Article details: 2014-0112	
Title	Maternal placental syndromes among women living with HIV in Ontario: a population-based study
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Reviewer 1	Dr. Agnihotram Ramana-Kumar
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General comments (author response in bold)	Comment #1: " Page-1: Introduction is lacking description about temporal relationships and basic information about prevalence of HIV and maternal placental syndromes in Ontario, and the relevance of HIV to maternal placental syndromes." **Response: We have added additional background information about the prevalence of HIV and maternal placental syndromes in Ontario, as well the relevance of HIV to maternal placental syndromes, on page 4.** Comment #2: "Page-7, Para 1: Comorbidity index were calculated using the John Hopkins ACG system. Since comorbidities play an important role in immune compromised population, authors may need to justify this is the better system than other existing standard indices (ex. Charlson Comorbidity Index)." **Response: We have previously compared the two approaches to comorbidity adjustment in a population of persons with HIV.2 The two approaches were similar with respect to predicting mortality, although the Johns Hopkins ACG system had slightly better discriminative performance for hospital admission. We have added this information to page 7 of the manuscript.** Comment #3: "Authors need to mention about completeness and reliability of the HIV-registry, as these two quality indicators are key to assess the efficiency of this system." (see response below) Comment #4: "Authors may want to investigate the presence of ICD-10 diagnostic code for HIV in the administrative claims database in order to assess completeness of the HIV-registry." **Response: Comments #3 and #4 relate to the same point – the validity of the Ontario HIV registry. As noted earlier, we have provided additional information regarding this database to page 6 of the manuscript. During the development and validation of the database, we did not find that ICD-10 codes for HIV and associated opportunistic infections improved the performance of the case-finding algorithm. Because details regarding the validation of the Ontario HIV Database have been published elsewhere3, we have not made additional changes to the manuscript in regards to the latter point, but could do so if the Editors thought it was useful.** Comment #5: "Results. Since we are comparing 634 HIV cases with over a million non-HIV population, it would be nice to check the consistency of these results with a sensitivity analysis of sample-matching without replacement." **Response: Because we used the entire population of HIV-positive and HIV-negative women who had given birth over the study period, rather than having drawn random samples from each of these groups, we are unsure of the value of this sensitivity analysis. We have therefore not made any changes regarding this point, but could do so if the Editors felt this was important.** Comment #6: "Table-1. There are significant differences between HIV and non-HIV groups; however, the differences among macro-level variables like immigration status, material deprivation income quintiles, and residential instability quintiles are more striking. Since all immigrants were tested for HIV before their arrival in Canada, and may not possess a unique identifier for the deterministic matching, it would be important for the authors to justify them as a potential confounding variable. On the other hand, matching based on the postal codes may also have additional issues." **Response: We adjusted our models for all macro-level variables identified by the Reviewer. Immigration status was associated with the risk of maternal placental syndromes in an earlier study.1 Because immigration status is associated with both maternal placental syndromes and HIV, without being on the causal pathway, it is an important confounder for adjustment. We have**

	added a brief justification for selection of this variable to page 7 of the manuscript. Comment #7: "It seems the conclusion of this study was strong considering the results were null for the main outcome. In this context, if expertise permits, Bayesian approach is more advisable than GEE models that were used. [Ed note: Our statistician was not convinced that the Bayesian approach is necessary]" **Response: In light of the Editors' note, we have not re-analyzed our data using a Bayesian approach.** Comment #8: "Given the nature of the data (panel structure), it may be interesting to know whether GEE model considered the time-varying nature of the relevant variables (the women may develop a comorbidity prior to subsequent pregnancy)." **Response: We agree, and have re-analyzed the data using GEE models that are time-updated for all time-varying variables, including comorbidity (page 8).** Comment #9: "Page-10 Para-3, line34-36. It seems the authors over-interpreted the results that are statistically not significant. Caution is needed while interpreting the literature in terms of population, design and other aspects." **Response: We agree with this assessment. Because both reviewers identified this as a concern, we have deleted this paragraph from the manuscript.** Comment #10: "Please use same terminology for covariates in the text and the footnotes of the tables (footnote of table-2 and page 8 lines 22-29). Another example, Table-2 (pre-existing hypertension instead of chronic hypertension)." **Response: We thank the reviewer for highlighting these inconsistencies, and have made these changes.**
Reviewer 2	Dr. Nikolaos P. Polyzos
Institution	University of Ioannina School of Medicine, Department of Hygiene and Epidemiology, Epirus, Greece
General comments (author response in bold)	Comment #1: "This is a very interesting study with population based data which makes it the most robust up to date regarding the association between HIV status and maternal placental syndromes. The manuscript is well written and the data presented are clear." **Response: We thank the reviewer for this comment.** Comment #2: "Adjustment was made for multiple risk factors. However I didn't see any adjustment for race. Do the authors have the data for race? Black race is a known risk factor for preeclampsia. Do they have data on race to input this variable in the logistic regression?" **Response: Our datasets do not include information on race. However, we were able to adjust for world region of origin, including Africa and the Caribbean. We agree that residual confounding due to race may still occur, as Canadian-born women of black ethnicity will not be accounted for using this approach. We have noted this limitation on page 11.** Comment #3: "Why don't the authors also present data on preterm birth and low-birth weight infants? Previous studies have done so and demonstrated that PTB and LBW are lower in HIV patients (Haeri et al., AJOG 2009) with really high odds ratios (adjusted odds ratio, 2.27; 95% CI, 1.22-4.25). I would like to see these data if available! Although these cannot be considered maternal placental syndromes directly I have the impression that referring to obstetric outcomes in general will make their manuscript even more robust (although I need to highlight that in case these data are not available this is not a reason for the article to be rejected. However if they are available I would like to see them in the same manuscript so as to avoid salami publication in another manuscript. I believe such a paper has the potential to be even more highly cited." **Response: We have previously published a paper on the risk of preterm and low-birth weight infants in women with HIV.4 We have integrated these data with Reviewer #1's comment about the relevance of maternal placental syndromes to HIV (page 3). Because preterm and low-birth weight births are adverse neonatal outcomes and not maternal obstetric outcomes, we analyzed and published these data separately.** Comment #4: "Any data about smoking and history or previous PTB?" **Response: As noted in our earlier response to the Editors, we attempted to**

	capture smoking in our databases, and included this variable as part of a sensitivity analysis. We have added data on prior preterm birth to Table 1 for second and later pregnancies, since this variable will not apply to first pregnancies (i.e. cannot have a prior preterm birth for first pregnancy). Comment #5: "Page 10 Lines 31-41. The lack of significance and the wide odds ratio does not at all allow speculation that HIV patients might have lower risk for maternal placental syndromes. The whole paragraph needs to be removed." **Response: We agree, and have removed this paragraph.** Comment #6: "In conclusion, very nice work. If additional data on PTB LBW are available, will be more than welcome and will strengthen the work done." **Response: We thank the reviewer for this comment. As noted in response to an earlier comment, we have added these data to page 4 of the manuscript.**