Risk factors for pre-term birth in a Canadian cohort of HIV-positive women: role of ritonavir boosting?

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Abstract

Background: The risk of pre-term birth (PTB) associated with the use of protease inhibitors (PIs) during pregnancy remains a subject of debate. Recent data suggest that ritonavir boosting of PIs may play a specific role in the initiation of PTB, through an effect on the maternal–fetal adrenal axis. The primary objective of this study is to compare the risk of PTB among women treated with boosted PI versus non-boosted PIs during pregnancy.

Methods: Between 1988 and 2011, 705 HIV-positive women were enrolled into the Centre Maternel et Enfantile sur le SIDA mother–infant cohort at Centre Hospitalier Universitaire Sainte-Justine in Montreal, Canada. Inclusion criteria for the study were: 1) attendance at a minimum of two antenatal obstetric visits and 2) singleton live birth, at 24 weeks gestational or older. The association between PTB (defined as delivery at <37 weeks gestational age), antiretroviral drug exposure and maternal risk factors was assessed retrospectively using logistic regression.

Results: A total of 525 mother–infant pairs were included in the analysis. Among them, PI-based combination anti-retroviral therapy was used in 37.4%, boosted PI based in 24.4%, non-nucleoside reverse transcriptase inhibitor (NNRTI) or nucleoside reverse transcriptase inhibitor based in 28.1%, and no treatment was given in 10.0% of cases. Overall, 13.5% of women experiencing PTB. Among women treated with antiretroviral therapy, the risk of PTB was significantly higher among women who received boosted versus non-boosted PI (OR 2.01, 95% CI 1.02–3.97). This remained significant after adjusting for maternal age, delivery CD4 count, hepatitis C co-infection, history of previous PTB, and parity (aOR 2.17, 95% CI 1.05–4.51). There was no increased risk of PTB with the use of unboosted PIs as compared to NNRTI- or NRTI-based regimens.

Conclusion: While previous studies on the association between PTB and PI use have generally considered all PIs the same, our results would indicate a possible role of ritonavir boosting as a risk factor for PTB. Further work is needed to understand the pathophysiologic mechanisms involved, and to identify the safest ARV regimens to be used in pregnancy.

Keywords: pre-term birth; mother-to-child prevention; HIV transmission; antiretroviral drugs; protease inhibitors.

Introduction

The risk of pre-term birth (PTB) associated with the use of protease inhibitors (PIs) in pregnancy remains the subject of intense debate. While a number of studies from Europe and the United States have found an increased risk of PTB associated with PI use [1–4], further studies have not been replicated in North American cohort studies [5–9], or in a meta-analysis on the subject [10]. The conflicting reports and the difficulties in establishing such an association are in part due to the heterogeneity of comparison groups (comparing PI use to no treatment and or multiple different treatments), heterogeneity of populations studied and multiple confounders that have been inconsistently adjusted for in previous studies [11–13]. As a result, the question as to a link on PI use and prematurity remains unresolved, and in the absence of definitive evidence to support or refute this potential association, North American guidelines continue to recommend PI-based combination antiretroviral therapy (cART) as the preferred treatment of HIV-1-positive women during pregnancy [14].

The use of PIs during pregnancy has changed significantly over time, as newer drugs were approved for use in HIV-positive pregnant women, and data became available on their safety and efficacy in preventing vertical transmission. Nelfinavir (NFV) was the preferred PI in pregnancy until 2006, due to its tolerability and low side-effect profile [15]. This changed abruptly in 2007 after NFV was recalled from both United States and European markets for concerns regarding the presence of a potential carcinogenic element, ethyl methanesulfonate (EMS) in its formulation [16]. Ritonavir-boosted lopinavir (LPV/r) then became the preferred PI used in pregnancy [17], and NFV, even after safety issues regarding EMS were resolved, became an “alternative” choice to be used under special circumstances [18]. These changes were reflected in prescribing patterns in both North America and Europe, with an increased use of LPV-r as the preferred...
Pi for the treatment of HIV-positive pregnant women after 2007 [19].

Previous studies on PTB have generally considered PIs as a single group for comparison against no treatment, non-nucleoside reverse transcriptase inhibitor (NNRTI) or nucleoside reverse transcriptase inhibitor (NRTI) based regimens, not distinguishing whether they were used with or without ritonavir (RTV) boosting [20]. However, RTV, used individually or as a boosting agent, has its own unique side-effect profile. It is a potent inhibitor of cytochrome CYP3A4, which is implicated in the regulation of the adrenal axis [21]. Fetal signals coming from the hypothalamic–pituitary–adrenal axis are suspected to play a fundamental role in the initiation of spontaneous labour, through elevations in cortisol levels are suspected to play a fundamental role in the initiation of spontaneous labour, through elevations in cortisol levels.
was 13.5%. In the unadjusted analysis, the use of boosted PI regimens was associated with a significantly increased risk of PTB compared to non-boosted PI regimens (OR: 2.01, 95% CI 1.02–3.97), while no increased risk was observed with the use of NNRTI/NRTI-based regimens as compared to non-boosted PI-based therapy (OR: 0.81, 95% CI 0.40–1.66). The highest risk of PTB was seen among women receiving no ARV treatment when compared to unboosted PIs (OR: 2.70, 95% CI 1.85–3.97), while no increased risk was observed with the use of NNRTI/NRTI-based regimens as compared to non-boosted PI-based therapy (OR: 0.81, 95% CI 0.40–1.66). Among untreated women (n = 91) (18.7%), with no cases of PTB seen among TPV/r (n = 4) or FPV/r (n = 4) treated women. These differences were not statistically significant (p = 0.33). Among unboosted PIs, the highest risk of PTB was among NFV-treated women (n = 161) (11.8%), followed by IDV (n = 18) (11.1%) and SQV (n = 16) (6.3%). These differences were not statistically significant (p = 0.83). Among NNRTI backbone combinations used, there was no increased risk of PTB when comparing 3TC-, ddl- or d4T-based regimens to AZT monotherapy. Other significant risk factors associated with PTB on univariate analysis included parity [multiparous with a history of previous pre-term delivery (PPTD) vs. nulliparous, OR: 15.19, 95% CI 1.85–125.8], and hepatitis C co-infection (OR: 3.20, 95% CI 1.25–8.19).

The multivariable analysis was restricted to only those women with complete data on all variables assessed, and after excluding those women with missing data on the following variables (age = 4, delivery CD4 count = 23, ethnicity = 35 and parity = 2), this analysis was conducted on 525 of the 589 patients. The association between type of PI (boosted vs. unboosted) and risk of PTB remained significant after adjusting for maternal age, delivery CD4 count, parity, hepatitis C status and ethnicity (aOR 2.17, 95% CI 1.02–4.51). Other significant risk factors remained parity (multiparous with a history of PTB vs. nulliparous, aOR 13.28, 95% CI 1.89–93.5) and hepatitis C co-infection (OR: 4.66, aOR 1.71–12.75).

Discussion

In this single centre retrospective study, we identified a number of risk factors for PTB among HIV-positive women delivering in Canada, including type of antiretroviral therapy (ART), previous history of PTB, and hepatitis C co-infection. While untreated HIV infection is a well-known risk factor for PTB [24], among women treated with ART, we found an increased risk of PTB among those who received boosted versus unboosted PI-based regimens during pregnancy (aOR 2.04, 95% CI 1.02–4.14). Our findings of increased PTB associated with RTV boosting are consistent emerging findings from both developed and developing world settings. A study by the Agence Nationale de Recherche sur le Sida (ANRS) of France showed an increased rate of PTB among women treated with boosted versus unboosted PI (aHR 2.03, 95% CI 1.06–3.89), more specifically with respect to spontaneous delivery [25]. Our PTB rate of 19.3% among

Table 1. Maternal characteristics by treatment group

| Maternal characteristics | N     | Boosted PI | Unboosted PI | Other | None | ρa | ρb |
|--------------------------|-------|------------|--------------|-------|------|----|----|
| Year of delivery         |       |            |              |       |      |    |    |
| 1988–1996                | 107   | 0 (0)      | 0 (0)        | 59 (35.5) | 48 (81.4) | <0.001 | <0.001 |
| 1997–2006                | 318   | 18 (12.5)  | 196 (89.1)   | 97 (58.4) | 7 (11.9) |    |    |
| 2007–2011                | 164   | 126 (87.5) | 24 (10.9)    | 10 (6.0) | 4 (6.8) |    |    |
| Age (years)              |       |            |              |       |      |    |    |
| < 25                     | 72    | 9 (6.3)    | 24 (11.0)    | 22 (13.3) | 17 (29.3) | <0.001 | 0.13 |
| 25–35                    | 367   | 86 (59.7)  | 137 (62.8)   | 108 (65.5) | 36 (62.1) |    |    |
| > 35                     | 146   | 49 (34.0)  | 57 (26.2)    | 35 (21.2) | 5 (8.6) |    |    |
| CD4 count (cells/mm³)    |       |            |              |       |      |    |    |
| < 200                    | 58    | 16 (11.9)  | 18 (8.6)     | 18 (11.2) | 6 (11.3) | 0.18 | 0.58 |
| 200–350                  | 101   | 19 (14.2)  | 33 (15.8)    | 40 (24.8) | 9 (17.0) |    |    |
| > 350                    | 398   | 99 (73.9)  | 158 (75.6)   | 103 (64.0) | 38 (71.7) |    |    |
| Parity                   |       |            |              |       |      |    |    |
| Multip with PPTD         | 7     | 4 (2.8)    | 1 (0.45)     | 1 (0.6) | 1 (1.7) |   | <0.001 |
| Multip without PPTD      | 107   | 47 (32.9)  | 35 (15.9)    | 22 (13.3) | 3 (5.1) |    |    |
| Nulliparous              | 474   | 92 (63.3)  | 184 (83.6)   | 143 (86.1) | 55 (93.2) |    |    |
| Hepatitis C              |       |            |              |       |      |    |    |
| Negative                 | 557   | 135 (93.8) | 201 (91.4)   | 163 (98.2) | 58 (98.3) | 0.015 | 0.40 |
| Positive                 | 32    | 9 (6.25)   | 19 (8.64)    | 3 (1.70) | 1 (1.69) |    |    |
| Race                     |       |            |              |       |      |    |    |
| Black                    | 379   | 103 (79.2) | 130 (62.8)   | 108 (65.9) | 38 (64.4) |   | <0.001 |
| Caucasian                | 140   | 20 (15.4)  | 58 (28.0)    | 42 (25.6) | 20 (33.9) |    |    |
| Other                    | 41    | 7 (5.40)   | 19 (9.2)     | 14 (8.54) | 1 (1.70) |    |    |

*aChi-square test across all categories; *bChi-square test comparing only boosted to unboosted PIs.
women treated with boosted PIs is also similar to that found in the Mma Bana study (21.4%) from Botswana, where all women in the PI treated arm received LPV-r during pregnancy [26]. In light of previous conflicting reports between North American and European cohorts, the concordance of our findings to the French perinatal cohort is reassuring.

In the present study, the use of unboosted PIs was not associated with an increased risk of PTB compared to NRTI- or NNRTI-based regimens. Interestingly, in a subset of previous studies (including one from our own centre) in which the type of PI used was reported, no association between PI use and PTB was seen in studies where NFV was reported as the primary PI used [7,27/C1 29], while those in which LPV/r was used preferentially have demonstrated an increased risk of PTB [9,25,27]. We hypothesize that in the majority of studies conducted prior to 2007, unboosted PIs may have been used preferentially, thereby explaining the lack of association seen with PIs and PTB in these earlier studies. Subsequent attempts at pooling the data, considering boosted and unboosted PIs together, may have contributed to the conflicting results.

While the mechanisms underlying the potential association between RTV boosting and PTB have yet to be fully understood, the observed differences in risk may be related to the timing of exposure and the specific PIs used. Further research is needed to elucidate the role of different PIs in the timing of PTB and to understand the underlying biological mechanisms.

### Table 2. Maternal characteristics and risk of pre-term delivery

| Predictor variable | Pre-term N (%) | Term N (%) | Unadjusted OR | p      | Adjusted OR | p      |
|--------------------|----------------|------------|---------------|--------|-------------|--------|
| Total              | 71 (13.5)      | 454 (86.5) |               |        |             |        |
| Year of delivery   |                |            |               |        |             |        |
| 1988–1996          | 17 (16.8)      | 84 (83.2)  | 1.05 (0.48–1.48) | 0.9   |             |        |
| 1997–2006          | 34 (11.6)      | 259 (88.4) | 0.73 (0.38–1.38) | 0.33  |             |        |
| 2007–2011          | 20 (15.3)      | 111 (84.7) | 1             |        |             |        |
| Age (years)        |                |            |               |        |             |        |
| > 35               | 15 (11.8)      | 112 (88.2) | 0.91 (0.35–1.63) | 0.84  | 0.71 (0.27–1.87) | 0.49  |
| 25–35              | 47 (14.2)      | 285 (85.8) | 1.09 (0.48–1.52) | 0.82  | 0.98 (0.45–2.15) | 0.97  |
| < 25               | 9 (13.8)       | 56 (86.2)  | 1             |        |             |        |
| ART treatment      |                |            |               |        |             |        |
| No treatment       | 13 (25.0)      | 39 (75.0)  | 2.70 (1.20–6.09) | 0.017 | 1.50 (0.33–6.78) | 0.60  |
| NRTI/NNRTI         | 14 (8.8)       | 145 (91.2) | 0.81 (0.40–1.66) | 0.56  | 0.67 (0.27–1.63) | 0.37  |
| Boosted            | 23 (19.3)      | 96 (80.7)  | 2.01 (1.02–3.97) | 0.045 | 2.17 (1.05–4.51) | 0.038 |
| Unboosted          | 21 (10.8)      | 174 (89.2) | 1             |        |             |        |
| NRTI backbone      |                |            |               |        |             |        |
| None               | 13 (25.5)      | 38 (74.5)  | 2.59 (1.04–6.42) | 0.041 | 1.40 (0.26–7.59) | 0.69  |
| AZT/3TC            | 37 (11.5)      | 285 (88.5) | 1.12<sup>a</sup> (0.53–2.35) | 0.44  | 0.50 (0.18–1.36) | 0.17  |
| Tdf/3TC            | 4 (33.3)       | 8 (66.7)   | 2.62 (1.18–5.84) | 0.017 | 1.40 (0.26–7.59) | 0.69  |
| ABC/3TC            | 5 (20.0)       | 20 (80.0)  | 1.00 (0.40–2.48) | 0.98  | 1.40 (0.26–7.59) | 0.69  |
| D4T base           | 1 (8.3)        | 11 (91.7)  | 0.42<sup>b</sup> (0.05–3.67) | 0.77  | 0.20 (0.02–1.86) | 0.16  |
| DDI base           | 0 (0.0)        | 8 (100.0)  | 1             |        |             |        |
| Other              | 1 (25.0)       | 3 (75.0)   | 2.67 (0.21–38.56) | 0.44  | 1.59 (0.08–33.3) | 0.77  |
| AZT                | 9 (11.7)       | 68 (88.3)  | 1             |        |             |        |
| CD4 count (cells/mm<sup>3</sup>) | | | | | | |
| < 200              | 6 (11.1)       | 48 (88.9)  | 0.68 (0.27–1.73) | 0.43  | 0.59 (0.22–1.57) | 0.29  |
| 200–350            | 8 (8.3)        | 88 (91.7)  | 0.50 (0.24–1.07) | 0.07  | 0.56 (0.26–1.19) | 0.13  |
| > 350              | 57 (15.2)      | 318 (84.8) | 1             |        |             |        |
| Parity             |                |            |               |        |             |        |
| Multip with PPTD   | 3 (75.0)       | 1 (25.0)   | 15.19 (1.85–125.8) | 0.012 | 13.28 (1.89–93.5) | 0.009 |
| Multip without PPTD| 16 (17.4)     | 76 (82.6)  | 1.64 (0.86–3.04) | 0.12  | 1.56 (0.81–3.01) | 0.18  |
| Nulliparous        | 52 (12.1)      | 377 (87.9) | 1             |        |             |        |
| Hepatitis C        |                |            |               |        |             |        |
| Positive           | 7 (33.3)       | 14 (66.7)  | 3.20 (1.25–8.19) | 0.015 | 4.66 (1.71–12.75) | 0.003 |
| Negative           | 64 (12.7)      | 440 (87.3) | 1             |        |             |        |
| Race               |                |            |               |        |             |        |
| Black              | 48 (13.3)      | 312 (86.7) | 1.01 (0.54–1.87) | 0.40  | 1.49 (0.71–3.15) | 0.29  |
| Other              | 7 (18.4)       | 31 (81.6)  | 1.49 (0.59–3.79) | 0.97  | 3.27 (1.16–9.16) | 0.025 |
| Caucasian          | 16 (12.6)      | 111 (87.4) | 1             |        |             |        |

<sup>a</sup>Combined OR for AZT/3TC, Tdf/3TC, ABC/3TC backbones; <sup>b</sup>Combined OR for d4T- and DDI-based backbones.
understood, there is increasing evidence that maternal and fetal adrenal dysfunction from RTV exposure may play a role in the initiation of PTB. Progesterone is a sex hormone essential for the maintenance of pregnancy, and in a mouse pregnancy model, mice exposed to PIs during pregnancy were shown to have lower progesterone levels, more pregnancy loss, less viable pups per litter, and lower fetal and placental weights compared to mice exposed only to double NRTI therapy; among the PIs studied, RTV had the strongest inhibitory effect on progesterone levels in the mouse model [30]. Lower levels of progesterone among RTV-treated women, something not assessed in the present study, may in part explain the higher rate of PTB among them. Moreover, transient fetal adrenal dysfunction from post-natal RTV exposure has been reported in a cohort of HIV-exposed uninfected newborns, with increased 17-hydroxy progesterone and dehydroepiandrosterone sulfate (DHEA-S) concentrations among newborns who received LPV-r prophylaxis compared to newborn treated with other ARV agents in the neonatal period [23]. Given that fetal signals coming from the hypothalamic–pituitary–adrenal axis play a fundamental role in the initiation of spontaneous labour [31], we suspect that transient fetal adrenal dysfunction from in utero RTV exposure may further contribute to the initiation of PTB.

The major limitations of our study are its retrospective nature, and our inability to adjust for other potential confounders. Due to the changing nature of the HIV epidemiology in our cohort over time, there were significant differences in maternal characteristics according to the type of PI treatment received. Nulliparous women were more likely to have received unboosted PIs, possibly reflecting first pregnancies among the first wave of prenatally infected women to have been followed and treated with ARVs. Caucasian women were also more likely to have received unboosted rather than boosted PIs, likely reflecting the increasing number of women diagnosed with HIV through immigration, compared to IV drug use or blood transfusion [32,33]. While these were adjusted for in the multivariable analysis, we were unable to adjust for maternal weight gain during pregnancy, hard drug and alcohol use, and smoking. We were also unable to control for the timing of ARV initiation, which has been reported to influence PTB [1,34,35]. Finally, we do not have information on mode of delivery, and of what proportion of pre-term births were iatrogenic caesarean section versus spontaneous PTB, which is an important consideration in the aetiology of PTB.

Given these limitations, our findings of increased risk of PTB among women treated with boosted PIs should be interpreted with caution. The success of cART in reducing mother-to-child transmission rates is a tremendous achievement, and cART remains the cornerstone of prevention. Nonetheless, in light of increased morbidity and mortality from prematurity among HIV-exposed infants [36], and the availability of alternatives to RTV-boosted PIs in pregnancy, further study is necessary to understand the role of RTV boosting, and to identify the safest most effective cART regimens for HIV-positive women.

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Competing interests
The authors declare that they have no competing interests

Authors’ contributions
FK designed the study, conducted the initial analysis, interpreted the data, drafted the abstracts and final manuscript. IB analyzed and interpreted the data, revised and approved the final manuscript. VL collected the CMIS clinical cohort data, interpreted the data, revised and approved the final manuscript. TD analyzed the data, revised and approved the final manuscript. DA interpreted the data, revised and approved the final manuscript. HS was responsible for the CMIS biobank, interpreted the data, revised and approved the final manuscript. NL designed the original CMIS cohort and collected the clinical data, interpreted the data, revised and approved the final manuscript. MB collected the CMIS clinical cohort data, interpreted the data, revised and approved the final manuscript.

Acknowledgements
We thank Ms. Silvie Valois, the CMIS study research coordinator, and all members of the research and clinical team for the ongoing care provided to patients. This work was supported in part by grants to support the CMIS cohort and biobank from Re#se Arch SIDA et maladies infectieuses of the Fonds de Recherche du Quebec-Sante (FRQ-S).

This work has been presented in part at the 18th Conference on Retroviruses and Opportunistic Infections (CROI), March 5–8th, 2012, Seattle, Washington, USA, Abstract #1026 and at Canadian HIV AIDS Research (CAHR) meeting, April 19–21th, 2012, Montreal, Quebec, Canada (CG090).

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