Formatted for *The Pediatric Infectious Disease Journal*

Preterm Birth and Antiretroviral Exposure in Infants HIV-Exposed Uninfected

Running Title: Preterm Birth in Infants HIV-Exposed Uninfected

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Funding: This study was funded by the Canadian Institutes of Health Research (CIHR, [TCO-125269 to HCFC] Team Grant on Cellular Aging and HIV Comorbidities in Women and Children (CARMA)

Disclosure summary: The authors have no conflicts of interest to disclose.
Conflicts of interest: There are no conflicts of interest to disclose.

Word count [2934/3000 words]
Tables & Figures: 4 Tables 1 Figure

Disclosure from Population Data BC: "All inferences, opinions, and conclusions drawn in this retrospective study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s)."

Keywords: HIV-exposed uninfected; IHEU; HIV infant; preterm birth; maternal antiretroviral therapy; maternal HIV

ABSTRACT

Background: Infants who are HIV-exposed and uninfected (IHEU) born to women living with HIV (WLWH) are at an increased risk of preterm birth (PTB). Antenatal exposure to certain maternal antiretroviral therapy (ART) regimens has been associated with PTB, although existing studies in this domain have been limited with discordant findings. We determined odds of PTB among IHEU by antenatal ART regimens and exposure durations, adjusting for maternal risk factors.

Methods: We retrospectively studied IHEU born in British Columbia (BC), Canada between 1990 to 2012 utilizing provincial health administrative databases. Data was collected for infants HIV-unexposed and uninfected (IHUU) controls matched ~3:1 for each IHEU on age, sex and geocode. We determined adjusted odds ratios (AORs) of PTB via multivariable logistic regression.

Results: A total of 411 IHEU and 1224 IHUU were included in univariate analysis. PTB was more frequent among IHEU compared to IHUU (20% vs. 7%). IHEU were more often antenatally exposed to alcohol, tobacco, and prescription, non-prescription, and illicit drugs (IHEU: 36%, 8%, 35%; IHUU: 3%, 1%, 9% respectively). After adjusting for maternal substance use and smoking exposure, IHEU remained at increased odds of PTB [AOR:2.66; 1.73, 4.08] compared to matched IHUU controls. ART-exposed IHEU had lower adjusted odds of PTB compared to IHEU with no maternal ART exposure, regardless of regimen (excluding NRTIs only) (AOR: 0.16-0.29[0.02-0.95]) or exposure durations (AOR:0.16-0.25 [0.06-0.78]).

Conclusions: BC IHEU were over twice as likely to be born preterm compared to demographically matched controls. While maternal substance use in pregnancy modulated this risk, we found no adverse associations of PTB with antenatal ART regimens or exposure durations.

INTRODUCTION

Globally, more than 15 million infants are born preterm each year (1). Preterm birth (PTB), defined as a birth less than 37 weeks of gestational age, is the leading cause of early neonatal death (1,2) and is associated with an increased risk of postnatal health problems in mothers (3,4) and an increased risk of child morbidities and diseases later in life (1,5–10). For these reasons, PTB is a key contributor to global economic burdens (2,11). Understanding and preventing PTB are thus crucial international goals for maternal and child health. Risk factors for PTB in the general population include multiple births, extreme maternal age and weight, substance use, infections, and inflammation; (12–21) several of these factors are more prevalent among women living with HIV (WLWH).

More than half of all adults living with HIV are women (22), and an increasing proportion of their infants are exposed to antiretroviral therapy (ART) antenatally, and for longer duration(23). Combination antiretroviral therapy (cART) during pregnancy can reduce the risk of vertical transmission to <1% (24). This success means that a vast majority of WLWH who have access to ART give birth to infants who are HIV-Exposed Uninfected (IHEU) and are exposed in utero to maternal ART. Maternal HIV infection is argued to be associated with a risk of preterm delivery proportional to the stage of the disease (25–27); however WLWH are still at a significantly higher risk for preterm delivery even if treated with cART and virally suppressed (28–30). cART regimens commonly include three or more antiretroviral drugs; many of which can cross the placenta (31,32). Several studies have suggested possible links between certain antiretrovirals or types of cART regimens and increased risks of PTB, (25,33–35) while others report no such association (36–40). While the benefits of cART in pregnancy for the prevention of vertical transmission are undisputed, evaluation of cART regimens associated with the lowest risk of PTB has not systematically studied.

PTB additionally creates a higher risk for many adverse acute and long-term outcomes in children including in development (41–44). This is further supported by our previous retrospective study on 441 IHEU born in British Columbia (BC) Canada, which reported

children born preterm have a nearly three- times greater odds of developmental disorders compared to those born at term, irrespective of HIV-exposure (45).

From the same retrospective study of a provincially representative controlled cohort of IHEU, the current study determined odds of PTB and associations with maternal ART exposure among BC IHEU compared to matched control infants who are HIV-Unexposed Uninfected (IHUU) while adjusting for maternal sociodemographic risk factors.

METHODS

Study Design

Retrospective, de-identified data (perinatal and maternal demographic records) were collected for all IHEU who were born to WLWH in BC between January 1, 1990 and December 31, 2012, who had a BC personal health number recorded. Additionally, the same information was collected for an IHUU cohort matched 3:1 (~99%) to each IHEU on year of birth, sex, and geocode (first three-digit postal code of the mother's primary address at the time of the child's birth). In BC, pregnancies in WLWH are considered high risk, and thus obstetrical care of WLWH is centralized, with the vast majority of women being cared for in a single center, with intensive case management.

Data Sources

All data were retrieved through Population Data BC, and from health administrative data sources including: BC Vital Statistics Agency (maternal and gestational age and birth outcomes)(46) Perinatal Services BC (maternal substance use)(47), and medical chart information obtained from the Canadian Perinatal HIV Surveillance Program (CPHSP) hosted by the BC Women's Hospital and Health Centre, Vancouver, BC (ART regimens and durations during pregnancy)(48). Datasets were merged from these sources to develop two models.

Measures

Virologic testing protocols to determine HIV-infection for infants born to WLWH in BC are described in **Supplementary Appendix.** The primary outcome of interest, PTB, was defined as being born before 37 completed weeks of gestation and classified as a binary outcome. Gestational age was measured from the first day of the last menstrual period and expressed in completed weeks. The BC Perinatal Data Registry developed and implemented maternal substance use screening questions for care providers beginning April 1, 2000 for all BC pregnant women through medical chart record. Maternal smoking (tobacco) was defined as any smoking during the pregnancy and alcohol was defined as any alcohol use that was identified as a risk to the pregnancy by a physician. Maternal substance use during pregnancy recorded from April 1, 2000 until March 31, 2008 was defined as whether the health care provider reported any

prescription, non-prescription, or illicit drug use by the mother as a risk factor to the pregnancy. From April 1, 2008 until 2012, this variable reflected whether the mother had used any: heroin/opioids, cocaine, methadone, solvents, or marijuana at any point during the pregnancy; or whether the healthcare provider indicated use of prescription, 'other', or unknown drugs as a risk to the pregnancy. Due to collinearity, smoking and drug/substance use were combined as a categorial variable with options of 1) either smoking or substance use; 2) both smoking and substance use; 3) neither smoking or substance use (reference group).

IHEU in this dataset were analyzed based on the type of maternal ART regimen they were exposed to in utero: 0) None; 1) Nucleoside Reverse Transcriptase Inhibitors (NRTIs) only; 2) NRTIs + Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI); 3) NRTIs + Protease Inhibitor (PI) (unboosted *i.e.* no ritonavir); 4) NRTIs + PI (boosted with ritonavir) and compared to matched IHUU (for IHEU within each regimen class), and IHEU with no ART exposure. Details on BC ART guidelines over study period are provided in Supplementary Appendix. IHEU exposed to other types of regimens were excluded (N<6). Among all IHEU for whom treatment duration was known, those with no antenatal ART exposure were additionally compared to IHEU with any antenatal ART exposure (irrespective of class type), stratified by the duration of exposure in weeks: 0) None; 1) >0-13 weeks; 2) >13-26 weeks; 3) >26 weeks. If ART regimens were interrupted or changed during pregnancy, the predominant regimen (of longest duration) was considered and durations were combined to calculate total in utero exposure length. Preconception use was not ascertained.

Statistical Analysis

Two statistical models were developed to investigate PTB in the IHEU and IHUU cohorts. The first model included univariate analysis of infants born throughout the study period for whom maternal age, gestational age at birth, birth weight, and APGAR score information was available from BC Vital Statistics. Analyses were restricted to infants for whom this information was complete (Figure A1). The second model included infants born April 1, 2000 onward, a period during which information on maternal substance use during pregnancy was collected by Perinatal Services BC. IHEU were then analyzed for frequency of PTB stratified according to four predominant in-utero ART regimen exposures. PTB frequencies were compared with respective

matched IHUUs (for age, sex and geocode) for each ART exposure type. Associations were measured as ORs of PTB between: IHEU and IHUU; and in ART analysis between: IHEU and matched IHUUs or among IHEU only (by ART exposure type or duration). Final AORs presented were obtained from multivariable logistic regression. Among IHEU, univariate comparisons between ART regimen types and durations were represented as unadjusted ORs of PTB. The 95% confidence intervals were calculated using the Cornfield method (49). Statistical analysis was performed using STATA IC 13 (StataCorp. 2013. College Station, TX).

Ethics

This study was approved by the Children's & Women's Health Centre of British Columbia Research Ethics Board (CWREB, H10-00992).

RESULTS

A total of 411 IHEU and 1224 IHUU were included in the first univariate model for the full study period. Mothers of IHEU did not significantly differ in age compared to mothers of IHUU (**Table 1**). Gestational age at delivery and birth weight were lower in IHEU, and a significantly greater proportion of IHEU (20%) were born preterm relative to IHUU (7%). Relative to IHUU, a significantly higher proportion of IHEU were antenatally exposed to maternal smoking (IHEU: 35% vs. IHUU: 9%), alcohol use (IHEU: 8% vs. IHUU: 1%), and maternal substance use (IHEU: 36% vs. IHUU: 3%). A majority (86%) of IHEU were antenatally exposed to ART during the study period and 74% were exposed to cART.

IHEU had significantly higher odds of being born preterm in univariate analysis (**Table 2**) (OR= 3.58[95% CI: 2.57,5.00]) which was not significantly associated with sex or maternal age. Similarly, in the second model, including infants born after April 1, 2000, adjustment for maternal substance use and/or smoking attenuated the OR of PTB in IHEU relative to IHUU (OR: 3.33 [2.27, 4.91]; AOR: 2.66[1.73,4.08]), although the association remained significant.

ART regimens for pregnant WLWH in BC have changed over the study period from zidovudine monotherapy becoming more widely adopted after 1994, to mono/dual treatment with NRTIs only, and eventually to cART (beginning in 1997) with regimens involving a minimum of two different drug classes **(Figure 1 Panel A)**. The number of women diagnosed with HIV and experiencing at least one pregnancy each year has increased since the 1990's, remaining relatively stable in more recent years. Less than 13%(N=55) of the IHEU cohort was born before 1997, prior to increased use of cART during pregnancy. Not surprisingly, the majority of IHEU with no maternal ART exposure were born before cART uptake increased for pregnant WLWH in BC. Gestational age at delivery among the IHEU cohort over the study period is illustrated in **Panel B**.

Overall, odds of PTB between IHEU with maternal ART exposure and those with no ART exposure did not reach significant difference (OR: 0.56[0.30,1.04]); although there was a tendency toward lower odds of PTB among IHEU with any in utero ART exposure (**Table 3**).

Odds of PTB were lower among IHEU with any maternal ART exposure in the post 2000 era (OR: 0.09,0.60). Odds of PTB were highest for IHEU with no antiretroviral exposure compared with their matched IHUU (OR: 5.17[2.32,11.51]). This trend persisted with ORs of PTB for IHEU in each ART exposure type remaining consistently higher compared to their respective matched IHUU controls. IHEU exposed to the NRTIs + PI (unboosted) class had the lowest OR of PTB among the different types of ART, although it was still significantly higher relative to matched IHUU (OR: 2.39[1.28,4.49]).

After adjusting for maternal substance use and/or smoking in a smaller subset of IHEU, IHEU in nearly all ART exposure classes had significantly lower odds of PTB, relative to IHEU with no antenatal ART exposure, except for those who were predominately exposed to regimens containing 1-4 NRTIs (AOR: 0.16[0.02,1.69]) (**Table 4**). IHEU with any antenatal ART exposure (regardless of ART type) were compared to IHEU with no exposure. Univariately compared to IHEU with no maternal ART exposure, IHEU with >13 weeks of ART exposure had as much as 55% lower odds of PTB (>13-26 weeks OR: 0.48[0.24,0.96], >26 weeks OR: 0.45[0.04,0.79]); however, the odds of PTB did not significantly differ between IHEU with >0-13 weeks of maternal ART exposure and IHEU who received none (OR: 0.75[0.36,1.58]). After adjusting for maternal substance use and/or smoking in a smaller subset of IHEU (model 2), IHEU in all maternal ART exposure durations with over 0 weeks of exposure had significantly lower odds of PTB relative to IHEU who were not exposed to any maternal ART (AOR:0.16-0.26[0.06,0.78]).

DISCUSSION

This study comprehensively reported on PTB among nearly all known IHEU born in BC over a 22-year period. Compared with CHUU, we found a significantly higher frequency of PTB occurred among IHEU born in BC between 1990 and 2012 (20%). This frequency was nearly three-times higher than observed in our demographically matched controlled cohort of IHUU infants, and nearly two-times higher than in provincial estimates in 2012(50). We found IHEU remained at an increased risk of being born preterm compared to IHUU, regardless of exposure to maternal ART; however, IHEUs who with no maternal ART had the highest frequency of PTB (30%).

The 20% PTB rate observed in our IHEU cohort is consistent with other studies from Canada (51) (up to 25%), Spain (29)(20%), and Botswana (28)(24%). In IHUU, the observed PTB rate (7%) was lower than found in the Botswana study (17%)(28) but similar to rates reported in Canada (8%)(52) and Spain (9%)(29). These data suggest the PTB rates are similarly elevated for IHEU, even in areas where maternal substance use is not as prevalent as in our study, but likely differ with sociodemographic and environmental influences in other settings. Our findings therefore support evidence reporting a higher PTB rate among IHEU and highlight that this outcome is modulated by other maternal factors such as substance use and treatment for HIV. A recent retrospective cohort study suggested high rates of PTB among WLWH in their study may be partly explained by the higher likelihood of preterm premature rupture of membranes and urinary tract infections which are known risk factors for PTB(53); while a recent meta-analysis has attributed this adverse outcome to the suppressed immune system of WLWH and reduced CD4+ cell count(54). Additionally, maternal HIV and its acquisition through injection are reportedly associated with pregnancy hypertension(55), while cART has been linked to increased risks of preeclampsia(56) - both are known risk factors for PTB.

Reassuringly, consistent with a similar study spanning later years with newer ART (57), we observed no adverse associations between PTB and any specific antenatal ART exposure regimens or durations although this is in contrast to other studies reporting an association between certain ART regimens (including PI-based regimens) and PTB(25,33–35,58,59). It may

be possible that the current study's sample size was not large enough to detect this effect. Our findings of increased PTB prevalence among WLWH without maternal ART are similar to other studies reporting higher PTB in women with untreated HIV (60,61). Rates of PTB were lower among IHEU whose mother received ART during pregnancy from 2000 onwards compared to IHEU who were not exposed to maternal ART although there were fewer IHEU without ART in this period, as ART for pregnant women became more available after the 1990s. These rates were similarly observed for all exposure classes investigated, with the exception of regimens with NRTIs only. However, very few infants (N=7) included in the analysis were exposed to this type of regimen after 2000.

This data is consistent with a separate analysis on spontaneous PTB (excluding iatrogenic PTB and non-singleton births) in a partially overlapping provincial dataset of WLWH spanning a later period, from 1997 to 2018(57). It similarly reported an overall PTB frequency of 20.3% (spontaneous PTB frequency 15.5%) among WLWH in their dataset; however the study did not have a control group. The study documented the highest risk of PTB was from unsuppressed viral load at delivery and substance use exposure and any cART exposure in pregnancy was not associated with PTB (HR:0.55[0.29,1.04]). The present complementary study supplements this work, providing additional data from a pre-cART era on all PTB among BC WLWH, and importantly, providing a socio-demographically matched control cohort of IHUU for comparisons.

The results are reported with several limitations. A majority of mothers who did not receive ART were from the pre-cART era (before 1997), and may therefore have had more advanced HIV disease, may not have been able to access adequate antenatal care, and may have differed socioeconomically from women who did receive treatment. Furthermore, we used geocodes for area-level matching which divides large urban areas into smaller sub-municipal units. Individuals within the same geocode may differ socioeconomically and we could not account for other individual-level socioeconomic factors such as education and income. Additionally, PTBs that were spontaneous versus iatrogenic were not separately analysed. We included multiple births in the analysis as this data was limited; however, some studies have restricted their analysis to singleton births since having multiple births is a risk factor for PTB(62). This study additionally

had limited data on other variables known or suggested to influence PTB such as maternal ethnicity, preeclampsia, placental abruption or fetal anomalies that could result in iatrogenic PTB, as well as insufficient information on maternal immune health (CD4 levels), HIV plasma viral load, ethnicity, non-HIV medications, in addition to psychosocial and economic factors (63,64). Nonetheless, our findings are consistent with another study on a similar and more recent dataset investigating spontaneous PTB among IHEUs, and together provide a comprehensive scope of PTB among BC WLWH.

The differences observed in IHEU and IHUU in our study may be attributable to other maternal and environmental factors that were unaccounted for in the data. Of note, we estimate that maternal substance use was likely under-reported among mothers who are HIV-uninfected in our cohort. Low-barrier, trauma-informed tertiary and multidisciplinary care for WLWH in BC mostly provided by the Oak Tree Clinic at BC Women's Hospital, is reflected in the detailed and comprehensive medical records on more than 95% of all BC IHEU births, resulting in accurate reporting of maternal substance use among pregnant WLWH in this cohort. Mothers to IHUU are therefore not seen as often as IHEU mothers in our context, thereby potentially resulting in differential misclassification of this variable. Further large-scale studies with higher statistical power and more comparable groups are needed to elucidate and confirm our observations in other settings.

In conclusion, research in the causes and prevention of PTB should consider the important associations with antenatal HIV-exposure and the proper receipt of ART. Moving forward, as the number of IHEU births continues to rise, the complex pathophysiology contributing to preterm delivery and its various risk factors warrant further investigations on methods of prevention for this outcome, particularly among WLWH.

ACKNOWLEDGEMENTS

We gratefully acknowledge all information obtained from Population Data BC, BC Ministry of Health, Vital Statistics BC, Perinatal Services BC and BC Perinatal HIV Surveillance database hosted by The Oak Tree Clinic, BC Women's Hospital and Health Centre, Vancouver BC, Canada. This work was funded through the Canadian Institutes of Health Research (CIHR, TCO-125269) team grant on cellular aging and comorbidities in women and children (CARMA).

REFERENCES

1. March of Dimes, PMNCH, Save the Children, WHO. Born too soon. The Global Action Report on Preterm Birth. CP Howson, MV Kinney, JE Lawn Eds World Heal Organ Publ Geneva . 2012;(5):1–126. Available from: http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf

2. Harrison MS, Goldenberg RL. Global burden of prematurity. Seminars in Fetal and Neonatal Medicine. 2016. 2016;21(2):74-79.

3. Henderson J, Carson C, Redshaw M. Impact of preterm birth on maternal well-being and women's perceptions of their baby: a population-based survey. BMJ Open . 2016;6(10):e012676.

4. Vigod SN, Villegas L, Dennis C-L, Ross LE. Prevalence and risk factors for postpartum depression among women with preterm and low-birth-weight infants: a systematic review. BJOG. 2010;117(5):540–50.

5. Hack M, Youngstrom EA, Cartar L, Schluchter M, Gerry Taylor H, Flannery D, et al. Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. Pediatrics. 2004;114(4):932-940.

6. Crump C, Sundquist J, Winkleby MA, Sundquist K. Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood: National cohort study. BMJ. 2019;365:l1346.

7. Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy AK. Preterm Birth and Risk of Heart Failure Up to Early Adulthood. J Am Coll Cardiol. 2017;69(21):2634-2642.

8. Dong Y, Yu JL. An overview of morbidity, mortality and long-term outcome of late preterm birth. World Journal of Pediatrics. 2011;199(7).

9. Lund LK, Vik T, Skranes J, Brubakk AM, Indredavik MS. Psychiatric morbidity in two low birth weight groups assessed by diagnostic interview in young adulthood. Acta Paediatr Int J Paediatr. 2011;100(4):598-604.

10. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. Vol. 21, Seminars in Fetal and Neonatal Medicine. 2016;21(2):68-73.

11. Petrou S. Health economic aspects of late preterm and early term birth. Semin Fetal Neonatal Med. 2019;24(1):18-26.

12. Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, Bommarito K, Madden T, Olsen MA, et al.

Maternal Age and Risk of Labor and Delivery Complications. Matern Child Health J. 2015;19(6):1202–11.

13. Han Z, Mulla S, Beyene J, Liao G, McDonald SD. Maternal underweight and the risk of preterm birth and low birth weight: A systematic review and meta-analyses. Vol. 40, International Journal of Epidemiology. 2011;40(1):65-101.

14. York TP, Strauss JF, Neale MC, Eaves LJ. Racial differences in genetic and environmental risk to preterm birth. PLoS One. 2010;5(8).

15. Peelen MJCS, Kazemier BM, Ravelli ACJ, De Groot CJM, Van Der Post JAM, Mol BWJ, et al. Impact of fetal gender on the risk of preterm birth, a national cohort study. Acta Obstet Gynecol Scand. 2016;95(9):1034–41.

16. Kurdi AM, Mesleh RA, Al-Hakeem MM, Khashoggi TY, Khalifa HM. Multiple pregnancy and preterm labor. Saudi Med J. 2004;25(5):632–7.

17. O'Leary CM, Nassar N, Kurinczuk JJ, Bower C. The effect of maternal alcohol consumption on fetal growth and preterm birth. BJOG An Int J Obstet Gynaecol. 2009;116(3):390–400.

18. Salihu HM, Wilson RE. Epidemiology of prenatal smoking and perinatal outcomes. Vol. 83, Early Human Development. 2007;83(11):713-720.

19. Addis A, Moretti ME, Ahmed Syed F, Einarson TR, Koren G. Fetal effects of cocaine: An updated meta-analysis. Reprod Toxicol. 2001;15(4):341–69.

20. Kim CJ, Romero R, Chaemsaithong P, Kim J-S. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. Am J Obstet Gynecol. 2015;213(4):S53–69.

21. Himes KP, Simhan HN. Risk of recurrent preterm birth and placental pathology. Obstet Gynecol. 2008;112(1):121–6.

22. Unaids. UNAIDS fact sheet - Latest statistics on the status of the AIDS epidemic. 2017;(July):8. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

23. World Health Organization. Global Health Observatory data repository. Prevention of mother-to-child transmission estimates by country. 2019. Available from: https://apps.who.int/gho/data/node.main.627?lang=en

24. AIDSinfo. HIV Prevention - Preventing Mother-to-Child Transmission of HIV. 2015;1–2.

Available from: https://aidsinfo.nih.gov/education-materials/fact-sheets/20/50/prevention-of-mother-to-child-transmission-of-hiv#

25. Newell M-L, Aebi C, Battegay M, Bernasconi E, Biedermann K, Cheseaux J-J, et al. Combination antiretroviral therapy and duration of pregnancy. AIDS. 2000;14(18):2913–20.

26. Zack RM, Golan J, Aboud S, Msamanga G, Spiegelman D, Fawzi W. Risk Factors for Preterm Birth among HIV-Infected Tanzanian Women: A Prospective Study. Obstet Gynecol Int. 2014;2014:1–9.

27. Ezechi OC, David AN, Gab-Okafor C V, Ohwodo H, Oladele DA, Kalejaiye OO, et al. Incidence of and socio-biologic risk factors for spontaneous preterm birth in HIV positive Nigerian women. BMC Pregnancy Childbirth. 2012;12(1):93.

28. Chen JY, Ribaudo HJ, Souda S, Parekh N, Ogwu A, Lockman S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis. 2012;206(11):1695–705.

29. Lopez M, Figueras F, Hernández S, Lonca M, Garcia R, Palacio M, et al. Association of HIV infection with spontaneous and iatrogenic preterm delivery: effect of HAART. AIDS. 2012;26(1):37–43.

30. Boer K, Nellen JF, Patel D, Timmermans S, Tempelman C, Wibaut M, et al. The AmRo study: Pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. BJOG. 2007;114(2):148-155.

31. Rimawi BH, Johnson E, Rajakumar A, Tao S, Jiang Y, Gillespie S, et al. Pharmacokinetics and Placental transfer of elvitegravir, dolutegravir, and other antiretrovirals during pregnancy. Antimicrob Agents Chemother. 2017;61(6).

32. Else LJ, Taylor S, Back DJ, Khoo SH. Pharmacokinetics of antiretroviral drugs in anatomical sanctuary sites: The fetal compartment (placenta and amniotic fluid). Vol. 16, Antiviral Therapy. 2011;16(8):1139-1147.

33. Sibiude J, Warszawski J, Tubiana R, Dollfus C, Faye A, Rouzioux C, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: Role of the ritonavir boost? Clin Infect Dis. 2012;54(9):1348–60.

34. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR. The PHACS SMARTT study: Assessment of the safety of in utero exposure to antiretroviral drugs. Front Immunol. 2016;7:199.

35. Zash R, Jacobson DL, Diseko M, Mayondi G, Mmalane M, Essex M, et al. Comparative Safety of Antiretroviral Treatment Regimens in Pregnancy. JAMA Pediatr. 2017;171(10):e172222.

36. Patel K, Shapiro DE, Brogly SB, Livingston EG, Stek AM, Bardeguez AD, et al. Prenatal Protease Inhibitor Use and Risk of Preterm Birth among HIV-Infected Women Initiating Antiretroviral Drugs during Pregnancy. J Infect Dis. 2010;201(7):1035-1044.

37. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: A meta-analysis. AIDS. 2007;21(5):607-615.

38. Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, et al. Antiretroviral Therapy during Pregnancy and the Risk of an Adverse Outcome. N Engl J Med. 2002;346(24):1863-1870.

39. Weinberg A, Huo Y, Kacanek D, Patel K, Watts DH, Wara D, et al. Markers of Spontaneuous Preterm Delivery in Women living with HIV. JAIDS J Acquir Immune Defic Syndr. 2019;82(2):181-187.

40. Saleska JL, Turner AN, Maierhofer C, Clark J, Kwiek JJ. Use of antiretroviral therapy during pregnancy and adverse birth outcomes among women living with HIV-1 in low- A nd middle-income countries: A systematic review. J Acquir Immune Defic Syndr. 2018;79(1):1-9.

41. Marlow N, Wolke D, Bracewell MA, Samara M, EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med. 2005;352(1):9–19.

42. Whitfield MF, Grunau R V, Holsti L. Extremely premature (< 800 g) schoolchildren: multiple areas of hidden disability. Arch Dis Child Fetal Neonatal Ed. 1997;77(2):F85-90.

43. Saigal S, Ouden L d., Wolke D, Hoult L, Paneth N, Streiner DL, et al. School-Age Outcomes in Children Who Were Extremely Low Birth Weight From Four International Population-Based Cohorts. Pediatrics. 2003;112(4):943–50.

44. Cheong JL, Doyle LW, Burnett AC, Lee KJ, Walsh JM, Potter CR, et al. Association Between Moderate and Late Preterm Birth and Neurodevelopment and Social-Emotional Development at Age 2 Years. JAMA Pediatr. 2017;171(4):e164805.

45. Piske M, Budd MA, Qiu AQ, Maan EJ, Sauvé LJ, Forbes JC, et al. Neurodevelopmental outcomes and in-utero antiretroviral exposure in HIV-exposed uninfected children. AIDS. 2018;32(17):2583-2592.

46. BC Vital Statistics Agency [creator] (2014): Vital Statistics Births. Population Data BC [publisher]. Data Extract. BC Vital Statistics Agency (2014). http://www.popdata.bc.ca/data.

47. Perinatal Services BC [creator] (2015): British Columbia Perinatal Data Registry. Population Data BC [publisher]. Data Extract. PSBC (2014). http://www.perinatalservicesbc.ca/health-professionals/data-surveillance/perinatal-data-registry.

48. The Oak Tree Clinic [creator] (2015): BC HEU Data. Population Data BC [publisher]. Data Extract. OTC (2014). http://www.popdata.bc.ca/data.

49. Cornfield J. A statistical problem arising from retrospective studies. Third berkeley Symp Cornf. 1956;4:135–48.

50. Perinatal Services BC. Perinatal Health Report: Deliveries in British Columbia 2016/17. Available from: www.perinatalservicesbc.ca

51. Kakkar F, Boucoiran I, Lamarre V, Ducruet T, Amre D, Soudeyns H, et al. Risk factors for pre-term birth in a Canadian cohort of HIV-positive women: Role of ritonavir boosting? In: Journal of the International AIDS Society. 2015;18(1):19933.

52. Public Health Agency of Canada. Perinatal health indicators for Canada 2011. Perinatal Health Indicators for Canada 2011. Available from: https://www.canada.ca/en/public-health/services/injury-prevention/health-surveillance-epidemiology-division/maternal-infant-health/perinatal-health-indicators-canada-2011.html

53. Arab K, Spence AR, Czuzoj-Shulman N, Abenhaim HA. Pregnancy outcomes in HIV-positive women: a retrospective cohort study. Arch Gynecol Obstet. 2017;295(3):599-606.

54. Xiao PL, Zhou YB, Chen Y, Yang MX, Song XX, Shi Y, et al. Association between maternal HIV infection and low birth weight and prematurity: A meta-analysis of cohort studies. BMC Pregnancy Childbirth. 2015;15:246.

55. Wang A, Wang X, Dou L, Wang F, Wang Q, Qiao Y, et al. Incidence of and related risk factors on preterm delivery among HIV-infected pregnant women in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2015;36(4):349-353

56. Sansone M, Sarno L, Saccone G, Berghella V, Maruotti GM, Migliucci A, et al. Risk of preeclampsia in human immunodeficiency virus-infected pregnant women. Obstet Gynecol. 2016;127(6):1027-1032.

57. Albert AYK, Elwood C, Wagner EC, Pakzad Z, Chaworth-Musters T, Berg K, et al.

Investigation of Factors Associated with Spontaneous Preterm Birth in Pregnant Women Living with HIV. AIDS. 2020;34(5):719-727.

58. Kourtis AP, Fowler MG. Antiretroviral use during pregnancy and risk of preterm delivery: More questions than answers. Journal of Infectious Diseases. 2011;204(4):493-494.

59. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS. 2007;21(8):1019-1026.

60. Joseph O, Biodun O, Michael E. Pregnancy outcome among HIV positive women receiving antenatal HAART versus untreated maternal HIV infection. J Coll Physicians Surg Pakistan. 2011;21(6):356–9.

61. Wedi COO, Kirtley S, Hopewell S, Corrigan R, Kennedy SH, Hemelaar J. Perinatal outcomes associated with maternal HIV infection: A systematic review and meta-analysis. Lancet HIV. 2016;3(1):e33-e48.

62. Dekker GA, Lee SY, North RA, McCowan LM, Simpson NAB, Roberts CT. Risk factors for preterm birth in an international prospective cohort of nulliparous women. PLoS One. 2012;7(7): e39154.

63. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2018;52:3-12.

64. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The Lancet. 2008;371(9606):75-84.

TABLES & FIGURES

Table 1. Cohort characteristics

	Model 1: 1990 - 2012			Model 2: 2000 - 2012		
	IHEU	**IHUU**	**P-value**	**IHEU**	**IHUU**	**P-value**
N	411	1224	-	309	917	-
Characteristic						
Maternal age	29.9 ± 5.6	30.5 ± 5.6	0.056	30.2 ± 5.4	30.7 ± 5.6	0.083
Infant age at data collection[1]	8.4 ± 5.6	8.4 ± 5.6	0.90	5.9 ± 3.6	5.8 ± 3.6	0.79
Infant male sex	190 (46)	573 (47)	0.84	144 (47)	432 (47)	0.88
Gestational age at birth (weeks)	37.7 ± 3.1	38.9 ± 1.8	<0.0001	37.7 ± 2.4	38.8 ± 1.8	<0.0001
Born preterm (<37 weeks)	83 (20)	85 (7)	<0.0001	61 (20)	63 (7)	<0.0001
34-36 weeks	63 (15)	67 (5)	<0.0001	43 (14)	50 (5)	<0.0001
<34 weeks[2]	22 (5)	16 (1)	<0.0001	18 (6)	13 (1)	<0.0001
Non-singleton births	13 (3)	28 (2)		11 (4)	26 (3)	
Non-singleton preterm births[3]	6 (46)	11 (39)		<6 (und.)	10 (38)	
Birth weight (g)	2985 ± 616	3384 ± 572	<0.0001	2993 ± 588	3379 ± 576	<0.0001
Birth weight <2500 g	68 (17)	55 (4.5)	<0.0001	48 (16)	42 (5)	<0.0001
APGAR 1 min	7.9 ± 1.8	8.1 ± 1.5	0.32	7.9 ± 1.9	8.2 ± 1.5	0.34
APGAR 5 min	8.8 ± 1.3	9.1 ± 0.8	<0.0001	8.8 ± 1.2	9.1 ± 0.8	<0.0001
Antenatal exposure						
Smoking (any)	-	-	-	107 (35)	78 (9)	<0.0001
Alcohol use[4]	-	-	-	26 (8)	12 (1)	<0.0001
Substance use[5]	-	-	-	111 (36)	24 (3)	<0.0001
Maternal ART regimens	**N**			**N**		
None	57 (14)			17 (6)		
Monotherapy (NTRIs only)						
1 NRTI	30 (7)			29 (9)		
2 NRTIs	11(3)			8 (3)		
3 NRTIs	<6			<6		
Combination regimens						
NRTIs + NNRTI	66 (16)			59 (19)		
NRTIs + PI (unboosted)	129 (31)			114 (37)		
NRTIs + PI (boosted)	109 (27)			73 (24)		
Other/unknown	<6			<6		

IHEU: infants HIV-exposed uninfected; IHUU: infants HIV-unexposed uninfected; APGAR: appearance, pulse, grimace, activity, respiration (scores at 1 minute and 5 minutes after birth) ART: antiretroviral therapy. Data shown as mean ± SD or N (%). P-value calculated from Pearson chi-squared test (proportions) or from Mann-Whitney U test (continuous variables). N<6 and percentages undisclosed as per data disclosure agreement.[1]Infant age at data collection (years), as of December 31, 2012. [2] WHO preterm categories: Model 1: IHEU and IHUU born <28 weeks (extremely preterm) N<6, IHEU and IHUU born 28-31 weeks (moderate preterm) N<6, IHEU born 32-36 weeks N=73 (18), IHUU born 32-36 weeks N=72 (6); Model 2: IHEU born 32-36 weeks N=61 (20), IHUU born 32-36 weeks N=55 (6). [3] Percentage determined from total non-singleton births as denominator. [4]Identified as risk to the pregnancy. [5]Any prescription, non-prescription, or illicit drug use by the mother as a risk factor to pregnancy (2000 to 2008); OR any heroin/opioids,

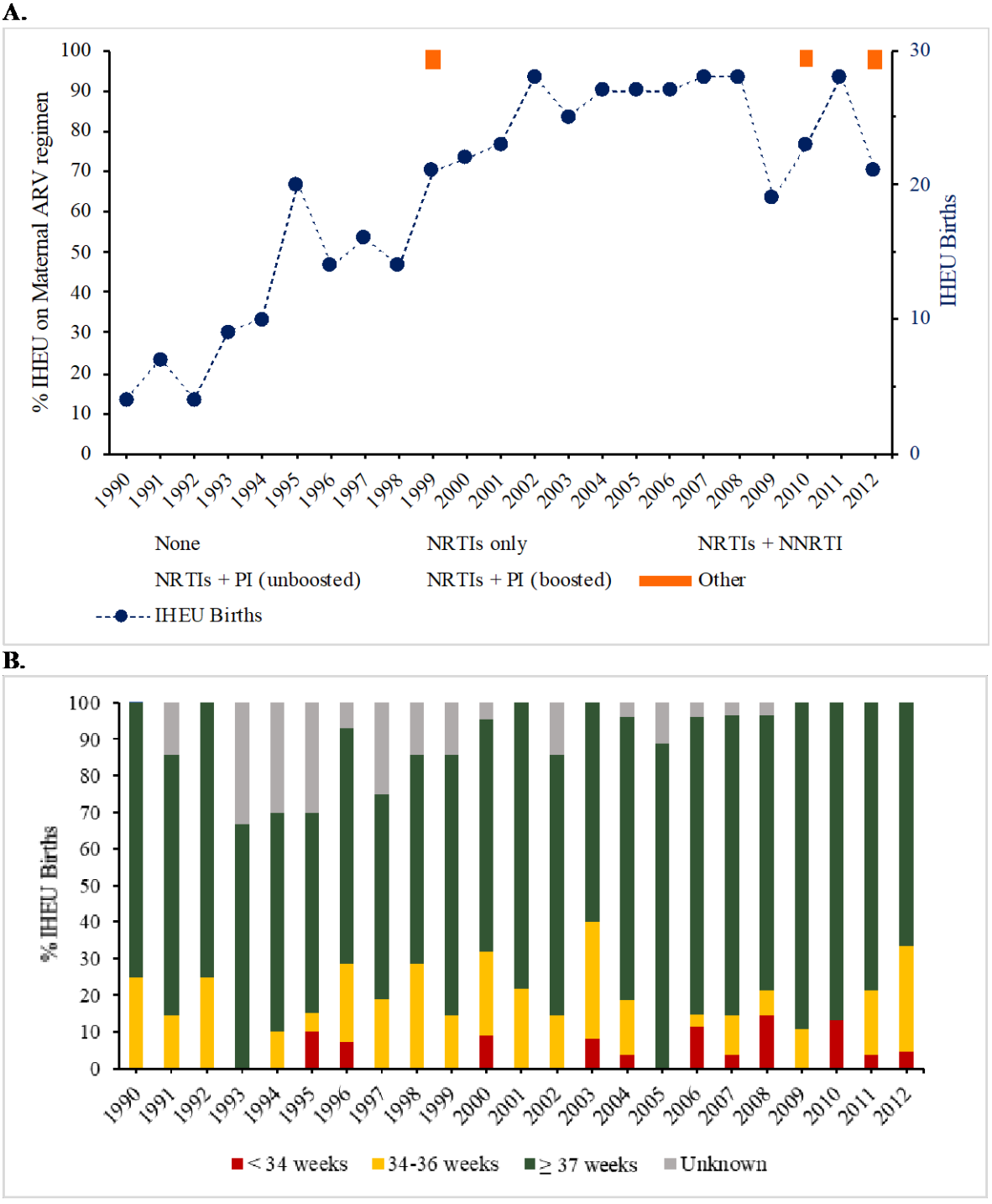
cocaine, methadone, solvents or marijuana at any point during pregnancy/whether provider indicated use of prescription, ‘other’, or unknown drugs as a risk factor to the pregnancy (2008 to 2012).

Table 2. Odds ratios of preterm birth in infants HIV-exposed uninfected adjusted for maternal substance use and/or smoking

Model 1: 1990-2012	**Total N (% PTB)**	**Unadjusted OR (95% CI)**	**Adjusted OR* (95% CI)**	**P-value**
HIV Exposure				
IHUU (reference)	1224 (7.0)	1	-	<0.0001
IHEU	411 (20.0)	3.58 (2.57, 5.00)	-	
Model 2: 2000-2012				
HIV Exposure				
IHUU (reference)	917 (6.9)	1	1	<0.0001
IHEU	309 (19.7)	3.33 (2.27, 4.91)	2.66 (1.73, 4.08)	

PTB: preterm birth; IHEU: infants HIV-exposed uninfected; IHUU: infants HIV-unexposed uninfected; OR: odds ratio; CI: confidence interval. *Adjusted for maternal substance use and/or smoking calculated from multivariable logistic regression. Other variables that were tested but not included in the model include infant sex, maternal age and alcohol identified as risk to pregnancy.

Figure 1. Antiretroviral regimens among infants HIV-exposed uninfected (IHEU) births (A) and cohort gestational age (B) from 1990 to 2012 in British Columbia



ART: antiretroviral therapy; IHEU: infants HIV-exposed uninfected; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor. N=411 IHEU births over study period.

Table 3. Preterm birth by antenatal antiretroviral regimen in infants HIV-exposed uninfected compared to matched infants HIV unexposed uninfected controls (1990-2012)

Maternal ART Exposure (IHEU only)	**<37 weeks GA N (%)**	**N**	**Odds Ratio (95% CI)**	**P-value**
Entire *Study period: 1990-2012*				
IHEU with **no** ART exposure (reference)	17 (29.8)	57	1	0.07
IHEU with **any** ART exposure	68 (19.2)	354	0.56 (0.30, 1.04)	
Pre 2000 *Study period: 1990-1999*				
IHEU with **no** ART exposure (reference)	8 (20.5)	39	1	0.68
IHEU with **any** ART exposure	14 (24.1)	58	1.23 (0.46, 3.29)	
Post 2000 *Study period: 2000-2012*				
IHEU with **no** ART exposure (reference)	9 (50.0)	18	1	0.003
IHEU with **any** ART exposure	55 (18.6)	296	0.22 (0.09, 0.60)	
Maternal ART Exposure/Regimen (IHUU matched controls vs. IHEU 1990-2012)	**<37 weeks GA N (%)**	**N**	**Odds Ratio (95% CI)**	**P-value**
None				
IHUU matched controls (reference)	13 (7.6)	171	1	0.0001
IHEU	17 (29.8)	57	5.17 (2.32, 11.51)	
NRTIs Only				
IHUU matched controls (reference)	9 (6.6)	137	1	0.007
IHEU	11 (23.9)	46	3.64 (1.42, 9.34)	
NRTIs + NNRTI				
IHUU matched controls (reference)	12 (6.2)	193	1	0.0004
IHEU	15 (22.7)	66	4.44 (1.95, 10.08)	
NRTIs + PI (unboosted)				
IHUU matched controls (reference)	26 (6.7)	386	1	0.007
IHEU	19 (14.7)	129	2.39 (1.28, 4.49)	
NRTIs + PI (boosted)				
IHUU matched controls (reference)	22 (6.8)	324	1	0.0001
IHEU	23 (21.1)	109	3.67 (1.95, 6.90)	

ART: antiretroviral therapy; IHEU: infants HIV-exposed uninfected; IHUU: infants HIV-unexposed uninfected; CI: confidence interval; GA: gestational age; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor. IHEU compared by ART exposure and to IHUU matched controls for each antiretroviral exposure class.

Table 4. Preterm birth by antenatal antiretroviral regimen and duration among infants HIV-exposed uninfected only

	Model 1: 1990-2012 (N=407)				Model 2: 2000-2012 (N=306)			
Maternal ART regimen	**IHEU ART Total N (% PTB)**	**IHEU No ART exposure Total N (% PTB)**	**Unadjusted OR (95% CI)**	**P-value**	**IHEU ART Total N (% PTB)**	**IHEU No ART exposure Total N (% PTB)**	**Adjusted OR[1] (95% CI)**	**P-value**
NRTIs only vs. None	46 (23)	57 (30)	0.68 (0.31, 1.76)	0.40	7 (und.[†])	17 (53)	0.16 (0.02, 1.69)	0.13
NRTIs + NNRTI vs. None	66 (23)		0.68 (0.31, 1.54)	0.34	59 (und.[†])		0.29 (0.09, 0.95)	0.04
NRTIs + PI (unboosted) vs. None	129 (15)		0.40 (0.19, 0.85)	0.01	114 (13)		0.16 (0.05, 0.49)	0.001
NRTIs + PI (boosted) vs. None	109 (21)		0.61 (0.31, 1.30)	0.19	73 (23)		0.28 (0.09, 0.83)	0.02
Antenatal ART regimen duration[2] (weeks)								
>0-13 vs. None	89 (25)	55 (30)	0.75 (0.36, 1.58)	0.46	62 (24)	17 (53)	0.25 (0.08, 0.78)	0.02
>13-26 vs. None	156 (17)		0.48 (0.24, 0.96)	0.04	130 (16)		0.16 (0.06, 0.49)	0.001
>26. vs. None	104 (16)		0.45 (0.04, 0.79)	0.04	97 (17)		0.19 (0.06, 0.58)	0.003

ART: antiretroviral therapy; IHEU: infants HIV-exposed uninfected; IHUU: infants HIV-unexposed uninfected; PTB: preterm birth; OR: odds ratio; CI: confidence interval; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor
[†]Cell sizes <6 undisclosed as per Population Data BC disclosure agreement. [1]Adjusted odds ratio calculated from multivariable logistic regression odds of preterm birth adjusted for maternal substance use and/or smoking, comparing ART exposed IHEU to ART unexposed IHEU. Other variables tested but not included in the model include sex, maternal age and alcohol identified as risk to pregnancy. [2]Any antenatal ART exposure, IHEU with unknown ART regimen duration data excluded (N<6).

Preterm Birth and Antiretroviral Exposure in Infants HIV-Exposed Uninfected

Supplementary Appendix

Section A1. HIV testing and gestational age assessment in British Columbia

1.1 Virologic testing for infants exposed to HIV at birth

In our cohort of infants who were HIV-exposed but uninfected (IHEU), no HIV-infected infants were included. Infants classified as HIV-exposed and uninfected in this provincial database are determined by virologic testing as per the guidelines for the care of pregnant women living with HIV as documented by the Society of Obstetricians and Gynaecologists of Canada.[1] Infants exposed to HIV in British Columbia are tested for HIV infection by a virological test at birth, at 4 weeks and at 3 to 4 months of age to determine HIV status. HIV RNA PCR (nucleic acid amplification test) is used for additional testing for infants at high risk of vertical transmission. Two negative tests after 4 weeks of age and the other at least 4 weeks after the end of prophylactic antiretrovirals excludes HIV infection. Additionally, a confirmatory HIV EIA test is also performed after 18 months of age to document seroreversion after the clearance of maternal antibodies.[1]

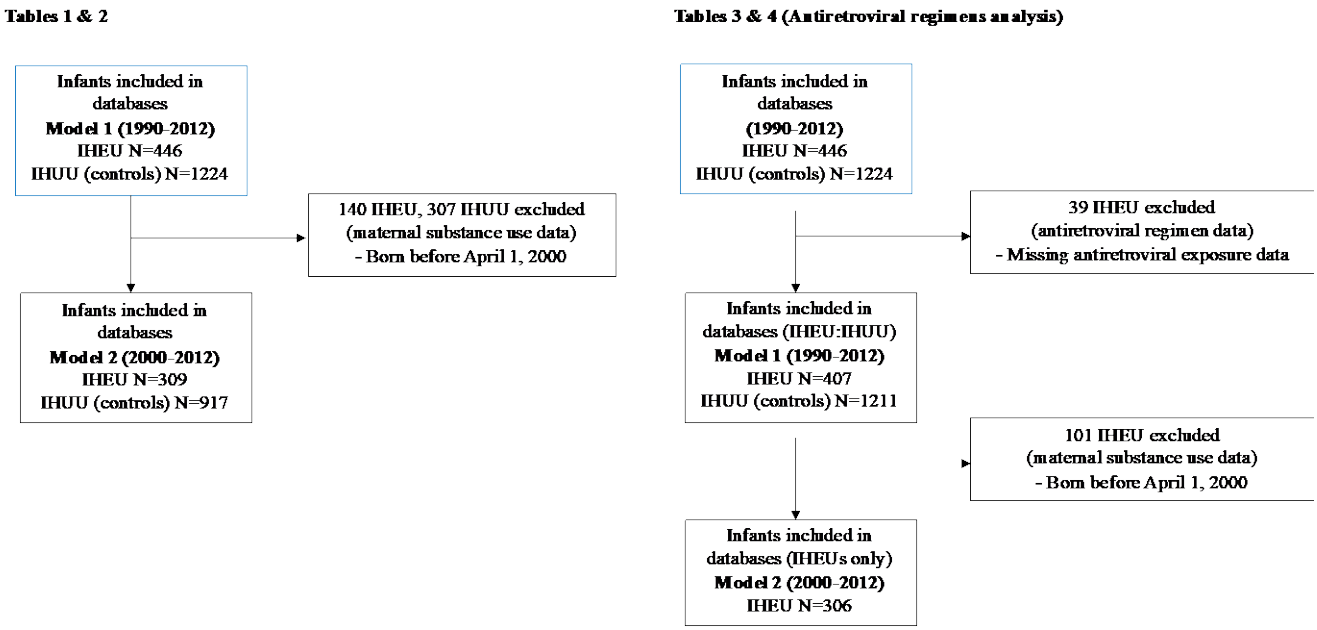
1.2 Gestational age assessment

The current standard for routine gestational age assessment in BC is via first trimester ultrasound dating.[2] Gestational age in this study was measured from the first day of the last menstrual period and expressed in completed weeks (e.g. Events which occurred 280-286 days after the onset of the last normal menstrual period were considered to have occurred at 40 weeks of gestation). Preterm birth was classified as less than 37 weeks of gestation.

Table A1. Antiretroviral Drugs Used During Pregnancy for Mothers Living with HIV in British Columbia (1990-2012)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
Zidovudine (AZT)
Didanosine (ddI)
Zalcitabine (ddC)
Stavudine (d4T)
Lamivudine (3TC)
Abacavir (ABC)
Tenofovir (TVF)
Emtricitabine (FTC)
Integrase Inhibitors (IIs)
Raltegravir (RAL)
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
Nevirapine (NVP)
Efavirenz (EFV)
Etravirine (ETR)
Protease Inhibitors (PIs)
Indinavir (IDV)
Ritonavir (RTV) alone or as a booster
Saquinavir (SQV)
Nelfinavir (NFV)
Lopinavir (LPV)
Darunavir (DRV)

Figure A1. Study sample and analysis flow chart



IHEU: ARV: antiretroviral; Infants HIV-exposed uninfected; IHUU: Infants HIV-unexposed uninfected.

References

1. Money D, Tulloch K, Boucoiran I, Caddy S, Yudin MH, Allen V, et al. Guidelines for the Care of Pregnant Women Living With HIV and Interventions to Reduce Perinatal Transmission: Executive Summary. J Obstet Gynaecol Canada. 2014;36(8):721–34. Available from: http://dx.doi.org/10.1016/S1701-2163(15)30515-6.

2. Butt K, Lim K, Bly S, Cargill Y, Davies G, Denis N, et al. Determination of Gestational Age by Ultrasound. J Obstet Gynaecol Canada. 2014;36(2):171-181.