# Investigation of Factors Associated with Spontaneous Preterm Birth in Pregnant Women Living with HIV

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## Abstract

**Objective:** To investigate factors contributing to preterm birth (PTB), including cART use and clinical and social determinants of health, in women living with HIV (WLWH) from British Columbia, Canada.

**Design:** Retrospective observational cohort.

**Methods:** We investigated the effect of cART use and other clinical and demographic factors on spontaneous PTB (sPTB) rates (<37 weeks gestational age) among 631 singleton pregnancies between 1997-2018. Exposure to cART was modelled in comparison to no exposure, exposure in the first trimester, and between regimens. Differences in sPTB risk were estimated using time-dependent Cox's proportional hazards models.

**Results:** Overall, the sPTB rate was 16%. Cumulative cART use was associated with lower risk of PTB (Wald test p=0.02; HR=0.98, 95% CI=0.96-0.99) and specific cART regimens were not associated with increased risk of sPTB. Exposure in the first trimester was not associated with sPTB and for each week of cART exposure, the risk of sPTB decreased by 2%. In a multivariable model, HIV viral load and substance use remained associated with risk of sPTB, but not cART exposure.

**Conclusions:** The sPTB rate among pregnant WLWH was more than three times higher than in the general population. However, sPTB was not related specifically to use of cART; in fact, cART appeared to reduce the risk of sPTB. Uncontrolled HIV replication and substance use were associated with increased risk of sPTB among pregnant WLWH. This emphasizes the important role of prenatal care, access to cART, and smoking cessation and harm reduction to reduce the risk of sPTB in WLWH.


**Keywords:** HIV, preterm birth, women, antiretroviral therapy

## Introduction

Advances in the care and clinical management of pregnant women living with HIV (WLWH), particularly the use of combination antiretroviral therapy (cART) during pregnancy, have been highly successful in reducing the rate of perinatal transmission, from approximately 25% in the absence of cART to <1% with use of cART during pregnancy [1-3].

Potential adverse outcomes of cART use during pregnancy have been reported, both in the mother and the infant exposed *in utero* [4-9]. Of particular concern has been an increased rate of preterm birth (PTB) and its associated health implications for the infant [10-12]. However, studies on the associations between cART regimens and risk of PTB have produced conflicting results. A comprehensive review of 27 studies (1986-2015) from across the globe found that only 59% of these studies (16/27) reported a positive association between ART use and PTB (RR/OR 1.2-3.4) while the remaining 11 studies did not show an association between ART use and PTB [13]. Additionally, a meta-analysis of 14 studies (n=11 224) found that ART exposure during pregnancy was not associated with an increased risk of PTB (OR 1.01; 95% CI 0.76-1.34) [14].

With frequent use of ritonavir-boosted protease inhibitors (boosted PIs) in pregnancy, more recent studies have focused on exploring whether these specific regimens increase the risk for PTB. A study of WLWH in France found a higher PTB rate with boosted compared to non-boosted PI exposure (adjusted HR 2.03; 95% CI 1.06-3.89, p=0.03) [9]. However, this was mainly in the case of iatrogenic rather than spontaneous PTB. A Canadian study also found higher PTB risk with boosted compared to non-boosted PI therapy, even after adjusting for known risk factors for PTB (adjusted OR 2.17; 95% CI 1.05-4.51) [15]. Exposure to some PIs

may increase estradiol levels, such as unboosted atazanavir, but the impact varies between PIs and is diminished when boosted as ritonavir causes a decrease in estradiol [16]. An increase in estradiol has been purported to result in an increased risk of PTB [17].

Given the disparities in study findings, concern remains about the effect of cART in pregnant WLWH. In particular, there is concern about the effects of boosted PI-based regimens on PTB. In addition, due to concern about PI-based regimens in pregnancy, there was a shift to integrase inhibitor regimens which has resulted in significant numbers of pregnant women on dolutegravir containing regimens [18, 19]. In light of data suggesting potentially higher risk of neural tube defects in infants born to mothers on dolutegravir in the first trimester, there is an even more urgent need to determine if returning to PI-based regimens will result in increased preterm birth rates [20-23]. Overall, this concern has reemphasized the value of being able to prescribe older medications with a longer track record of safety in pregnancy. In addition, given the universally observed high PTB rates in WLWH, it is important to understand if there are other factors contributing to this. The objectives of this study were to 1) Determine rates of sPTB in a population based cohort 2) Determine if the use of any cART during pregnancy was related to an increased risk of spontaneous PTB relative to no cART 3) Compare the rates of spontaneous PTB in WLWH exposed to different cART regimens at different times in pregnancy; and 4) Identify additional clinical and demographic characteristics that are associated with PTB in this population.

## Methods

*Study Population*

Data for this study comes from a provincial surveillance database, which houses data on all women known to be pregnant and living with HIV who delivered in British Columbia (BC), Canada. Clinical, demographic, and behavioural data were abstracted from clinical charts and entered annually into this surveillance database. This database has received ethical approval from the University of British Columbia Children's and Women's Research Ethics Board (Approval Number H10-01186) and was supported through infrastructure from the Women's Health Research Institute at BC Women's Hospital and Health Centre.

Between January 1, 1997 and December 31, 2018, there were 631 singleton pregnancies (from 400 pregnant WLWH). Of these, there were 100 spontaneous or therapeutic abortions, four ectopic pregnancies, one fetal demise due to maternal trauma, 10 pregnancies that were lacking information about gestational age at delivery, and 12 pregnancies with no ARV data, leaving 516 eligible pregnancies for analysis. Gestational age at delivery was determined by ultrasound in the first and/or second trimester.

*Statistical Analysis*

All statistical analyses were carried out in R v.3.4.2 [24].

*Analysis for preterm birth risk and exposure to any cART*

We used the timing of prescription of cART in pregnancy to construct a time-dependent Cox's proportional hazards model to look for differences in the risk of delivering preterm between women who were exposed to any cART (all types combined) during pregnancy vs. those who were unexposed. Women were coded as not exposed to any cART until they were prescribed cART, or if they were on cART at conception they were coded as exposed from the start. They were thereafter coded as exposed until week of delivery and/or censored at 37 completed weeks

of gestation as they could then no longer deliver preterm. Women in British Columbia were prescribed antiretrovirals according to provincial and national guidelines of the time period, which varied significantly over time [25, 26]. Most recently, most women are prescribed cART at the time of diagnosis and recommended to be on lifelong therapy. Some women do not access care or are diagnosed later in pregnancy, resulting in variable exposures.

To investigate potential dosage effects, we calculated a time-varying cumulative exposure variable that indicated the number of weeks of exposure to any cART for each week of gestation, and used this in a Cox's proportional hazards model as above. Finally, to investigate potential early pregnancy effects we also examined exposure to cART in the first trimester vs. none using a Cox's proportional hazards model.

*Analysis for preterm birth risk and exposure to cART regimen types*

We used the same time-dependent Cox's model as above, but examined the exposure to each cART regimen type separately (NNRTI, PI, ritonavir boosted PI, or Integrase Inhibitor). Classificiation of regimen types and ARVs are available in supplementary Table S1. Twenty pregnancies had exposure to mono/dual/triple NRTI therapy. These were excluded from this analysis as there were too few to properly estimate hazards.

*Analysis for preterm birth and demographic factors/social determinants of health*

Non time-varying covariates were included in the time-dependent Cox's proportional hazards model as possible predictors of PTB in addition to exposure to any cART. These additional variables were maternal ethnicity (White, Aboriginal, African/Caribbean/Black, Other/Unknown) [27], maternal age at delivery (years) [28], previous PTB (first pregnancy vs. no previous preterm, or at least one previous preterm) any substance use in pregnancy (none vs.

any nicotine only, any alcohol, crack/cocaine, and/or heroin without nicotine, and nicotine plus at least one of alcohol, crack/cocaine, and/or heroin) [27, 29, 30], HIV viral load at delivery (suppressed vs. unsuppressed [>50 copies/mL from 1999 onwards, >400 copies/mL in 1997-1998] vs. unknown), and presence of hepatitis C virus (HCV) antibodies [31] (reactive vs. non-reactive vs. unknown). All substance use variables were self-reported and not recorded in a time-varying fashion throughout pregnancy.

We used the 'MuMIn' package in R to run information theoretic based model selection procedures [32] starting with a model containing all of the variables listed above. We selected a final model with a subset of the variables that had the lowest $AIC_c$. We report both the univariable hazard ratios for each variable, and the adjusted hazard ratios for those variables in the final selected model.

*Sensitivity analyses*

We conducted two additional sensitivity analyses to further explore the relationship between cART and PTB. 1) We removed those women with no exposure to cART before 37 weeks as they may represent a different sub-population who either had barriers to accessing prenatal care earlier in pregnancy, or who were diagnosed with HIV during late pregnancy (441 pregnancies and 60 spontaneous PTB remaining in the analyses). 2) We removed those women who self-reported any use of heroin, alcohol, or cocaine during pregnancy, as again they may represent a different population with different risk factors for PTB (294 pregnancies and 26 spontaneous PTB remaining in the analysis). For both of the sub-groups above we then investigated if exposure to cART, or variables chosen in the model selection procedure above were still associated with PTB using time-dependent Cox's proportional hazard models.

All models met the assumption of proportional hazards as assessed using the 'cox.zph' function in the *survival* package in R.

*Sample size and power*

There is no consensus on the best method for estimating power in the context of time-varying covariates in a Cox model. Here, we have used calculations for non time-varying models bearing in mind that these estimates may not be accurate. Using the equations in Schoenfield 1983 [33], we estimated that with our 74 cases of PTB and a rate of non-cART use of 7.5%, we would have 80% power to detect a HR of 3.2 for cART exposure leading to increased risk of PTB, or a HR = 0.31 for cART exposure leading to a reduced risk of PTB, both of which are moderate effect sizes. However, given that the proportion of pregnancies with non-cART use is more than 7.5% earlier in pregnancy, it is likely that our realized power is higher than suggested by these calculations, as the time-varying nature of cART exposure was taken into account.

## Results

*Population*

There were 105 PTB (<37 weeks) in the total cohort of 516 (20.3%) compared to an overall rate of PTB in BC of 10.6% [34]. With the removal of iatrogenic PTB (i.e. PTB triggered by the care provider due to maternal or fetal health concerns such as pre-eclampsia, intrauterine growth restriction, or other maternal or fetal indications), there were 74 spontaneous PTB out of 477 pregnancies meeting inclusion criteria (15.5%), three times higher than the BC population (5.3%) [34]. Of these 74 spontaneous PTB, 30 (41%) were <35 weeks gestation and the remaining 44 (59%) were between 35 and 36+6 weeks of gestation. The median gestational age

was 35 weeks (range = 24.1 to 36.9), with seven very preterm deliveries prior to 32 weeks. Thirty-six of the pregnancies (7.5%) had no exposure to cART prior to delivery or 37 weeks gestation (Table 1), and 209 (44%) had exposure to cART in the first trimester (either on cART at conception or started in the first trimester). The median length of exposure in weeks was 19 (IQR = 13 to 36). Exposure to different regimen types varied over the course of the data collection period with more recent pregnancies more likely to be treated with boosted PIs or integrase inhibitors, however no discernable pattern was seen in the rate of PTB (Figure 1).

Ethnicity, HCV antibody presence, nicotine, alcohol, heroin, crack/cocaine use, and HIV viral load near delivery did differ between the groups while other factors did not (Table 1). Most women delivered at 38 weeks. For those on cART before 37 weeks, the median gestational age at cART start was 18 weeks (IQR = preconception to 22 weeks).

*Spontaneous PTB risk and exposure to cART*

The risk of sPTB was not related to any cART exposure vs. no cART exposure (Wald test p=0.07). The Hazard Ratio (HR) for exposure vs. none was 0.54 (95% CI = 0.29 to 1.04), which suggests that the risk of preterm birth was approximately 46% lower for those with any exposure to cART, although it does not meet a p-value threshold of 0.05. When cART exposure was modeled as cumulative weeks of exposure during pregnancy, there was a significant relationship between length of exposure (in weeks) and the hazard of preterm delivery (Wald test p=0.02; HR = 0.98, 95%CI = 0.96 to 0.99) with longer exposure showing a lower the risk of preterm delivery: for every increase in one week of exposure to cART, the risk of preterm delivery went down by approximately 2% (Figure 2). There was no relationship between exposure to cART in

the first trimester vs. no exposure and preterm birth (Wald test p = 0.30; HR = 0.77, 95% CI = 0.48-1.23).

*PTB and exposure to individual cART regimens*

cART regimen type was not related to risk of spontaneous PTB overall (likelihood-ratio test p = 0.23). For specific cART regimens, NNRTI and boosted PIs vs. none were not significantly associated. However, consistent with any cART exposure, all ART regimen types showed trends in the direction of reduced risk relative to no exposure. In support of this, a PI regimen alone appeared to reduce the risk of PTB compared to no exposure (0.42, 95% CI = 0.19 to 0.94).

*PTB and clinical and social determinants of health*

Maternal age (p = 0.21) and history of preterm delivery (p = 0.40) were not associated with PTB. However, there was a significant relationship between spontaneous PTB and maternal ethnicity ($p < 0.0001$), positive HCV antibody status ($p < 0.0001$), unsuppressed HIV viral load near delivery (p = 0.002), and substance use ($p < 0.0001$; Table 2). For substance use, post-hoc pairwise comparisons with p-value correction suggested that all three substance use categories had significantly higher risk of PTB compared to no substance use (all $p < 0.001$), however none of the three substance use categories was significantly different from any of the others (all p > 0.25). Nonetheless, there appears to be a potential synergistic association with nicotine whereby substances without nicotine had the lowest HR, followed by nicotine alone, and then finally substances with nicotine with the highest HR (Table 2). Unsuppressed HIV viral load near delivery and substance use remained associated with increased risk of preterm delivery in the

final model after multivariable model selection using $AIC_c$, although the confidence interval for unsuppressed HIV VL crossed 1. cART exposure and unsuppressed HIV viral load are directly linked and are therefore too collinear to remain in a model together.

*Sensitivity Analyses*

For those women with some exposure to cART prior to 37 weeks, there was no significant association between total cumulative exposure (HR = 0.99, 95%CI = 0.96 to 1.01, Wald test p=0.20) and PTB, although the trend continued towards a reduction in PTB with cART exposure. Substance use remained significantly associated with PTB (HR for without nicotine = 4.73, 95%CI = 1.82 to 12.30, HR for nicotine along = 7.14 (3.05 to 16.73), and HR for other substances with nicotine = 8.78 (3.98 to 19.35), likelihood ratio test $p < 0.0001$) in a multivariable model. Likely due to cART exposure, the relationship with HIV VL was reduced and no longer remains significant (HR for viremic vs. undetectable = 1.46, 95%CI = 0.83 to 2.55, likelihood ratio test p = 0.28).

For women who did not self-report any use of heroin, alcohol, or cocaine during pregnancy, there was no significant association between PTB and total cumulative exposure to cART (HR = 0.99, 95%CI = 0.96 to 1.03, Wald test p=0.73), or any cART vs. none (HR = 0.41, 95%CI = 0.10 to 1.73, Wald test p=0.22). Estimates did continue to show a trend to reduced PTB rate similar to the full dataset model. When HIV VL near delivery and nicotine use were included in a model together, nicotine use was associated with PTB (HR = 8.02, 95%CI = 3.47 to 18.54, likelihood ratio test $p < 0.0001$), and the relationship with HIV VL became non-significant (HR for viremic vs. undetectable = 1.63, 95%CI = 0.60 to 4.44, likelihood ratio test p = 0.08).

## Discussion

This study presents a real world, population-based analysis of outcomes for pregnant WLWH and shows a high preterm birth rate compared to the baseline population rate (15.5% vs. 5.3%) [34]. Iatrogenic PTB was not included in our analysis to focus on the role of cART in spontaneous PTB. PTB rates in pregnant WLWH are consistently reported to be well above national population rates all over the world [10, 35-37]. Our study continues to show a three-fold increase in PTB compared to the general population. The reasons speculated for elevated PTB rates in pregnant WLWH have included the use of cART initiated before pregnancy with exposure in the first trimester during placentation and embryogenesis, cART during pregnancy [37], and possibly the use of regimens containing PIs [10]. However, few studies are able to account for population differences between WLWH and women without HIV [36], history of prior PTB [10, 38], and substance use including alcohol and nicotine use [38]. The very nature of studying PTB and the requirement for large prospective studies makes studying the influence of cART regimens on PTB challenging.

In this cohort we did not find elevated risk of spontaneous PTB associated with cART exposure when using a time-varying analysis. In fact, we found the opposite including a possible protective association of cART reducing risk of PTB and a 2% reduction in PTB risk per week of exposure to cART. The women in this cohort were exposed on average to 17 weeks of cART prior to delivery. In addition, use of cART in this setting also represents the ability to access prenatal care, social resources, and possible engagement in harm reduction strategies for substance use. Once other co-factors were adjusted for in the multivariable model, the

association between cumulative cART exposure compared to no cART was no longer significant. However, it is difficult to unlink cART exposure and HIV viral load at delivery, as one is not achievable without the other and both are likely along the causal pathway. Unsuppressed HIV viral load at delivery and substance use remained associated with spontaneous PTB in the multivariable model. Smoking and unsuppressed viral load have been associated with placental mitochondrial toxicity and thus may be a convergent pathway for increased risk of spontaneous PTB in WLWH [6]. Regardless, in any analysis and modelling, cART did not increase the risk of PTB. In addition, our findings emphasize smoking cessation and harm reduction strategies, which are feasible to implement and may prove even more important in pregnancy.

Our study findings are consistent with a 2007 meta-analysis, where use of cART was not found to be associated with an increased risk of PTB [14]. These findings are in direct contrast to many other studies, which did find an association between cART use and an increased risk of PTB [39]. However, the majority of these studies continue to not differentiate between spontaneous and iatrogenic PTB and in many cases did not have extensive information on other co-factors for preterm birth [40]. One factor potentially associated with PTB that we did not have data on was cervical length, however, this is not a routine screening assessment in BC, as our currently national guidelines do not recommend the routine assessment of cervical length. In addition, systematic differences in population characteristics, prescribing regimens and access to prenatal care may also be contributing to the different outcomes observed. Our results also contrast with studies which have reported higher PTB rates with ritonavir boosted PI exposure compared to non-boosted PI exposure and despite our small numbers, we were powered to determine

moderate effects [9, 15]. The differentiation of iatrogenic and spontaneous PTB is critical. Our results align with other studies that have examined spontaneous PTB separately, which found no association between cART use and spontaneous PTB [41, 42]. This rigorous approach was designed to evaluate if there was a plausible biologic effect on the initiation of spontaneous PTB as a toxic effect of exposure of the pregnant woman and the fetal/placental unit to these compounds in utero, such as an impact on progesterone metabolism or estradiol levels. In a future analysis we will look at our iatrogenic preterm births to determine whether any were plausibly related to cART toxicity.

Limitations of our study include its observational retrospective design and the inherent challenge that the standards of care for pregnant WLWH have changed over the years and the cART regimens have shifted as well. However, with the more recent concerns regarding dolutegravir containing regimens, a shift back to boosted PI based regimens in some regions make these findings even more important. The advantage of setting this study in BC is that all care being delivered to pregnant women living with HIV and their children is coordinated through a women and family centred multidisciplinary HIV clinic (The Oak Tree Clinic, BC Women's Hospital, Vancouver, BC). This clinic provides direct comprehensive HIV care addressing comorbidities as well as maternity and HIV care. Women cared for elsewhere in the province receive distance support provided by clinic-based experts on the multidisciplinary team (www.bcwomens.ca/our-services/specialized-services/hiv-care-for-women-families).

*Conclusions*

This study provides a comprehensive cohort analysis of WLWH during pregnancy exposed to cART accounting for different types of PTB, maternal characteristics, clinical history and social determinants of health. We showed that the highest risk for PTB came from unsuppressed viral load at delivery and substance use exposure. Individual cART regimens including boosted PIs did not increase the risk of PTB. cART overall reduced the risk of PTB and is required to achieve a suppressed viral load at delivery in order to prevent vertical transmission to the infant. Implementation of smoking cessation and harm reduction programs is an important intervention to consider during pregnancy to reduce the risk of spontaneous PTB associated with exposure to substances.

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## Figure Legends

**Figure 1.** Number of women taking different treatment types between 1997 and 2015. Main regimen is defined as the regimen taken closest to delivery if the cumulative time exposed was > 4 weeks.

**Figure 2.** Percent of deliveries preterm by weeks of cART exposure among the 74 preterm births.