean sections. Pearson chi squares and Fisher's exact tests were also used to compare event rates before and after 1997 within the population of HIV positive maternal infant pairs. This includes rate of IV drug use in mothers, use of combination therapy in pregnancy, rate of caesarean sections, access to treatment, use of antiretroviral therapy in infants and rate of HIV seropositivity of infants. Pearson chi square analysis were also conducted on specific subgroups, such as First Nation populations, and intravenous drug users. A p value of 0.05 was considered statistically significant, and all reported p values are two sided.

Odds ratios with confidence intervals were conducted for variables to provide a measure of the strength of association between two variables. Due to the relatively low event rate, it is not possible to conduct multivariable analysis, such as logistic regression, on this longitudinal dataset. In situations where known confounders were present, the Mantel-Haenszel method was used for estimating the common odds ratio while controlling for the effect of the confounding variable. These include controlling for intravenous drug use when comparing the rate of low birth weight and preterm infants, and controlling for ART use when comparing the rate of transmission between caesarean sections and vaginal births. As well, Mantel-Haenszel methods were used to compare rates of transmission in certain subgroups, such as injection drug users or First Nations when other factors such as access to treatment were controlled for.
In June 1996, there was a significant shift in the approach to care given to HIV positive individuals (60). Data had demonstrated that use of combination ART for non-pregnant HIV positive individuals offered significantly improved morbidity and mortality outcomes for individuals compared to monotherapy. As this information was presented and reported prominently in the national and international literature and media, most clinicians providing HIV care were aware of this new information relatively quickly after its release. This lead to a rapid adoption of this new approach to care, and treatment protocols for both non-pregnant and pregnant HIV positive individuals soon included combination therapy. Thus, January 1997 has been deemed for the purposes of this analysis as a turning point in HIV care in British Columbia, and event rates are examined before and after this seminal change in care.

Ethical Considerations

This study was approved by the Clinical Research Ethics Board, Faculty of Medicine, University of British Columbia, in Vancouver, Canada and by the Research Review Committee of Children’s and Women’s Health Centre of British Columbia.
RESULTS

Estimate of HIV Positive Pregnancies in British Columbia

In 1999 there were 41,739 live births in British Columbia (97). Using the most liberal estimate of 7.3 HIV positive pregnancies per 10000 pregnancies (7) (the highest estimate from the 95% confidence interval of 1994), one could expect a maximum of 30 pregnancies to HIV positive women in British Columbia in 1999. Current data from care providers working with HIV positive women indicate that clinicians are caring for approximately 25 HIV positive pregnancies annually in British Columbia, implying that most, if not all, HIV positive pregnancies are known prior to delivery.

Pregnancies at the Oak Tree Clinic

Since January 1994, 145 HIV positive maternal infant pairs were identified at the Oak Tree clinic, either during or after their pregnancies (Figure 1). Seventy-three pregnancies were prior to 1997 and 72 of these pregnancies occurred after 1997. Nineteen HIV positive women were known to terminate their pregnancies, and eight women had spontaneous abortions before twenty weeks gestational age. Eleven terminations took place between 1994 and 1996, and eight terminations happened between 1997-1999. Two spontaneous abortions took place prior to 1997 and six took place between 1997-1999. There were 118 pregnancies that were carried beyond 20 weeks. Two still births occurred, one in 1996 and one in 1999. Of the remaining 116 live births that occurred between 1994 and 1999, one woman had a set of twins and another singleton birth,
fifteen women had two pregnancies and 83 women had one pregnancy. Thus, there were
116 live births to 99 HIV positive women between January 1994 and December 1999 in
British Columbia.

The Canadian Perinatal Surveillance System reports that in 1995 there were 106 658
abortions obtained by Canadian females. In that same year, there were 378 011 live
births and 2353 stillbirths in Canada. Thus, in 1995, 21.9% of pregnancies were
terminated. At Oak Tree Clinic, 19 of the 145 pregnancies were known to have been
terminated (13.1%).

Maternal Demographics
HIV positive mothers had an average age of 27.6 (± 5.3, 95% CI 26.6-28.6) years at the
time of the birth(s) of their infants, with the youngest mother aged 18 years old, and the
oldest mother being 43 (Table 1). Thirty-nine women (39.4%) were 25 years old or less
at the time of their infants birth. Sixty-two of the ninety nine mothers contracted HIV
from IV drug use (62.6%), 35 contracted the virus from sexual intercourse with an
infected partner (35.3%), and 2 (2.0%) women stated that they did not know how they
contracted the virus.
Cultural Background

Forty-one (41.4%) HIV positive pregnant women self identified their cultural background Caucasian, and were responsible for forty-eight (41.4%) of the live births to HIV positive women. Thirty one percent (31) identified themselves as being First Nations and had thirty eight live births (32.8%). Eighteen women described themselves as black (18.2%) and were responsible for nineteen (16.4%) of the live births. Seven women (7.1%) who were Asian (including South Asia, Southeast Asian and China) had nine infants (7.8%). One woman was from South America (1.0%) and the remaining woman did not describe a cultural background.

In the province of British Columbia, 139 655 individuals are from First Nations background, making 3.8% of the population in the province First Nations (139 655/ 3 689 755). At Oak Tree, 31.9% of HIV positive women who are pregnant are from a First Nations cultural group (31.9% vs 3.8%, p<0.000). Thus, a pregnant HIV positive individual is 11.9 times more likely to be of aboriginal origin than those in British Columbia who are not pregnant and HIV positive [(37)(3550021)/(79)(139618), 95% CI 8.1 – 17.5)].

Forty one of the fifty seven HIV positive mothers who delivered between 1994 and 1996 identified themselves as intravenous drug users (71.9%) and twenty one mothers contracted HIV through intravenous drugs use between 1997 and 1999 (21/42 = 50.0%).
There has been a significant reduction in the rate of mothers who report IV drug use as their risk behaviour for contracting HIV over the past six years (68.0% vs 37.5%, OR 3.6; 95% CI 1.7-7.7, p<0.05). However, when we compare the rate of intravenous drug use in maternal infant pairs over the past six years, 43 out of 60 pairs (71.7%) reported IV drug use as their risk for viral contraction prior to 1997 compared to 31 out of 56 (55.3%) after 1997. There has been no difference in the rate of maternal infant pairs with IV drug use as their risk behaviour in the past six years (71.7% vs 55.3%, OR 2.0; 95% CI 0.9-4.4, p =0.07) (Table 7).

Antiretroviral Therapy in Pregnancy and Infants

Antiretroviral treatment for maternal infant pairs fall into three categories: maternal treatment during the pregnancy, maternal treatment during labour and infant treatment after delivery. Ideally, maternal infant pairs receive treatment at each of these times. Between 1994 and 1999, fifty one HIV positive women received no antiretroviral treatment in pregnancy, forty five did not receive any ART in labour and thirty four infants did not receive any post partum HIV treatment (Table 2). Sixty-five maternal infant pairs (65/116) received some kind of antiretroviral treatment during their pregnancies between January 1994 and December 1999. Unfortunately, the duration of therapy during the antepartum period was not available for every maternal infant pair. Before January 1997, nineteen pregnant HIV positive women received AZT monotherapy and four women received dual therapy during their pregnancy (23/60=38.3%). After January 1997, ten women received AZT monotherapy, eight women received dual therapy, twenty two received triple drug combinations, and two patients received four
drug combination therapy during their pregnancy (42/56 = 75%). By 1999, all women who were taking antiretroviral therapy during their pregnancies were receiving combination therapy. There was a significant increase in the rate of any type of medication use in pregnancy for HIV positive women between 1994-6 and 1997-9 (38.3% vs 75%, OR 0.2; 95% CI 0.09-0.5, p<0.01) (Table 7).

Combination therapy regimens vary widely, and are often dictated by the regimen the client is taking prior to becoming pregnant (Table 3). Most women who received dual therapy received AZT and 3TC (9/12), two received AZT/ddC and one received d4T and 3TC. With combination therapy, nine women received AZT, 3TC and indinavir, four women received AZT, 3TC and nelfinavir, two women received AZT, ddI and nevirapine, two women received d4T, ddI and nelfinavir and only one woman took the following combinations during their pregnancies: d4T/3TC/nelfinavir, d4T/3TC/nevirapine, d4T/ddI/nevirapine, AZT/3TC/nevirapine and one unknown combination therapy. One patient received quadruple drug combination regimen of d4T, ddI, 3TC, and saquinavir, and one received a quadruple drug combination of AZT/ddI/Nevirapine/Nelfinavir.

Maternal Serologic and Virologic Outcomes

 Mothers had a mean CD4 count of 458.2 (±189, 95% CI 408 – 508) when their CD4 count was measured near or at delivery. Mothers who delivered between January 1994 to December 1996 had a mean CD4 count of 465 (±207, 95% CI 317 – 613)/mm$^3$, and
mothers who had infants between January 1997 to December 1999 had mean CD4 count of 456 (±188, 95% CI 401—511)/mm³. Six women who delivered after January 1997 had CD4 counts less than 200/mm³. Of note is that CD4 counts were available on 45 women after 1997. Prior to 1997, only 10 women had CD4 counts available for evaluation. This may indicate that women who had measurements were being closely followed by a clinical team, and therefore have CD4 counts that are actually lower than what is truly reflected in the population of HIV positive pregnant women.

Viral loads have been measured in British Columbia since late 1996. Viral loads were available on 10/60 women who delivered prior to January 1997, and on 45/56 women who delivered after January 1997. Prior to 1997, women who had viral loads measured had mean viral loads of 4120. Mean viral load overall for women delivering after January 1997 was 7931.2 (±17 832.9). Twenty women who delivered after January 1997 had viral loads that were undetectable at or close to delivery. Two of these pregnancies received AZT monotherapy, one received dual therapy of AZT and 3TC and seventeen of these women received combination therapy; one woman received quadruple therapy and the remaining women received triple therapy. Five women with undetectable viral loads were First Nation, seven were Caucasian, one was Asian, one was South American and six were black. Only women who had received ART during their pregnancies achieved undetectable viral loads at delivery, and triple or quadruple drug treatment was significantly associated with undetectable viral loads at delivery (17/24 vs 3/41, OR 30.76; 95% CI 7.1 – 133.59, p<0.000). In women with undetectable viral loads, none of their infants contracted HIV.
Treatment During Labour and Delivery

Forty five HIV positive pregnant women did not receive any treatment during labour (45/116 = 38.8%). Thirty two of these women gave birth prior to 1997, while the remaining 13 delivered after 1997. There has been a significant increase in the use of ART during labour between 1994-6 and 1997-9 (53.3% vs 23.2%, OR 3.8; 95% CI 1.7-8.4, p=0.0009). Three women received combination therapy during their deliveries, and the remaining women who were treated during their deliveries received AZT therapy.

Obstetrical Complications with Combination Therapy

During the pregnancies, two patients were diagnosed with gestational diabetes mellitus. One patient had received AZT during her pregnancy, and one had not taken any ART during her pregnancy. Five women developed oligohydramnios during their pregnancy – four of the five women had taken AZT monotherapy during their pregnancies and one took no ART in her pregnancy. Five mothers experienced intrauterine growth retardation during their pregnancies. Four of these women had received AZT during their pregnancies, and one received triple drug therapy including AZT, 3TC and indinavir. One of the pregnancies which experienced IUGR was a twin pregnancy. One of the pregnancies that experienced IUGR resulted in a still birth at 34 weeks gestation. None of the infants who experienced IUGR in utero became HIV positive. One patient who had received AZT during her pregnancy developed chorioamnionitis at delivery.
Mode of Delivery

Thirty five HIV positive maternal infant pairs were delivered by cesarean section between 1994 and 1999. Between 1994 and 1996, eight of the sixty infants born to HIV positive women in British Columbia were delivered by caesarean section (13.3%), but after 1997, 27 of the fifty six infants born to HIV positive women were delivered by section (48.2%). The rate of caesarean sections has significantly increased for HIV positive women since 1996 (13.3% vs 48.2%, OR 0.2; 95% CI 0.1-0.41, p<0.000) (Table 7). In 1999, 9282 of the 41739 live births in the province were delivered by caesarean section. A pregnant woman at Oak Tree is 1.5 times more likely to have a Caesarean section than a pregnant woman in British Columbia (OR 1.5, 95% CI, 1.0 –2.3). Four infants born by caesarean section were HIV positive (4/35=11.43%), and fourteen infants born by vaginal delivery were HIV positive (14/81= 17.28%). Three of these four maternal-infant pairs did not receive any ART in pregnancy, and one of these pairs received treatment during pregnancy and delivery, but did not receive post partum treatment. When treatment is controlled for in the analysis, the odds of having an HIV positive infants is 1.66 in those who had caesarean sections compared to those who had vaginal deliveries (95% CI 0.4-6.8, p=0.9).

Infant Demographics and Outcomes

There were one hundred and sixteen live births to HIV positive women between January 1994 and December 1999. Eighteen of the 116 infants born to HIV positive mothers in British Columbia between January 1994 and December 1999 were HIV positive, for an overall HIV transmission rate of 15.5% (18/116). Fifteen infants born to sixty HIV
positive pregnancies were HIV positive between 1994 and 1997 (15/60=25%, 95% CI 0.16-0.37). Two of these fifteen HIV positive infants died; one died from AIDS in 1996 and one died from other causes in 1994. After 1997, three of the fifty-six infants born to HIV positive mothers were HIV positive (3/56=5.4%, 95% CI 0.02–0.1). Since 1997, there has been a significant reduction in the rate of HIV seropositivity in infants born to HIV positive mothers (25% vs 5.4%, OR 5.9; 95% CI 1.6-21.6, p<0.003) (Table 7). Sixteen of the eighteen HIV positive infants were born to mothers who received no ART in pregnancy and thirteen of the eighteen maternal infant pairs that resulted in a seropositive infant received no treatment either in pregnancy, at labour and delivery or postpartum. The two maternal infant pairs where transmissions occurred in the face of ART during pregnancy received AZT monotherapy. There were no transmissions in maternal infant pairs when the mother received combination medications during the prenatal period.

HIV Perinatally Exposed Infants

Infants born to HIV positive women were born at a mean of 37.2 (±2.6, 95% CI 36.7 – 37.7) weeks gestational age, and the mean birth weight for infants was 2.9 (±0.6, 95% CI 2.8 – 3.1) kg. In British Columbia in 1999, there were 2,672 preterm births (less than 37 weeks gestation), and 23 infants perinatally exposed to HIV were born preterm between 1994 and 1999. Infants born to HIV positive mothers were significantly more likely to be born preterm than other infants born in British Columbia (19.8% vs 6.4%, OR 3.6; 95% CI 2.3-5.7, p<0.000). Twenty of the twenty three preterm HIV exposed infants were born to mothers who contracted HIV through IV drug use, and thirteen of these twenty
mothers admitted to IV drug use during their pregnancies. In the twenty three pre-term infants, twelve of the mothers did not receive any antiretroviral therapy during their pregnancy, and eleven received therapy during the pregnancy. Five received AZT monotherapy, three received dual therapy and three received combination therapy. Three of the preterm infants were HIV positive.

Seventeen infants perinatally exposed to HIV were of low birth weight (<2500gm), and 1,981 infants in British Columbia weighed less than 2500 grams at birth. Infants born to HIV positive mothers were also more likely to be low birth weight infants, compared to the rest of the British Columbia population (14.7% vs 4.7%, OR 3.5; 95% CI 2.1-5.8). Thirteen mothers who had low birth weight infants contracted HIV through IV drug use, and six reported IV drug use during their pregnancies. Of the seventeen infants who were born with low birth weights, seven of their mothers received no ART during their pregnancy and ten received therapy. Five received AZT monotherapy, one received dual therapy, and four received combination therapy. One of the low birth rate infants was HIV positive.

Relatively few congenital abnormalities were reported in this cohort. In the 116 live births, one child had an atrial septal defect and had been exposed to AZT monotherapy in utero; one child had a single kidney and had been exposed to AZT monotherapy in utero, one child had a lumbar myelomeningocele and was not exposed to any antiretroviral treatment in utero. Finally, one child that had been exposed to AZT, 3TC and indinavir in utero developed a mild atrial shunt.
HIV Transmission Rates in Pregnancy treated and non-treated Maternal Infant Pairs

In the fifty-one women who received no antiretroviral therapy in pregnancy, 16 infants were HIV positive, and 35 infants were HIV negative, for a transmission rate of 31.4% (16/51) (Table 4). Of these fifty-one women, 10 received AZT in labour, and nine of the infants born to these ten women received AZT therapy for the first six weeks of life. In these 10 women who received AZT in labour, 3 infants were HIV positive (30.0%). In the 41 women who did not receive AZT therapy in labour, 9 (9/41=22.0%) of their infants received a course of AZT for six weeks, and 32 did not (32/41=78.0%). Thus, there were 32 maternal infant pairs who received no treatment in pregnancy, labour or post partum (32/116). In the 9 maternal–infant pairs who received AZT therapy post partum having received neither treatment during pregnancy or in labour, none of them tested positive for HIV. However, in the 32 maternal infant pairs that did not receive ART at any stage (pregnancy, labour and delivery, postpartum) 13 infants were HIV positive (0/9 vs 13/32, Fisher’s exact p=0.04). Since 1997, there has been a significant reduction in the number of maternal infant pairs who receive no ART treatment in any stage (43.3% vs 10.7%, OR 6.4; 95% CI 2.4-17.1, p<0.0001) (Figure 2).

In the sixty-five women who received some kind of antiretroviral therapy for some period of time during their pregnancy, only two of their infants were HIV positive (3.04%) and both of these transmissions occurred in women who took AZT monotherapy. There were no HIV transmissions in women who took dual, triple or quadruple drug combination therapy for any duration of time. Any use of ART in pregnancy significantly lowered the...
chance of transmission of HIV from mother to infant (31.4% vs 3.1%, OR 14.4, 95% CI 3.2-66.3, p<0.000).

Only 6 of the 56 infants born between 1997 and 1999 did not receive AZT therapy after their birth (10.7%), while forty six percent (28/60) of infants born between 1994 and 1996 did not receive AZT therapy after their birth. There has been a significant increase in the percentage of infants who received AZT after birth (10.7% vs 46.7%, OR 7.3; 95% CI 2.7-19.6, p<0.001).

HIV Positive Infants

Eighteen infants contracted HIV perinatally in British Columbia between January 1994 and December 1999, for a transmission rate of 15.5% (18/116) (Table 5). Their birth weight ranged from 1.9 kg to 4.9 kg, with a mean birth weight of 3.3 kg (95% CI, 2.7-3.8), and their gestational age ranged from 33 weeks to 42.0 weeks, with an average gestational age of 37.8 weeks (95% CI, 35.9—39.8). Three HIV positive infants were born preterm (16.7%) and one was a low birth weight infant (5.6%). In the eighteen infants who contracted HIV perinatally, 14 were born vaginally and 4 were born by caesarean section. In the 98 uninfected infants, 67 were born vaginally and 31 were born by caesarean section. Nine (50%) of the positive infants were born to First Nations mothers, 5 (27.8%) were born to white mothers, two (11.1%) were born to Asian mothers, one (5.6%) was born to a black mother and one (5.6%) was born to an Indian mother. Although 12 of the mother’s of positive infants contracted the virus through IV drug use (66.7%), only 5 of these mothers used IV drugs in pregnancy (27.8%).
Infant Exposed to ART in utero

The mean gestational age of infants who were not exposed to ART in utero was 37.0 weeks (+/-3.1, 95% CI 36.1-37.8), while the mean gestational age for infants born to mothers who took ART in pregnancy was 37.4 weeks (+/-2.3, 95% CI 36.8-38.1). There is no significant difference between the gestational age of these two groups of infants (t-test, -0.9, p =0.4, two sided test). The mean birthweight for infants who were not exposed to ART in utero was 2.9 kg (+/-0.7, 95% CI 2.7-3.1), while the mean birthweight for exposed infants was 2.95 kg (+/-0.6, 95% CI 2.8 – 3.1). There is no significant difference between the birthweight in these two groups (t-test =0.1, p=0.9).

Intravenous drug use is a known confounder for both low birth weight and for preterm deliveries, and is unevenly distributed in this cohort. When intravenous drug use is controlled for in the analysis, infants who are exposed to antiretrovirals in utero are not more likely to have a low birth weight than infants who have not been perinatally exposed to these treatments (OR 1.28, 95% CI 0.45-3.63). When IV drug use is controlled for in the analysis of gestational age, infants who were exposed to antiretroviral treatments in utero were no more likely to be born preterm than infants who were not exposed to ART in utero (OR 0.82, 95% CI 0.32-2.14).

Stillborn Infants

There were two still born infants born to HIV positive women in British Columbia between 1994 and 1999 of which we are aware. One was born in 1996 at 34 weeks gestational age. The mother received AZT during her pregnancy, and started
antiretroviral therapy at 30 weeks gestational age. This mother used intravenous drugs both prior to and during her pregnancy. The mother had intrauterine growth retardation during the pregnancy, developed chorioamnionitis during labour, and delivered the infant vaginally. The infant was HIV negative.

The second still born infant was born at 21 weeks gestational age in July 1999. This mother had received D4T, saquinavir and ritonavir throughout her entire pregnancy. At 13 weeks, the mother had experienced some vaginal bleeding. On post mortem, this infant had normal growth, placenta and no congenital abnormalities. This pregnancy loss was likely due to cervical incompetence.

Identification of HIV Positive Maternal-Infant Pairs

In order to receive treatment for HIV during pregnancy, HIV positive mothers must somehow be identified. In British Columbia, a universal screening program was developed in 1994, and this has lead to improved identification and subsequent treatment of HIV positive maternal infant pairs in the pregnancy, delivery and postpartum periods. Twenty-seven of the 116 HIV positive maternal infant pairs evaluated were identified after delivery (Figure 3). Three of these 27 mothers received treatment elsewhere, which means that they were aware of their HIV positive status prior to delivery, and transferred to British Columbia or Oak Tree Clinic after their deliveries. None of these three infants were HIV positive, and these three maternal infant pairs received treatment in all three stages. Excluding the three treated maternal infant pairs, twenty of these pairs delivered before 1997 (20/59) and since January 1997, only four HIV positive pregnancies were
identified to Oak Tree Clinic after delivery (4/54). HIV positive maternal infant pairs are much more likely to know their HIV status prior to delivery since 1997 compared to before 1997 (33.9% vs 7.4%, OR 6.4; 95% CI 2.025-20.3, p<0.0006). None of these twenty four HIV positive maternal infant pairs received ART in any of the three treatment stages, and twelve of these infants were HIV positive, for a transmission rate of 50% (12/24). Failure to be identified as HIV positive is significantly associated with having an HIV positive infant (50% vs 6.7% (6/89), Fisher's exact test, p<0.0000). Eight of these non-identified, non-treated maternal infant pairs were of First Nations background (8/24 = 33.3%). Excluding the three women treated elsewhere, the mean time to identification after delivery was 10.29 months.

Fifty-one maternal infant pairs did not receive ART in pregnancy, and as discussed twenty four of these pairs had unknown HIV status. These means that twenty-seven pairs who were aware of their HIV status did not received treatment during the antepartum period between 1994 and 1999 (Table 6). Seventeen (17/60) of these pregnancies delivered prior to January 1997 and ten (10/56) delivered after 1997 (28.3% vs 17.9%, OR 1.82, 95% CI 0.75-4.4). Ten of these maternal infant pairs were First Nations (37.3%), 13 were Caucasian (48.1%), 2 were black (7.4%) and 2 were Asian descent (7.4%). Twenty two maternal infant pairs (81.5%) identified intravenous drug use as their risk behaviour for HIV contraction, and the remaining pairs identified HIV contraction from an infected male partner. Twenty of these twenty-seven women used IV drugs during their pregnancies (20/27=74%), and four women stated that they did not use IV drugs during their pregnancies. Use of illicit drugs during the pregnancy is unclear for
3 of the maternal infant pairs. Four of these infants were HIV positive (14.8%). Nine of these pairs received no medication during delivery or for the infant, nine received treatment during delivery and for the infant and nine pairs only received infant treatment.

Compared to maternal infant pairs who received treatment in pregnancy, known HIV positive maternal infant pairs who did not receive treatment were more likely to have been pregnant in 1994-6 (62.9% vs 35%, OR 3.1; 95% CI 1.2-7.8, p=0.02) and have reported intravenous drug use as their risk behaviour for contracting HIV (81.4 % vs 55.4%, OR 3.5; 95% CI 1.2-10.5, p=0.02). In this cohort, there was no difference in the rate of aboriginal heritage between those maternal infant pairs who knew of their HIV status and did not receive treatment and those pairs that received treatment (Table 6).

Intravenous Drug Use and Treatment Access

In sixty-two women and in seventy-four pregnancies, intravenous drug use was identified as the risk behaviour for HIV contraction. Forty-three of these pregnancies occurred prior to 1997 and thirty-one occurred after 1997. During thirty-nine of these 74 pregnancies, women admitted to IV drug use (52.7%) while being pregnant. In maternal infant pairs who reported having contracted HIV from IV drug use, 36 received some type of ART treatment during pregnancy (36/74 =48.6%), while 29 of the 42 non IV drug using maternal infant pairs received ART in pregnancy. Women with a history of intravenous drug use were less likely to receive ART in pregnancy than women without a history of IV drug use (48.6% vs 69.0%, OR 0.4; 95% CI 0.2 – 0.9, p = 0.03). This difference in treatment access remains, when cultural background of the injection drug
using women is controlled for. Injection drug users are significantly less likely to access treatment in pregnancy, regardless of whether they are aboriginal or non aboriginals (adjusted OR 3.08, 95% CI 1.3-7.2, p = 0.01).

Fifteen of the injection drug using pairs that were treated in pregnancy were treated prior to 1997 (15/43=34.9%) and twenty one received treatment after 1997 (21/31=67.7%). Pairs with a history of IV drug use are significantly more likely to receive treatment now than prior to 1997 (34.9% vs 67.7%, OR 0.3; 95% CI 0.1-0.7, p=0.005). Twelve of the HIV positive infants were born to mothers who identified IV drug use as their HIV risk behaviour (12/18=66.7%) and five mothers of seropositive infants acknowledged IV drug use during their pregnancies (5/18=27.7%). Despite less access to treatment, women with a history of intravenous drug use in this cohort were not any more likely to transmit HIV than those who did not report a history of intravenous drug use (16.2% vs 14.3%, OR 1.2; 95% CI 0.4-3.4). When treatment access was controlled for, injection drug users were not any more likely to transmit HIV perinatally than non injection drug users (adjusted OR 0.7, p<0.5). When injection drug use was controlled for, access to treatment remains a very important predictor of perinatal HIV transmission, with those who accessed treatment in pregnancy being significantly less likely to transmit HIV perinatally than those who did not (adjusted OR 0.05, 95% CI 0.01-0.28, p<0.01). When maternal infant pairs that did not receive treatment in pregnancy were stratified based on whether or not they were aware of their HIV status at the time of pregnancy, injection drug users were not more likely to transmit HIV perinatally than non injection drug users (adjusted OR 1.6, 95% CI 0.3 –7.3, p=0.6).
Second Pregnancies

A unique feature of this database compared to most perinatal databases is its ability to identify and describe HIV positive women who have had more than one pregnancy or live birth. Fifteen women had two pregnancies between January 1994 and December 1999, and one woman had a set of twins and another pregnancy. Seven of these mothers are white, six are First Nations mothers, two are Indian and one is black. Twelve of the maternal infant pairs with second pregnancies reported intravenous drug use as their risk behaviour for viral contraction (12/17). Of the seventeen second deliveries, (fifteen singletons and one set of twins), five women received no ART during their pregnancies, eight received AZT monotherapy, three received AZT/3TC combination therapy, and one woman received D4T/DDI/NFV therapy. Five women received no treatment during labour, and all infants but one received AZT after delivery. Of note, the one infant who did not received treatment after birth has been lost to follow up. None of these seventeen infants were HIV positive.

First Nations HIV Positive Maternal Infant Pairs

Thirty-one of the ninety-nine HIV positive women who have been included in this study are First Nations women (31.3%). In British Columbia, aboriginal women comprise 28.7% (207/721) of the newly HIV positive women between 1995 and 2000. Aboriginal women are not over-represented in the cohort of pregnant HIV positive women in British Columbia (28.7% vs 31.3%, OR 1.1; 95% CI 0.7-1.8 p =0.6), compared to the proportion
which aboriginals represent in the overall HIV positive female population of British Columbia. As well, aboriginals live births are not over-represented compared to the overall rate of female HIV positive aboriginals in British Columbia (28.7% vs 32.8%, OR 0.8; 95% CI 0.5 -1.3, p=0.4).

Thirty-one aboriginal women had thirty-eight of the 116 live births evaluated in this study. Four of the thirty-one women acquired the virus through heterosexual transmission. The remaining 27 women contracted the virus through IV drug use (87.1%). In British Columbia, thirty two percent of aboriginal HIV positive women report contracting the virus due to IV drug use, indicating that pregnant positive women followed through Oak Tree Clinic are more likely to have contracted the virus through IVDU than the overall aboriginal population (32% vs 87.1%, OR 14.2; 95% CI 4.9-40.9, p<0.000). Compared to the population at Oak Tree, aboriginal women were significantly more likely to report intravenous drug use as a risk behaviour (87.1% vs 51.5%, OR 6.4; 95% CI 2.0-20.2, p<0.01). Fourteen aboriginal mothers were under the age of 25 at the time of delivery, compared to 25 women in the rest of the Oak Tree cohort. Aboriginal mothers were not any more likely to be under the age of 25 than the rest of the HIV positive pregnant population of British Columbia (58.3% vs 32.1%, OR 1.2; 95% CI 0.5-3.0, p=0.8) (Table 7).

Aboriginal infants born to HIV positive aboriginal mothers had an average gestational age of 37.3 weeks (+/- 2.6, 95% CI 36.3 – 38.3), while non-aboriginal infants born to HIV positive mothers were born at 37.3 weeks (+/- 2.7, 95% CI 36.6 – 37.9). There was
no significant difference between the age of perinatally HIV exposed aboriginal infants and perinatally HIV exposed non-aboriginal infants (t1-t2=0, 95% CI -1.1 – 1.1).

Aboriginal infants had a mean birth weight of 2.9 kg (+/- 0.6, 95% CI 2.7 – 3.1) while non-Aboriginal infants had a mean birth weight of 2.9kg (+/- 0.6, 95% CI 2.8 – 3.1).

There was not a significant difference in the birth weight between Aboriginal and non-aboriginal infants (t1-t2=0.01, 95% CI -0.3 – 0.3). Five of the thirty-six infants born to First Nations mothers were pre-term (5/38 =13.2%), and eighteen preterm infants were born to non-aboriginal mothers (18/78=23.0%). Aboriginal infants are not more likely to be born preterm than non-aboriginal infants (13.2% vs 23.0%, OR 0.5; 95% CI 0.2-1.5, p=0.2). Three of the aboriginal infants were low birth weight (3/38=7.9%), while fifteen non-aboriginal infants were low birth weight (15/78=19.2%). There is also no significant difference in the rate of low birth rate infants between non-aboriginal and aboriginal infants (7.9% vs 19.2%, OR 0.4; 95% CI 0.1-1.3, p=0.11).

ART Treatment in First Nation Maternal Infant Pairs

Eighteen aboriginal maternal infant pairs did not receive antiretroviral therapies during their pregnancies (18/38 = 47.4%), 16 did not receive antiretroviral therapies during labour (16/38 = 42.1%) and nine infants did not receive AZT after their delivery (9/38 = 23.7%). Nine maternal infant aboriginal pairs did not receive any medication during pregnancy, labour or post partum (9/38 = 23.7%). There is no difference in the rate of non-treatment between aboriginal and non-aboriginal women in pregnancy (47.3% vs 42.3%, OR 1.2; 95% CI 0.5 – 2.9, p=0.8). When injection drug use in the aboriginal population is controlled for, there is still no difference between treatment access in
pregnancy between aboriginal maternal infant pairs and non-aboriginal pairs (adjusted OR 0.7, 95% CI 0.3-1.6, p=0.4).

Prior to 1997, fourteen aboriginal women did not receive ART in their pregnancies (14/23=60.9%), while after 1997, only 4 of 15 aboriginal women in the OTC cohort (26.7%) did not receive ART in pregnancy. This demonstrates improved access to treatment during pregnancy in the First Nations HIV positive pregnant population (60.9% vs 26.7%, OR 4.3; 95% CI 1.0-17.7, p=0.04).

Overall, nine First nation maternal infant pairs received no antiretroviral treatment at all, either in pregnancy, at labour or at delivery, compared to twenty three non-aboriginal pairs. Aboriginal maternal infant pairs were not less likely to not receive ART in the three treatment stages than non-aboriginal pairs (23.7% vs 29.5%, OR 0.7; 95% CI 0.3-1.8, p = 0.5). Eight of the twelve aboriginal mothers who received treatment in pregnancy after 1997 had combination therapy (triple or quadruple antiretroviral treatment). Four of these eight women achieved undetectable viral loads at delivery, and the remaining four mothers had viral loads ranging from 95 to 23,700 copies/ml. Two additional maternal infant pairs reached undetectable viral loads at the time of delivery, and these two pairs were on AZT monotherapy.

First Nation Infants

Between January 1994 and December 1999, eighteen infants born to HIV positive mothers in British Columbia were HIV positive themselves. Nine of these infants had
First Nation mothers, while nine were born to non-aboriginal mothers. Aboriginal infants are over represented in the cohort of HIV positive infants, compared to the rate of HIV positive women in the BC population (50% vs 28.7%, OR=2.4, 95% CI 1.0 – 6.3, p=0.0498). This indicates that HIV positive First Nation women who become pregnant were more likely to have transmitted the virus to their infants than non-First nations mothers. Within the cohort followed in this study, aboriginal infants were not significantly more likely to be HIV positive than non-aboriginal infants (23.7% vs 11.5%, OR 2.4, 95% CI 0.9 – 6.6, p=0.08). Looking at trends in transmission, only one First Nation maternal-infant pair resulting in transmission since 1997, compared to eight prior to 1997 (1/15 vs 8/23, Fisher’s exact, p=0.06), indicating an improved trend for HIV transmission for aboriginal maternal infant pairs. When treatment access in pregnancy is controlled for, First Nations individuals within this cohort are not any more likely to transmit HIV perinatally than non-First Nations individuals (adjusted OR 2.5, 95% CI 0.8-7.5, p=0.1)
Figure 1. BRITISH COLUMBIAN HIV POSITIVE MATERNAL INFANT PAIRS*
January 1994 – December 1999

145 pregnancies to HIV positive women

118 pregnancies carried beyond 20 weeks

27 abortions

116 Live Births

2 Stillbirths

19 terminations

8 spontaneous abortions

*See Appendix III for Obstetrical and Pediatric Clinical Definitions
Table 1. DEMOGRAPHIC PROFILE OF HIV POSITIVE PREGNANT WOMEN

Demographics of HIV Positive Pregnant Women in British Columbia, 1994-1999 (n=99)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age in years (95% CI)</td>
<td>27.6 (26.6 – 28.6)</td>
</tr>
<tr>
<td>Range</td>
<td>18-43</td>
</tr>
<tr>
<td>Less than 25 years old (%)</td>
<td>39 (39.4)</td>
</tr>
<tr>
<td>Cultural Background (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>41 (41.4)</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>31 (31.3)</td>
</tr>
<tr>
<td>Black</td>
<td>18 (18.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (7.1)</td>
</tr>
<tr>
<td>South American</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Risk Behaviour for HIV contraction (%)</td>
<td></td>
</tr>
<tr>
<td>Intravenous Drug Use</td>
<td>62 (62.6)</td>
</tr>
<tr>
<td>Heterosexual Intercourse</td>
<td>35 (35.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2.0)</td>
</tr>
</tbody>
</table>
Table 2. ANTIRETROVIRAL USE IN HIV POSITIVE MATERNAL INFANT PAIRS DURING PREGNANCY PERIOD

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Total</th>
<th>1994-6</th>
<th>1997-9</th>
<th>UND VL (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT monotherapy</td>
<td>29</td>
<td>19</td>
<td>10</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Dual Therapy</td>
<td>12</td>
<td>4</td>
<td>8</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Triple Therapy</td>
<td>22</td>
<td>n/a</td>
<td>22</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>Quadruple Therapy</td>
<td>2</td>
<td>n/a</td>
<td>2</td>
<td>1 (50.0)</td>
</tr>
</tbody>
</table>

Overall Use of ART (%) 65 (56.0) 23 (38.3) 42 (75)

Total Live Births 116 60 56 20 (17.2)

*undetectable viral load at delivery
Table 3. COMBINATION TREATMENT REGIMENS USED IN PREGNANCY

<table>
<thead>
<tr>
<th>Type of Combination Therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dual Therapy (n=12)</strong></td>
<td></td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>9</td>
</tr>
<tr>
<td>AZT/ddC</td>
<td>2</td>
</tr>
<tr>
<td>D4T/3TC</td>
<td>1</td>
</tr>
<tr>
<td><strong>Triple Therapy (n=22)</strong></td>
<td></td>
</tr>
<tr>
<td>AZT/3TC/Indinavir</td>
<td>9</td>
</tr>
<tr>
<td>AZT/3TC/Nelfinavir</td>
<td>4</td>
</tr>
<tr>
<td>AZT/ddI/Nevirapine</td>
<td>2</td>
</tr>
<tr>
<td>D4T/ddI/Nelfinavir</td>
<td>2</td>
</tr>
<tr>
<td>D4T/3TC/Nelfinavir</td>
<td>1</td>
</tr>
<tr>
<td>D4T/3TC/Nevirapine</td>
<td>1</td>
</tr>
<tr>
<td>D4T/ddI/Nevirapine</td>
<td>1</td>
</tr>
<tr>
<td>AZT/3TC/Nevirapine</td>
<td>1</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>1</td>
</tr>
<tr>
<td><strong>Quadruple Therapy (n=2)</strong></td>
<td></td>
</tr>
<tr>
<td>D4T/ddI/3TC/Saquinavir</td>
<td>1</td>
</tr>
<tr>
<td>AZT/ddI/Nevirapine/Nelfinavir</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 2. ABSENCE OF ANTIRETROVIRAL THERAPY USE IN HIV POSITIVE MATERNAL INFANT PAIRS

No Treatment in Pregnancy Stage, n=51

No Treatment in Labour, n=45

No Treatment for infant, n=34
Table 4. CHARACTERISTICS OF HIV POSITIVE INFANTS

<table>
<thead>
<tr>
<th>HIV Positive Infants (n=18)</th>
<th>N</th>
<th>% or 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART Treatment received during Pregnancy</td>
<td>16/18</td>
<td>88.9</td>
</tr>
<tr>
<td>No ART Treatment received in any of the three stages</td>
<td>13/18</td>
<td>72.2</td>
</tr>
<tr>
<td>AZT Monotherapy</td>
<td>2/18</td>
<td>11.1</td>
</tr>
<tr>
<td>Maternal Risk Behaviour for HIV Contraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous Drug Use</td>
<td>12</td>
<td>66.7</td>
</tr>
<tr>
<td>Heterosexual Transmission</td>
<td>6</td>
<td>33.3</td>
</tr>
<tr>
<td>Mean Gestational Age (weeks)</td>
<td>37.8</td>
<td>35.9-39.8</td>
</tr>
<tr>
<td>Preterm Infants</td>
<td>3</td>
<td>16.7</td>
</tr>
<tr>
<td>Mean Birth Weight (kg)</td>
<td>3.26</td>
<td>2.7 – 3.8</td>
</tr>
<tr>
<td>Low Birth Weight Infants</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>Mode of Delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Birth</td>
<td>14</td>
<td>77.8</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>4</td>
<td>22.2</td>
</tr>
<tr>
<td>Cultural Background</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>5</td>
<td>27.8</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>9</td>
<td>50.0</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>16.7</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>5.6</td>
</tr>
</tbody>
</table>
Figure 3. OUTCOMES OF MATERNAL INFANT PAIRS NOT TREATED IN PREGNANCY

51 HIV Positive Maternal Infant Pairs NOT treated during Pregnancy (31.4)*

41 received no treatment at delivery (31.7)*

10 treated in at delivery (30.0)*

32 receive no treatment for infant

9 receive treatment for infant

9 infants receive treatment

1 infant receives no treatment

13 infants HIV positive (40.6)*

0 infants HIV positive (0)*

3 infants HIV positive (33.3)*

0 infants HIV positive (0)*

*% of infants HIV positive
Table 5. DESCRIPTION OF MATERNAL INFANT PAIRS WITH KNOWN HIV STATUS NOT TREATED IN PREGNANCY COMPARED TO MATERNAL INFANT PAIRS WHO RECEIVED TREATMENT IN PREGNANCY

<table>
<thead>
<tr>
<th></th>
<th>No ART in Pregnancy (%)</th>
<th>ART in Pregnancy (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994-1996</td>
<td>17 (62.9)</td>
<td>23 (35.4)</td>
<td>3.10</td>
<td>1.22-7.88</td>
<td>0.015*</td>
</tr>
<tr>
<td>Aboriginal cultural background</td>
<td>10 (37.0)</td>
<td>20 (30.8)</td>
<td>1.32</td>
<td>0.52-3.39</td>
<td>0.56</td>
</tr>
<tr>
<td>Intravenous Drug Use as Risk Behaviour</td>
<td>22 (81.5)</td>
<td>36 (55.4)</td>
<td>3.54</td>
<td>1.20-10.5</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

*p < 0.05
<table>
<thead>
<tr>
<th>Factor</th>
<th>Aboriginal (%)</th>
<th>Non- Aboriginal (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART Use in Pregnancy (n)</td>
<td>18 (47.4)</td>
<td>33 (42.3)</td>
<td>1.23</td>
<td>0.56-2.68</td>
<td>0.75</td>
</tr>
<tr>
<td>No ART Use in Labour (n)</td>
<td>16 (42.1)</td>
<td>29 (37.2)</td>
<td>1.23</td>
<td>0.56-2.7</td>
<td>0.61</td>
</tr>
<tr>
<td>No ART Use in Neonate (n)</td>
<td>9 (23.7)</td>
<td>25 (32.0)</td>
<td>0.66</td>
<td>0.27-1.6</td>
<td>0.35</td>
</tr>
<tr>
<td>No Treatment in Any Stage (n)</td>
<td>9 (23.7)</td>
<td>23 (29.5)</td>
<td>0.74</td>
<td>0.30-1.8</td>
<td>0.51</td>
</tr>
<tr>
<td>IV Drug Use as Risk Behaviour</td>
<td>34 (89.5)</td>
<td>40 (51.3)</td>
<td>6.36</td>
<td>2.01-20.2</td>
<td>0.0007*</td>
</tr>
<tr>
<td>Rate of Preterm Infants (n)</td>
<td>5 (13.2)</td>
<td>18 (23.0)</td>
<td>0.505</td>
<td>0.17-1.48</td>
<td>0.21</td>
</tr>
<tr>
<td>Rate of Low Birth Weight Infants (n)</td>
<td>3 (7.9)</td>
<td>15 (19.2)</td>
<td>0.36</td>
<td>0.097-1.3</td>
<td>0.114</td>
</tr>
<tr>
<td>Mother with Age &lt; 25 (n)</td>
<td>14 (36.8)</td>
<td>25 (32.1)</td>
<td>1.24</td>
<td>0.507-3.0</td>
<td>0.76</td>
</tr>
<tr>
<td>Transmission Rate (n)</td>
<td>9 (23.7)</td>
<td>9 (11.5)</td>
<td>2.4</td>
<td>0.9-6.6</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*p<0.05
### Table 7. SUMMARY OF TRENDS IN PATIENT PROFILES AND CARE BETWEEN 1994-6 AND 1997-9

<table>
<thead>
<tr>
<th>Factor</th>
<th>1997 - 1999</th>
<th>1994 -1996</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Drug Use as Risk Behaviour for Viral Contraction in mother</td>
<td>21/42</td>
<td>41/57</td>
<td>3.60</td>
<td>1.67-7.75*</td>
</tr>
<tr>
<td>HIV Maternal Infant Pairs Not Identified Until After Delivery</td>
<td>4/54</td>
<td>20/59</td>
<td>6.4</td>
<td>2.03-20.3*</td>
</tr>
<tr>
<td>No Use of ART in Pregnancy, Labour or for Infant</td>
<td>6/56</td>
<td>26/60</td>
<td>6.37</td>
<td>2.37-17.13*</td>
</tr>
<tr>
<td>Intravenous Drug Users Accessing Treatment during Pregnancy</td>
<td>21/31</td>
<td>15/43</td>
<td>0.26</td>
<td>0.096-0.68*</td>
</tr>
<tr>
<td>No Use of ART in Pregnancy in Aboriginal Maternal Infant Pairs</td>
<td>4/15</td>
<td>14/23</td>
<td>4.28</td>
<td>1.036-17.66*</td>
</tr>
<tr>
<td>Cesarean Section Rate</td>
<td>27/56</td>
<td>8/60</td>
<td>0.165</td>
<td>0.066-0.411*</td>
</tr>
<tr>
<td>HIV Transmission Rate</td>
<td>3/56</td>
<td>15/60</td>
<td>5.89</td>
<td>1.6-21.65*</td>
</tr>
</tbody>
</table>

*p<0.05
**Figure 4. TIMING OF IDENTIFICATION OF SEROSTATUS OF HIV POSITIVE MATERNAL INFANT PAIRS**


- 24 pairs with HIV status NOT identified prior to delivery
- 92 with HIV status KNOWN to mother during pregnancy

- 24 received NO treatment during pregnancy
- 27 received NO treatment during pregnancy
- 65 received treatment in pregnancy

- 12 infants HIV positive (12/24)
- 4 infants HIV positive (4/27)
- 2 infants HIV positive (2/65)
Table 8. RISK FACTORS FOR HIV PERINATAL TRANSMISSION

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Transmission Rate</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART Use in Pregnancy</td>
<td>31.4 (16/51)</td>
<td>14.4</td>
<td>3.13-66.3*</td>
</tr>
<tr>
<td>No ART Use in Any Period</td>
<td>40.6 (13/32)</td>
<td>10.8</td>
<td>3.43-34.03*</td>
</tr>
<tr>
<td>Undetectable Maternal Viral Load at Term</td>
<td>0.0 (0/20)</td>
<td>0.11</td>
<td>0.006-1.88*</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>23.7 (9/38)</td>
<td>2.38</td>
<td>0.9-6.60</td>
</tr>
<tr>
<td>Intravenous Drug Use as Risk Behaviour</td>
<td>16.2 (12/74)</td>
<td>1.16</td>
<td>0.40-3.36</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>11.4 (4/35)</td>
<td>0.62</td>
<td>0.19-2.03</td>
</tr>
<tr>
<td>Preterm</td>
<td>13.0 (3/23)</td>
<td>0.78</td>
<td>0.21-2.96</td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>5.9 (1/17)</td>
<td>0.30</td>
<td>0.04-2.43</td>
</tr>
<tr>
<td>Non-identified HIV positive maternal infant pair</td>
<td>50.0 (12/24)</td>
<td>14.3</td>
<td>4.5-45.32*</td>
</tr>
</tbody>
</table>

*p<0.05
DISCUSSION

This thesis represents one of the first detailed analyses of perinatal HIV transmission in a province in Canada. Although data has been available describing the experience with perinatal transmission world wide, most Canadian data to date has been available primarily in abstract form (44,98,99) or as research letters (100). Relatively little has been published outlining the Canadian experience with HIV positive maternal infant pairs. With a continued rise in the number of HIV positive women in Canada, Canadian clinicians and researchers can expect to see an increase in the number of HIV positive women becoming pregnant. Thus, it is essential for Canadian researchers to continue to monitor perinatal HIV transmission, and factors associated with transmission, as perinatal HIV contraction appears to be virtually preventable given the resources available in the developed world and in Canada in particular. In addition, as this analysis was conducted on data from one province, its findings may speak only to the experience with perinatal transmission in British Columbia. Further evaluation is needed in other provinces, in order to provide a national picture of the nature and risk factors for perinatal HIV transmission across the country.

Impact of Antiretroviral Treatment on Perinatal HIV Transmission

Use of combination antiretroviral therapy in pregnant HIV positive women has increased significantly since 1994 in British Columbia. Since January 1997, 75% of pregnant HIV positive women in British Columbia received some kind of antiretroviral therapy during
their pregnancies, compared to less than 40% of maternal infant HIV positive pairs prior to 1997 (38.3% vs 75%, OR 0.2; 95% CI 0.09-0.5, p<0.01). This increase in use has been associated with a significant reduction in perinatal HIV transmission in British Columbia, from 25% to 5.4% over the same time periods (OR 5.9; 95% CI 1.6-21.6).

Antiretroviral use of any kind in the pregnancy period was significantly linked with HIV transmission, with only 2 infants of the 65 who received ART in pregnancy contracting the virus. Sixteen of the 51 maternal infant pairs (31.4%) not treated in the pregnancy period contracted HIV perinatally. Of note is the fact that the two maternal infant pairs where transmission occurred used only AZT monotherapy, and no transmissions occurred in maternal infant pairs who had received combination treatment during the pregnancy period. This study confirms the experience in other jurisdictions that combination treatment during the pregnancy is an effective intervention in decreasing the transmission rate of HIV. The importance of treatment in pregnancy in preventing perinatal transmission is underscored when injection drug use is controlled for in the cohort.

When we look at treatment access in pregnancy and perinatal HIV transmission with injection drug use controlled for, the impact of treatment on diminishing perinatal transmission remains significant (adjusted OR 0.05, 95% CI 0.1-0.28, p<0.001). Continued access to combination therapy is crucial to preventing perinatal HIV transmission in the maternal infant dyad.

In this cohort, in the 41 maternal infant pairs who received no treatment at delivery, 32 received no treatment in the infant period and 9 received treatment at this stage. The transmission rate in this subgroup was significantly different (40.6% vs 0%, p=0.032)
(Figure 2). In our cohort, infant treatment was significantly associated with a reduction in viral transmission in the group who had received no prior antiretroviral care. As there continue to be attempts worldwide to streamline the protocol for antiretroviral treatment for the mother-infant dyad (101), data from this study would indicate that the infant arm of the protocol is critical, particularly in pairs that have not received appropriate prenatal and intrapartum care. To eliminate this part of the maternal-infant treatment triad could have unforeseen but significant consequences on the rate of perinatal transmission.

Combination therapies are still used with some hesitation during the prenatal period, given medicine’s previous experience with medications such as thalidomide and DES (102). Unknown teratogenic effects can emerge much later in life, and the risks and benefits of these medications must be carefully weighed. In the setting of pediatric HIV, the risks of transmission are considerable. Even with the use of combination treatments for infants and children who have contracted the virus perinatally, recent reports have found that these children have a median survival time of 3.3 years (25). At this point, preventing what can be an often fatal illness seems to be well worth the potential and as yet undocumented risk of antenatal combination treatment exposure.

Currently a wide variety of antiretrovirals are used in pregnancy, with no apparent consistent adverse effects on the pregnancy or developing fetus (103,103-108). Certain antiretrovirals tend to be avoided such as delavirdine and efavirenz, based on teratogenic effects in animal studies (62). However, no other antiretrovirals are actively avoided, and
in this study, no specific treatment regimen was linked consistently with adverse effects in the pregnancy or in the infant.

Infants born to HIV positive mothers were significantly more likely to be born with a low birth weight and born preterm than infants born to non-infected mothers in the province. Substance abuse is a well-established predictor of low birth weight and prematurity (109) and thus it is not surprising that this cohort would have an increased rate of complications associated with substance abuse, given the high rate of intravenous drug use both as risk behaviour and actually reported during pregnancy. Within the cohort of infants born to HIV positive mothers, there was no difference in the gestational age and birth weight in infants exposed to ART in utero compared to those not exposed to ART. As well, the rate of low birth weight and prematurity between the ART exposed and non exposed individuals was not significant when intravenous drug use was controlled for in the analysis. Thus, in this cohort, ART use was not associated with either prematurity or with low birth weight infants. This finding is in contrast to some previous reports, which linked ART use in pregnancy with both low birth weight (110) and with prematurity (79). Continued evaluation of the impact of these treatments in controlled settings is needed, to ensure confounders for low birth weight and prematurity, such as substance abuse, are equally distributed between the groups. This will contribute to the discussion, and help to ascertain if in fact ART in pregnancy plays any role in causing low birth weight or prematurity.
The relatively small sample size of this cohort however, limits the generalizability of findings regarding adverse effects of combination treatments in pregnancy. It is thus imperative that ongoing, comprehensive and coordinated evaluation of perinatal combination drug use continue, in order to establish if rare but serious side effects are occurring with combination treatment use. An initiative to develop a national monitoring program is underway, and funding and policy agencies should actively support such a project, in order to ensure rapid identification and dissemination of information of interest to care providers and HIV positive individuals receiving combination treatment in the perinatal period (111).

The improved access to ART treatment in the pregnancy stage between the 1994-6 cohort and the 1997-9 cohort is likely due to a number of international, provincial and local factors. Since the International HIV Conference in Vancouver in 1996, and the subsequent dissemination of findings from that meeting, clinicians who treat HIV positive pregnant women have become increasingly comfortable, though not cavalier, in their use of combination treatment in pregnancy. This is a result of increasing collective experience with combination treatment in pregnancy, as well as a widespread acceptance of the principle that a HIV positive woman’s care should not be compromised simply because she is pregnant. In British Columbia, HIV drugs along with medical care, are fully covered by the provincial government, and thus payment for medications is not a barrier for HIV positive women. As well, there has been improved diagnosis of HIV in the prenatal period with the comprehensive BC antenatal screening program. Finally, the coordinated and centralized treatment program for HIV positive pregnant women at Oak...
Tree ensures consistent quality care is available for these women. Women can receive a wide range of services, from specialist physicians to pharmacists to outreach workers, and this level of support undoubtedly has contributed to the improved use of combination treatments. Continued support and improvement of these innovative programs is essential to ensure the continued reduction of perinatal HIV transmission that British Columbia has already experienced.

Further information is needed about the treatment decision process for HIV positive pregnant women in British Columbia. It was not possible in this study to identify the proportion of women who were on treatment regimens prior to pregnancy, and those who initiated treatment after diagnosis in pregnancy. There may also be a cohort of women who switched treatment regimens once they became pregnant, or who stopped treatment in the first trimester and then restarted treatment after 14 weeks gestational age. As well, with shifting treatment recommendations, there may be an increasing number of women who receive combination therapy during pregnancy to prevent perinatal transmission, but who then stop treatment after delivery as they do not meet current criteria for treatment. This is particularly likely given new information that demonstrates that in a cohort of pregnant women with undetectable viral loads, those who were on treatment had lower transmission rates than those who were not on treatment (36). Combination treatment offers additional protection from viral transmission even in women with undetectable viral loads. Finally, there is a need to follow HIV positive women to determine their treatment decisions after their pregnancies, as some may continue to need ART, but may not continue to access treatment due to a variety of circumstances.
Viral Loads and Perinatal Transmission

Viral load levels are consistently linked with transmission of HIV from mother to infant and have been identified as the single most important predictor of perinatal HIV transmission (26,112). In this study, only women who received ART treatment in pregnancy had undetectable viral loads, and 85% of these women received three or four drug combination treatments. Triple or quadruple drug treatment was significantly associated with undetectable viral loads at delivery (17/24 vs 3/41, OR 30.76; 95% CI 7.1-133.59, p<0.000). In this cohort, in order to achieve undetectable viral loads at delivery, women had to receive treatment in the antepartum period. In this cohort, no transmissions occurred in maternal infant pairs who had undetectable viral loads at delivery.

Mode of Delivery and Perinatal Transmission

There has been a significant increase in the caesarean section rate in British Columbia in HIV positive pregnant women in over the past six years, from thirteen percent to forty eight percent. This rise is not unexpected, given our fuller understanding of the factors leading to HIV transmission, and the evolving recommendations for caesarean sections when viral suppression is incomplete. In this cohort, viral transmission was not different based on mode of delivery when controlled for treatment, but again, this calculation was limited by the size of the sample. It still remains unclear in all available global literature
to date whether caesarean sections proffer any additional benefit in the setting of complete viral suppression or combination therapy use in pregnancy. Continued evaluation is needed to determine if caesarean sections offer an additional benefit for preventing transmission beyond effective combination antiretroviral treatments.

Perinatal HIV Transmission in the Aboriginal Population

The aboriginal population continues to face significant challenges regarding HIV and AIDS. Although aboriginals represent only 3% of the British Columbia population, 30% of HIV positive women and pregnant HIV positive women in this province are of First Nations heritage, and 50% of HIV positive infants are aboriginal. Aboriginal women face greater struggles with intravenous drug use than their non-aboriginal counterparts, and significantly more report contracting the virus through this method than the non-aboriginals in the cohort. As well, although treatment access on the surface appears to be similar between aboriginal and non-aboriginal women, in this cohort there is an increased transmission rate in our aboriginal population than what we expect on a provincial level (50% vs 28.7%, OR 2.4; 95% CI 1.0-6.3). Aboriginal women also appear to have no difference in treatment access compared to non-aboriginal women when injection drug use is controlled for in the cohort. Given that aboriginal women are accessing treatment at the same rate as non-aboriginal women, it is possible that this unexpected difference in transmission is due to other factors, including issues with medication compliance and adherence. As well, there is the potential risk for confounders, including higher rates of sexually transmitted infections, chorioamnionitis which were not evaluated in this study.
which could contribute to this finding. This data would indicate that continued and
expanded culturally appropriate support for aboriginal women who are identified as HIV
positive and pregnant are needed to enhance adherence to what are known as complicated
but effective treatment regimens. As well, further evaluation is needed to establish if First
Nations women face undisclosed, additional risk factors that are leading to an increased
perinatal transmission.

The experience with the aboriginal population in Canada with HIV and AIDS has not yet
been seen in any other country. In the United States, the American Indian population
comprises less than one percent of their total population, and represent a similar percent
of their HIV cases (113). In Australia, the proportion of aboriginals with HIV and AIDS
is also not more than would be expected, given their composition of the population (114).
Further information is needed to understand the reasons for the high rate of HIV infection
within the Canadian aboriginal population, particularly given the unique nature of this
phenomenon compared to aboriginal groups world wide.

The high rate of seropositivity in the aboriginal community also confirms existing
concerns about the disproportionate burden of HIV which the Canadian aboriginal
population bears. This study, along with a variety of other published research and
abstracts indicates a need for culturally appropriate and sensitive prevention and
treatment programs designed by and for aboriginals. Aboriginal communities need to
lead program development and assist health planners and policy makers to ensure that
programs address both the cultural and socioeconomic realities facing their populations.
Further data is also needed on the place of residence for the pregnant HIV positive aboriginal women in this cohort. Although the general perception may be that most of the HIV positive pregnant aboriginal women reside in the downtown eastside of Vancouver, many women may choose to move back to reserve during their pregnancies, or if they feel their health is compromised. Conversely, aboriginal women may be diagnosed with HIV on reserve and then feel ostracized in their communities and thus choose to leave their reserve and come to Vancouver to disappear. Accurately ascertaining the place of residence both at the time of diagnosis, pregnancy and delivery will help planners to direct prevention, treatment and follow up programs to the appropriate jurisdictions, in order to ensure women have timely access to programs.

Intravenous Drug Users and Combination Treatment

The treatment program for HIV positive pregnant women in British Columbia appears to have had significant success in accessing and offering treatment to intravenous drug using women, a cohort that is notoriously difficult to access and support. Since 1997, there has been a significant increase in the use of antiretroviral therapies in pregnancy in maternal infant pairs with a history of IV drug use (34.9% vs 67.7% OR 0.26; 95% CI 0.096-0.68). A comprehensive, HIV dedicated clinical team, coupled with free drug and medical treatment and outreach workers has likely been the cornerstone to this success rate. However, although there has been a significant increase in ART use in pregnancy for women with a history of IV drug use, this cohort shows that overall only 49% of
women with a history of IV drug use receive combination treatment in pregnancy.

Women with a history of intravenous drug use are significantly less likely to receive ART in pregnancy than women without a history of intravenous drug use (48.6% vs 69.0%, p=0.03). This difference in access remained when aboriginal status was controlled for in the cohort (adjusted OR 3.08, 95% CI 1.3-7.2; p=0.008). Since 1997, more than thirty percent of women with substance abuse histories did not receive ART during their pregnancies. As well, when we examine the women who knew of their HIV status and did not access treatment during their pregnancies, 82% reported a history of intravenous drug use, and 74% reported active use during their pregnancy. Clearly, intravenous drug use and its accompanying issues are impeding access to treatment during pregnancy for some HIV positive pregnant women. We also have no measure of adherence to treatment, and the cohort of drug users who receive treatment may have varying rates of actually taking their medications. As a result, twelve infants born to HIV positive women with histories of drug use were HIV positive (12/74=16.2%). Additional methods of support need to be explored, including methadone programs, safe housing programs and the use of streamlined treatment programs in order to facilitate improved treatment access for intravenous drug using women.

Of note, however, is that in this cohort, despite not receiving treatment in pregnancy, injection drug users were no more likely to transmit HIV perinatally in this cohort. This indicates that injection drug users are able to receive the less optimal care of treatment in labour and for the infant. These elements of the treatment protocol have been demonstrated to be effective in reducing perinatal transmission, and likely contributed to
the lack of difference in perinatal transmission between injection drug using cohort and the non-injection using cohort. As well, the small sample size of this study may also limit the ability to demonstrate a significant difference. When access to treatment was controlled for, injection drug users were also not more likely to perinatally transmit HIV, indicating that in this cohort, IV drug users did not have additional unknown factors beyond treatment access that contributed to increasing or decreasing transmission.

Data comparing prevalence of women with intravenous drug use as their risk behaviour for viral contraction who became pregnant indicates that there has been a reduction in the absolute number of mothers in this category between 1994-6 and 1997-9. However, when we compare the pregnancies that occurred to mothers who contracted the virus through intravenous drug use, there has been no significant reduction since 1997. This indicates that although there are fewer individuals new mothers presenting to the cohort, there are the same relative number of pregnancies occurring within this subgroup of the population.

Fertility in HIV Positive Women in British Columbia

Decisions regarding pregnancy in HIV positive women in the current context of effective treatment for both HIV and for preventing perinatal transmission is an area requiring significant exploration. The limited data available from this cohort indicates that women who present to Oak Tree Clinic pregnant are not any more likely to terminate pregnancies than women in the overall Canadian population. However, only women who presented to
the clinical staff were included in this analysis, and many women may terminate pregnancies without informing their usual care providers. In addition, women who may be unaware or unwilling to consider that they are HIV positive may also be having abortions. Few current studies describe the rate of HIV seropositivity in women having abortions in Canada and this is an area requiring further evaluation in order to more accurately assess the reproductive choices of HIV positive women (115).

Fifteen percent of women in this cohort had more than one live birth, and seventy percent of second live births occur in maternal infant pairs with a history of intravenous drug use. There is little data available as to whether these pregnancies were planned, represent a lack of contraception or contraceptive failures. It is important that we respect the reproductive choices of positive women. However, it is also important for clinicians to ensure that HIV positive women receive comprehensive counselling regarding contraception and fertility. In particular, if sexually active women are relying on condoms primarily for pregnancy prevention, they must be made aware of the failure rate associated with condoms for pregnancy prevention (116), and perhaps offered additional protection with either female controlled barrier methods or hormonal methods. Of course, it must be stressed that these methods do not offer protection from either further STI contraction or from increased doses of HIV from positive partners. Nor do they offer protection from viral contraction to the woman's partner. As well, further research is needed to understand if widely used hormonal methods of contraception, such as long acting depo-progesterones or oral contraceptives have altered effectiveness due to concomitant use of antiretrovirals, as both of these families of medication require
clearance by the liver. This will be critical research given the ever increasing numbers of HIV positive women, their increasing life span, and the duration of treatment with antiretroviral therapies.

Most available data on fertility in HIV positive women has been conducted in Africa, and is focused on the ability of sexually active HIV positive women to become pregnant (117,118). The African data has limited generalizability for our context, given the absence of treatment availability, lack of awareness of HIV serostatus for many of the women evaluated in these studies, and the different cultural realities facing African women. The developed world context is and will continue to become quite different, and few current Canadian studies have evaluated the fertility and factors influencing pregnancy decisions in HIV positive women. It will be important to ascertain if and how the new successes with combination treatment have altered the decisions around pregnancy termination or continuation in HIV positive women. Research is needed to further examine the reproductive choices, and factors entering into those decisions in HIV positive women.

Data Comprehensiveness

Although this report uses data based from a clinic in Vancouver, it is essential to underscore the high rate of coverage for HIV positive pregnant women that this clinic enjoys. The most recently available and liberally interpreted seroprevalence data for British Columbia estimates that approximately 25 HIV positive women give birth
annually in the province (7). Oak Tree clinic enrolls 25-30 pregnant clients annually, indicating that this clinic has a near census of HIV positive pregnancies. Thus descriptive data from this cohort is not capturing merely patients from one clinic, but is representative of the provincial experience with HIV in pregnant women.

However, this seroprevalence data is over five years old, and with recent shifts and changes in the virus, particularly in the intravenous drug using population of Vancouver, it is possible that the most liberal estimates employed in this analysis underestimate the actual HIV positive live birth rates. Continuing and ongoing provincial wide seroprevalence studies should be conducted, in order to ensure that all pregnant positive women are being identified, and offered the most current and effective medications for themselves and their developing fetus.

British Columbia HIV Prenatal Screening Program

Prenatal screening programs appear to have significantly impacted on the identification of HIV positive women. Since 1997, there has been a significant reduction in the number of women who were not identified as HIV positive until after their birth. This indicates that the British Columbia program has been successful in making women aware of their HIV status in pregnancy. However, there still remain a small percentage of women who are not identified as HIV positive until after delivery, and further understanding of the factors that lead up to their non-identification is crucial. A variety of factors, including physician and patient variables could be at play, and exploration of these issues will
allow policy planners and physician groups to make appropriate and effective changes in
the current screening program. It will also be important to review prenatal screening
programs in other provinces and jurisdictions, to see if lessons learned in those settings
may be relevant to challenges faced by British Columbia.

Non-Treated HIV Positive Pregnant Women

This study demonstrates that a proportion of women (23.3%), despite being aware of
their HIV status either are unable, are refused, not offered or choose to not access
treatment for themselves during their pregnancies. Although these women are described
from a cultural and risk behaviour profile, little data is available about the factors that
play into their decision not to access care. Perhaps, despite the presence of outreach
workers and a wide reaching provincial network, these women are unable to attend for
prenatal care due to financial reasons. Perhaps they are struggling with addiction issues,
and linking with prenatal care is not feasible. Perhaps they fear the stigmatization of
being identified as HIV positive in the hospital setting. Perhaps they feel they will be
coerced into taking treatments that they perceive as harmful to themselves or their
infants. Perhaps they do not fully understand their diagnosis and its implications.
Perhaps they fear contact with child protection authorities. Alternately, physician issues,
perceptions and attitudes towards women who are intravenous drug users may be
contribute to the lack of treatment in this cohort. Physicians may feel patients are
unable or unwilling to follow through with complicated treatment regimens, and may
make decisions around treatment for the patients. Further investigation into this group is
clearly needed, in order to clarify the reasons for their lack of treatment, and to provide appropriate interventions and support to ensure they receive the best possible care that respects their autonomy during their pregnancy and afterwards.

Limitations

Despite revealing some important findings, this study possesses some inherent limitations in its methods that could potentially influence the findings and implications of these results. This study relied on both prospective and retrospective data for analysis. The retrospective data was gathered by chart review, which means that errors could be made in data extraction and recording. Data was inputted into the spreadsheet by a team of research nurses, and there is risk for error within that process. As well, information desired for analysis may be missing from the patient records. In this particular study, in an effort to minimize error and enhance data quality, data was verified by both the supervising paediatrician and the researcher, and a random chart review of 10 charts was conducted that ensured data accuracy. When the researcher was unable to verify the data (such as date of starting antiretrovirals in pregnancy or adherence to treatment), this variable was excluded from the analysis. However, despite these steps, there remains the small chance of error within the data, which would then limit the conclusions that could be made from the results.

As with many clinical studies, much of the data for this thesis is self reported. In particular, information such as cultural background, use of intravenous drugs and recall
of treatment and management during pregnancy for non-identified women was obtained from patients. Because many of these factors rely on memory, information such as type of treatment and delivery histories can be difficult for patients to recall clearly. Self-reported data can also be inaccurate because in an effort to appease physicians and other care providers, patients will provide the “desirable” rather than the accurate answers. With this study, many of the questions involved sensitive areas, such as drug use in pregnancy, and so women had additional reasons to provide the desirable answers.

Information on continued drug use in pregnancy could lead to referrals to child protection authorities and increased pregnancy surveillance. Thus, women may either minimize or deny substance use, particularly use during pregnancy (119,120). In order to verify events such as substance use in pregnancy, women would be required to submit urine and hair samples. To enter this arena would be intrusive and would shift the physician patient relationship from one of care for the woman to one of a punitive nature. This would then jeopardize the further care the patient would receive, potentially drive them “underground” and limit the clinicians ability to ally and support the client through what is often a difficult process. At present, researchers must rely on patient self report or risk damaging the therapeutic process in order to gain accurate research data. Thus, in this study, as is the case with many studies examining drug use in pregnancy, likely underestimates the actual amount of intravenous drug use in pregnant HIV positive women.

Because the researcher was unable to verify certain pieces of data, such as adherence to medication regimens, type of and rationale for treatment initiation, treatment interruption
schedules and follow up use of antiretrovirals, these very important variables were excluded from the analysis. Certain of these factors, such as adherence, could potentially confound the results. However, a conservative approach has been taken to addressing all confounders in the analysis. As a result, the effectiveness of combination treatment in decreasing transmission may be underestimated, and negative outcomes may be inappropriately attributed to combination treatment use. This study has indicated that additional data needs to be gathered systematically for the HIV positive pregnant women in British Columbia, in order to continue to examine the positive and negative outcomes of combination ART use.

Data that was not gathered retrospectively from chart review was gathered prospectively. However, treatment for patients was not randomly allocated, but was determined based on a variety factors, including co-morbidities, previous treatments, tolerability of regimens and treatment recommendations at the time of prescribing. Although there is continued debate about the value of observational studies compared to randomized trials in the medical literature, there are an increasing number of authors who challenge the assertion that observational data is of little use in determining treatment effectiveness. Recent reviews by Ioannidis (121) and Benson (122) and other authors (123) have demonstrated that observational studies may overestimate the effect size of an intervention, but that the findings from observational studies usually correlate highly with the findings from the randomized findings. Thus, data derived from observational databases can be used, albeit with caution, to inform and direct clinical care. In the Canadian setting, given the relatively small number of HIV positive pregnant women
available for evaluation, establishing comprehensive observational data bases will be critical to providing clinicians with timely and accurate information about the impacts and consequences of antiretroviral use in pregnancy. In the case of Oak Tree Clinic, care must be taken to ensure that data is gathered and recorded in a uniform and consistent fashion, and a method for continued quality assurance monitoring is introduced, in order to preserve data validity and accuracy.

The provincial and national databases used for comparison purposes in this study also possess their own inherent limitations. Perinatal surveillance on a comprehensive national level has only recently begun with the National Perinatal Surveillance Survey, and this program relies on provincial reporting systems. These systems rarely gather ethnicity data, and report live births as events, rather than pregnancies as events. There is a need to establish fertility and birth rates for different cultural and ethnic groups, in order to ensure that programs are appropriately geared for these cultural communities. There is also a need to broaden the scope of reporting, from a few provinces, to a national program, in order to ensure uniformity in data collection, reporting and interpretation. There is also a need to include data regarding the pregnancy as well as the live birth, in order to facilitate evaluations at the level of the mother, and not only at the level of the newborn.

This study was powered to evaluate the rate of use of combination antiretrovirals in HIV positive pregnancies over a period of six years. However, there were numerous other evaluations that were conducted as part of this thesis, which potentially face type II
errors, due to the small sample size and relatively small difference between the groups being compared. It is important to view these comparisons with caution, when significant differences have not been established. However, it is also important these preliminary analyses be conducted and made public, despite their limitations. On a global scale, relatively few women receive antiretroviral therapy during pregnancies – those who do tend to reside in the developed world, and the overall number of positive women in these settings is small. Clinicians in the Western world are currently prescribing these regimens with relatively little information on outcome and prognosis, and every piece of information will assist in making treatment decisions and in evaluating trends and consequences of using these medications in the antepartum, intrapartum and postpartum period.
CONCLUSIONS AND RECOMMENDATIONS

Combination antiretroviral use in HIV positive pregnancies has increased significantly since 1994 in British Columbia. With use of these medications, there has been a significant reduction in the perinatal transmission of HIV in the province of British Columbia over the same time period. This study has confirmed the importance and safety of combination ART use in the HIV positive maternal infant pair. In this study, the infant period of treatment was significantly associated with a reduction in HIV transmission in maternal infant pairs that had no previous treatment. Thus researchers who are attempting to streamline the treatment regimens for the HIV positive maternal infant dyad should be cautious if they intend to remove or reduce the infant arm of the treatment protocol.

The HIV prenatal screening program in British Columbia has been successful in identifying HIV positive pregnant women, and has contributed to the reduction in the number of HIV positive women who do not receive treatment in the pregnancy period. Women who are unaware of their HIV status in pregnancy have a significantly higher rate of perinatal HIV transmission, and thus continued expansion of this program to ensure that all women are offered HIV testing in pregnancy is needed. There also remains a cohort of women who are aware of their HIV status but do not access treatment during their pregnancies. Further exploration into these women’s choices and rationale for not accessing treatment is essential in order to support and provide them with optimal health care.
Aboriginal women continue bear a disproportionate burden of HIV and have an unexpectedly high rate of perinatal HIV transmission. This study confirms the need for culturally appropriate HIV prevention and treatment program for aboriginal women, but also has shown that comprehensive treatment models can significantly improve the uptake of medically needed interventions in different cultural populations.

Women who are intravenous drug users face challenges with accessing treatment during their pregnancies, despite their overall increased use of ART in pregnancy in the past six years. Women with a history of drug use are also more likely to know their HIV status and not access treatment, and to have second pregnancies. Reasons for their difficulty accessing treatment are unclear, and may both be patient and provider related. As the proportion of Canadian women who contract HIV from intravenous drug use continues to rise, policy makers and planners will need to develop a coordinated approach to supporting and treating HIV positive women with a history of past or current intravenous drug use, in order to ensure both the women and their infants receive the best care available.

Fertility data, decisions regarding pregnancy, contraceptive issues and issues regarding reproductive choice in HIV positive women require further exploration. With the continued shifting demographics of HIV in North America, from an illness primarily affecting men to an illness that both men and women suffer from, clinicians will increasingly require information about fertility and pregnancy in order to provide HIV positive women with appropriate care.
Finally, continued, on-going and systematic review of HIV positive pregnancies and their outcomes is needed to ensure that any significant adverse effects of the treatment regimens are identified promptly. As well, there is a need for controlled trials evaluating the different treatment regimens to discern if any particular combination regimen offers HIV positive pregnant women with fewer adverse effects or is more effective at diminishing perinatal HIV transmission.
REFERENCES


Ref Type: Electronic Citation


### Appendix I. FOOD AND DRUG ADMINISTRATION PREGNANCY CATEGORY

<table>
<thead>
<tr>
<th>Antiretroviral Drug</th>
<th>FDA Category</th>
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</thead>
<tbody>
<tr>
<td><strong>NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS</strong></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (ZDV)</td>
<td>C</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>C</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td>B</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>C</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>C</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>C</td>
</tr>
<tr>
<td><strong>NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS</strong></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>C</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>C</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>C</td>
</tr>
<tr>
<td><strong>PROTEASE INHIBITORS</strong></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>C</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>B</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>B</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>B</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>C</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>C</td>
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</tbody>
</table>
FOOD AND DRUG ADMINISTRATION PREGNANCY RISK RATING

A  Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).

B  Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted.

C  Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.

D  Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risk.

X  Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.
Appendix II. SAMPLE SIZE CALCULATION

\( \alpha = 0.05 \)

\( \beta = 0.2 \)

\( p_1 = 0.75 \quad p_2 = 0.25 \quad p_{\text{overall}} = (0.75 + 0.25)/2 = 0.625 \)

\( n_1 = n_2 = \left\{ \frac{(1.96)\sqrt{2}(0.625)(0.375) + 0.84\sqrt{0.75}(0.25) + (0.5)(0.5)}{(0.75-0.5)} \right\}^2 \)

\( n_1 = n_2 = \left\{ \frac{(1.96)(0.685) + (0.84)(0.66)}{0.25} \right\}^2 \)

\( n_1 = n_2 = \left\{ [1.34+0.55]/0.25 \right\}^2 \)

\( n_1 = n_2 = 57.4 \)
Appendix III. OBSTETRIC AND PEDIATRIC CLINICAL DEFINITIONS

Obstetrical and pediatric outcomes were defined using standard accepted clinical definitions.

*Live birth* is the complete expulsion or extraction from its mother, irrespective of the duration of the pregnancy of a product of conception, which after the expulsion or extraction, there is: a) breathing, b) beating of the heart, c) pulsation of the umbilical cord or d) unmistakable movement of voluntary muscle, whether or not the umbilical cord has been cut or the placenta is attached.

An *abortion* is the delivery or loss of the products of conception before the 20th week of pregnancy. A spontaneous abortion occurs without any instrumentation while a therapeutic or induced abortion is an abortion that is caused by either medication or instrumentation.

A *stillbirth* is a complete expulsion or extraction from its mother has occurred after at least 20 weeks of pregnancy, or after attaining a weight of at least 500 grams, of a product of conception in which after expulsion there is no breathing, beating of the heart, pulsation of the umbilical cord or unmistakable movement of voluntary muscle.

*Gestational age* is the fetal age or duration of pregnancy measured from the first day of the last normal menstrual period. Gestational age can be expressed in either completed days or completed weeks. Prematurity is defined based on gestational age. *Extremely premature* is an infant with a gestational age of less than 28 weeks. *Moderately premature* is a gestational age between 28 and 36 weeks. *Premature or preterm* is any gestational age less than 37 weeks. An infant born at *term* has a gestational age between
37 weeks and 41 weeks. A post-term or postmature infant has a gestational age of 42 weeks or more.

**Gestational hypertension** is defined as a diastolic blood pressure of 90 mmHG or more that develops after 20 weeks gestational age. Proteinuria is defined as a protein excretion of greater than 0.3 g/d in a 24 hour collection.

**Intrauterine growth retardation** occurs when the birth weight of an infant is below the tenth percentile for a particular gestational age.

**Gestational diabetes** is diagnosed between 24 to 28 weeks gestational age, using a 50 gm glucose load given orally. Plasma glucose is then measured one hour later. If the one hour value is greater than 10.3 mmol/L, no further testing is required, and gestational diabetes is diagnosed. If the one-hour value is greater than 7.8 mmol/L, but less than 10.3 mmol/L then a glucose tolerance test (GTT) is completed. This involves a 75g glucose load, with blood glucose measurements done at fasting, and at hour one and two after ingestion of the glucose. If the fasting, one hour and two hour tests are greater than 5.3 mmol/L, 10.6 mmol/L and 8.9 mmol/L respectively, then gestational diabetes is diagnosed.

**Oligohydramnios** is defined as a marked decrease in the quantity of amniotic fluid. There is less than 5% of the expected amount of amniotic fluid on ultrasound evaluation of the uterus. Polyhydramnios is defined as an amniotic fluid volume of greater than 95% expected range.

**Cesarean Section** is a delivery involving the surgical incision of the abdomen and uterine walls.
**Chorioamnionitis** is inflammation of the chorion and/or amnion. Clinically, it is associated with uterine tenderness, irritability, fever and potentially rupture of membranes.

**Birth weight** is the first weight of the fetus or newborn after birth. Birth weights are grouped as

- *Extremely low birth weight* < 500 grams
- *Very Low birth weight* < 1500 grams
- *Low Birth weight* < 2500 grams
- *Normal Birth weight* 2500 to 4499 grams
- *High Birth weight* > 4500 grams