Correspondence

Pregnancy and HIV Disease Progression: Methodological Concerns

To the Editor—We thank Tai et al. [1] for their recent article in the Journal. We read the article with great interest. The authors noted a substantial reduction in the risk of AIDS or AIDS-related death associated with pregnancy among HIV-positive women attending clinics in Tennessee. Although we recognize the substantial effort expended to control for confounding in this study, several methodologic issues urge caution in interpreting the otherwise welcome findings of these authors.

First, we are troubled by the definition and classification of exposure in this study. In these analyses, all person-time contributed by a woman who became pregnant at any point during follow-up—including person-time contributed both before and after the period of actual pregnancy—was considered to be time exposed. As a result, “exposed” person-time is, in fact, a mix of exposed and unexposed person-time. Furthermore, the unexposed person-time included as “exposed” time is in fact “immortal person-time,” because these “exposed” women are necessarily alive and free of disease progression until the beginning of pregnancy. Although the authors note this latter concern in their discussion, although this misclassification should not influence analyses in which follow-up began after pregnancy, other analyses may well have been affected.

An additional concern is the authors’ decision to designate CD4+ lymphocyte counts obtained up to 365 days after the initial clinic visit as “baseline” measurements. CD4+ lymphocyte counts can change dramatically within a year of follow-up, depending on whether or not individuals are receiving antiretroviral therapy (ART); therefore, such counts are a potentially inaccurate measurement of the true CD4+ lymphocyte count at baseline.

An analytic approach that could help to address both of these concerns is to allow exposure and the CD4+ lymphocyte count, as well as other key confounders, to vary throughout follow-up. Because the CD4+ lymphocyte count and other confounders (including ART received) may vary with time, exposure, and each other, the use of marginal structural models (MSMs) may be necessary to obtain an unbiased estimate of effect. Regardless of whether MSMs are required, controlling for time-varying exposure and confounders may yield dramatically different results. For example, in a study analogous to that of Tai et al. [1], Hernan et al. [2] reported rate ratios of 2.3 (1.9–2.8) in a model controlling only for baseline confounders, but they reported rate ratios of 0.4 (0.3–0.5) in a model accounting for time-dependent confounding and 0.7 (0.6–1.0) in the appropriate MSM.

We also are concerned about the inclusion criteria used for the study. Given the authors’ focus on the highly active antiretroviral therapy (HAART) era, it is not immediately clear why 75 women who received non-HAART ART and 144 nonpregnant women; if the curves do not overlap, then the basis for counterfactual inference is more questionable.

We believe that the aforementioned concerns urge caution in the interpretation of the important findings of Tai and colleagues. However, we wish to emphasize that we are advocating skepticism, not cynicism; the remarkable consistency seen across subanalyses in this study urges deeper investigation of these issues.

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References

1. Tai JH, Udoji MA, Barkanic G, et al. Pregnancy and HIV disease progression during the era of...
Effect of Pregnancy on HIV Disease Progression during the Era of Highly Active Antiretroviral Therapy

To the Editor—A recent article by Tai et al. [1] described the relationship between pregnancy and HIV disease progression in women during the era of highly active antiretroviral therapy (HAART). The authors’ results suggested that pregnancy was associated with a lower risk of HIV disease progression. Two possible reasons for this finding were provided: either (1) women who became pregnant during the study had a healthier immune status from the start or (2) HIV-infected women may have benefitted from an interaction between pregnancy and HAART. The discussion in the article, in conjunction with the accompanying editorial commentary by Dr. Anastos [2] in the same issue of the Journal, provides readers with the strong impression that the latter explanation is the more likely. For example, in her commentary, Dr. Anastos cited the study findings and stated, “Not only was pregnancy not found to be associated with more rapid progression of HIV disease, it in fact had a marked protective effect” [2, p. 971].

However, we have serious concerns about the study design and data analysis, and we believe that the study findings could be misleading. The authors treated pregnancy as a baseline exposure when, in fact, pregnancy was a time-varying exposure that occurred during study follow-up. This treatment resulted in 2 potential sources of bias, neither of which was adequately accounted for in the analyses. First, according to the results presented in table 1 in the article by Tai et al. [1], the women who became pregnant were younger, healthier (with a lower viral load and a higher CD4+ lymphocyte count), and stayed in the study longer than women who did not become pregnant. This observation provides clear evidence of selection bias. Second, although “nonpregnant” women were at risk for an event at any time during the study, the “pregnant” women were only at risk after they became pregnant. Figure 1 in the article by Tai et al. [1] shows that study end points were reached by more than 20% of the nonpregnant women before the study end point was reached for the first time in the group of pregnant women, providing evidence of such length bias. These results provide reasonable doubt regarding the possibility of a causal association between pregnancy and delayed HIV disease progression.

In the study by Tai and colleagues, the use of the propensity score approach to provide balance between the pregnant and nonpregnant groups at baseline, in terms of important prognostic factors for AIDS, resulted in pregnancy being treated as a baseline exposure variable. This is inappropriate, because pregnancy occurred during follow-up. Thus, we are not surprised that the inclusion of the propensity score in the Cox regression models (table 4 in [1]) had very little impact on the estimated effect of pregnancy. Alternately, one should consider the use of other adjustment methods, such as risk set matching approaches [3, 4], in which each HIV-infected woman who was pregnant at time t is matched to another woman with a similar history of HIV infection up to time t but who was not pregnant.

In addition, the “before-pregnancy event” analysis that used one-to-one matched-pair data seems peculiar. There should have been few or no study end points for the pregnant group, because the event would have had to occur in the relatively short interval after the woman became pregnant but before the pregnancy event. The statistically significant result suggesting a reduced risk of prepregnancy events among women in the pregnant group provides further evidence that, from the start, women in the pregnant group were healthier than the women in the nonpregnant group. The analysis of an “after-pregnancy event” intuitively seems to be more reasonable. However, the analysis population no longer appears to allow a one-to-one match, because some nonpregnant women would have experienced AIDS-defining events (and thus would have been censored) before their paired partner experienced a pregnancy event.

As with most studies of HIV-infected persons, important information about the duration of HIV infection is unavailable in this study. Previous studies have indicated that HIV-infected women with greater immunosuppression have lower fecundity [5], so the study analyses could be confounded by the differing disease stages noted among women in the pregnant and nonpregnant groups.

Clearly, the issue of a possible association between HIV disease progression and pregnancy is important—especially for the millions of women living with HIV infection in sub-Saharan Africa. We believe that more research needs to be done to assess the relationship between pregnancy and HIV outcomes in the HAART era before it can be concluded that we have “good news for women living with HIV” [2]. Basing the conclusion that pregnancy provides a protective effect on a single, potentially flawed analysis could not only be misleading but harmful. Attempts by HIV-infected women to become pregnant in an effort to improve their own health could result in incidents of mother-to-child or woman-to-partner
transmission of HIV that would not have otherwise occurred.

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References


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Reply to Westreich and Kipp and to Chen et al.

To the Editor—We appreciate the interest of Chen et al. [1] and Westreich and Kipp [2] in our study [3], as well as their skepticism regarding our results. We have shared similar skepticism, particularly in the context of studies conducted before the availability of highly active antiretroviral therapy (HAART), in which pregnancy either had no effect on HIV disease progression or was associated with an increased risk of progression. Although one should be cautious in interpreting the results of our study, it should be noted that our methodology was comparable to or more rigorous than that used in previous studies, thereby suggesting that there may indeed be differences in the effect of pregnancy on disease progression in the HAART vs. pre-HAART eras. Our results were also consistent with those of earlier studies showing that the risk of HIV disease progression decreased as the number of pregnancies increased.

There are several limitations of observational studies, which we noted in our article. Multivariate Cox proportional hazards models, propensity scores for pregnancy, and a matched-pair analysis were used to help control for confounding variables (e.g., differences in age, CD4+ lymphocyte count, and HIV-1 RNA load). In cohort studies, the biggest concern regarding selection bias pertains to differences in loss of patients to follow-up. As we noted, the shorter duration of follow-up for nonpregnant women would likely result in ascertainment of fewer AIDS diagnoses or deaths in this group than among pregnant women, thus diminishing—not increasing—the difference in the risk of disease progression between the 2 groups. In addition, bias in relative risk occurs only if losses to follow-up are biased according to both outcome (AIDS and/or death) and exposure (pregnancy). Both pregnant and nonpregnant women were at risk for AIDS throughout the entire study; pregnant women were at risk both before and after they became pregnant. To avoid immortal time bias (when the time before pregnancy is credited toward disease-free survival after pregnancy), we performed an analysis of matched pairs after the pregnancy event. We also performed Cox proportional hazards models in which follow-up began after the pregnancy event rather than after study entry. We concluded that there was an association between pregnancy and a decreased risk of HIV disease progression, but we did not claim causality—which would be inappropriate based on observational data.

The propensity score was used to adjust for factors potentially associated with becoming pregnant (exposure), not with AIDS (outcome). Propensity scores attempt to control for differences in factors associated with the exposure of interest when there is no randomization. Baseline factors are likely to be important in this regard. The Stata statistical software package (Stata) divided patients into 9 groups, and the mean propensity score did not differ between pregnant and nonpregnant women in each group. After adjustment for the propensity score, there were no detectable associations between exposure and the risk factors included in the propensity score. Histograms and dot plots of the propensity scores are shown in figure 1. Given the substantial overlap in propensity scores, there is evidence for exchangeability. When Cox proportional hazards models were run among the subset of subjects with a propensity score of $\geq0.05$ (i.e., when the 384 nonpregnant women and 8 pregnant women with a propensity score of 0 were excluded), there was no difference, compared with the results of analyses involving the full cohort. The matched-pair analysis matched women on the basis of time of cohort entry (as well as on the basis of the CD4+ lymphocyte count at baseline, HAART use, and age at entry)—which is consistent with the risk set matching suggestion of Chen et al. [1].

In the matched-pair analysis, as in the other analyses, events (AIDS and/or death) were assessed from the time of cohort entry for all study participants; for pregnant women, time at risk was not just the time from conception until the pregnancy event. Because the pairs were matched according to the time of cohort entry, matched-pair analysis allowed for a similar follow-up period for each pair.

We agree that CD4+ lymphocyte counts can vary over time. A narrower window between the first clinic visit and the time that baseline laboratory values were obtained would have been preferable, but it would have also diminished the study sample size. Most baseline laboratory values were obtained on or close to the date of the first visit: 74% of such values were obtained within 30 days, and 98% were

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obtained within 120 days of the first visit. In addition, however, we conducted analyses using the CD4⁺ lymphocyte count and the HIV-1 RNA load noted at the end of pregnancy rather than those values noted at baseline, and the study results did not change. Additional methods to account for other time-dependent variables would be worth pursuing. We accounted for the use of HAART, non-HAART antiretroviral therapy, and durable virologic suppression in the analysis.

Figure 1. Propensity-score distribution, represented by histograms for 139 pregnant (A) and 620 nonpregnant women (B) and as a dot plot (C) for both groups. The propensity score was derived from the following variables: age, race, marital status, baseline CD4⁺ lymphocyte count of >200 cells/mm³, baseline HIV-1 RNA load of >10,000 copies/mL, durable virologic suppression, duration of highly active antiretroviral therapy (HAART), duration of non-HAART antiretroviral therapy, the mean no. of patient encounters per year, the mean no. of nutritional consultations per year, receipt of nutritional supplementation, and history of substance abuse.

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