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MAJOR ARTICLE

Pregnancy and HIV Disease Progression during the Era of Highly Active Antiretroviral Therapy

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(See the editorial commentary by [Anastos](#), on pages 971–3.)

Background. Before the availability of highly active antiretroviral therapy (HAART), there was no clear effect of pregnancy on human immunodeficiency virus (HIV) disease progression. This has not been assessed during the HAART era.

Methods. We conducted an observational cohort study among HIV-infected women with ≥ 1 outpatient clinic visit between January 1997 and December 2004. HIV disease progression was defined as the occurrence of an AIDS-defining event or death.

Results. Of 759 women who met the inclusion criteria, 139 (18%) had had >1 pregnancy, and 540 (71%) had received HAART. There was no difference in HAART duration by pregnancy status. Eleven pregnant (8%) and 149 nonpregnant (24%) women progressed to AIDS or death. After controlling for age, baseline CD4⁺ lymphocyte count, baseline HIV-1 RNA level, and durable virologic suppression in a Cox proportional hazards model that included propensity score for pregnancy, pregnancy was associated with a decreased risk of disease progression (hazard ratio [HR], 0.40 [95% confidence interval {CI}, 0.20–0.79]; $P = .009$). In a matched-pair analysis of 81 pregnant women matched to 81 nonpregnant women according to age, baseline CD4⁺ lymphocyte count, receipt of HAART, and date of cohort entry, pregnant women had a lower risk of disease progression both before (HR, 0.10 [95% CI, 0.01–0.89]; $P = .04$) and after (HR, 0.44 [95% CI, 0.19–1.00]; $P = .05$) the pregnancy event.

Conclusion. Pregnancy was associated with a lower risk of HIV disease

progression in this HAART-era study. This finding could be the result of the healthier immune status of women who become pregnant or could possibly be related to a beneficial interaction between pregnancy and HAART.

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Studies conducted before the availability of highly active antiretroviral therapy (HAART) showed that pregnancy either slightly increased the risk of HIV disease progression or had no effect. Early studies noted a possible association between pregnancy and accelerated disease progression [1–3]. Observational studies conducted in developing countries found that pregnancy was an independent predictor of increased HIV disease progression [4, 5]. Several studies conducted in the United States and Europe, however, did not demonstrate an increased risk of HIV disease progression in pregnant women [6–11]. All of the above studies were conducted in patient populations that received either no antiretroviral therapy (ART) or a single nucleoside reverse-transcriptase inhibitor, in accordance with treatment availability at that time. In a primarily pre-HAART-era study of HIV-infected women in the United States with 1 versus 2 pregnancies, there was little difference in CD4⁺ lymphocyte counts, HIV-1 RNA levels, and time to class C events, but women with 2 pregnancies had a small survival advantage [12].

HAART provides greater virologic suppression and immunologic recovery than pre-HAART regimens, and as a result there have been dramatic improvements in HIV-associated morbidity and mortality [13]. However, we are unaware of studies that have fully assessed the relationship between pregnancy and HIV disease progression in women during the HAART era.

SUBJECTS, MATERIALS, AND METHODS

Study population. The study included all HIV-infected women who received HIV care (≥ 1 visit) between 1 January 1997 and 31 December 2004 at the Comprehensive Care Center in Nashville, Tennessee. Follow-up started with the first clinic visit after 1 January 1997. For inclusion, women must have had either a

CD4⁺ lymphocyte count and/or HIV-1 RNA level available at baseline. Baseline CD4⁺ lymphocyte counts and HIV-1 RNA levels were considered to be the earliest test results obtained up to 120 days before, but no more than 365 days after, the initial clinic visit during the study period.

The index pregnancy was the first pregnancy that occurred after the initial clinic visit. Pregnant women lost to follow-up before the pregnancy outcome and women pregnant at the end of the study period were excluded. Before March 1999, most pregnant women receiving HIV care at the Comprehensive Care Center obtained obstetrical care at Vanderbilt University Medical Center. After March 1999, most women received prenatal care from an obstetrical clinic at the Comprehensive Care Center, which included regularly scheduled visits with a health care provider, nutritionist, and social worker.

Clinical data were entered into an electronic medical record by medical providers at the time of the patient encounter, by automated data upload (e.g., for laboratory results), or by clinic personnel (e.g., for deaths). Laboratory data, ART (including start and stop dates), dates of nutrition consults, use of nutritional supplementation, and history of substance abuse were validated by systematic chart review. If the chart noted (by patient self-report and/or the provider) that the patient had not been taking the prescribed ART, the patient was coded as not taking ART during that period.

The study protocol was approved by the Institutional Review Board of Vanderbilt University Medical Center. Clinical research was conducted in accordance with the human experimentation guidelines of the US Department of Health and Human Services and Vanderbilt University.

Study definitions. HAART was defined as regimens of ≥ 7 days' duration that contained 2 nucleoside reverse-transcriptase inhibitors plus either a protease inhibitor, a nonnucleoside reverse-transcriptase inhibitor, or a third nucleoside reverse-transcriptase inhibitor; 1 nucleoside reverse-transcriptase inhibitor, 1 protease inhibitor, and 1 nonnucleoside reverse-transcriptase inhibitor; 2 protease inhibitors plus 1 nucleoside or nonnucleoside reverse-transcriptase inhibitor; or any regimen containing enfuvirtide. Non-HAART ART included mono- or dual-nucleoside reverse-transcriptase inhibitor therapy. Durable virologic suppression was defined as having more undetectable (< 400 copies/mL) than detectable (≥ 400 copies/mL) HIV-1 RNA levels in persons with ≥ 2 levels available.

HIV disease progression was defined as any new AIDS-defining event or death (combined end point). AIDS-defining events were based on the 1993 US Centers for Disease Control and Prevention classification criteria [14], excluding the criterion of < 200 CD4⁺ lymphocytes/mm³. All events were reviewed and confirmed by study investigators. Subjects were censored at the time of their AIDS-defining event, the date of last clinic encounter, or 31 December 2004 if the last clinic encounter occurred after 31 December 2004.

Statistical analysis. To maximize power, all women who met the inclusion criteria were included; we deemed power to be sufficient to detect a clinically meaningful difference. Continuous variables were compared with the Wilcoxon rank-sum test, and categorical variables were compared with the χ^2 test and Fisher's exact test. The log-rank test was used for Kaplan-Meier survival analyses.

Multivariate Cox proportional hazards models were used to determine predictors of disease progression while adjusting for confounding factors. Variables with $P < .10$ in univariate analyses were eligible for inclusion in the multivariate model. Variables were retained in the final model only if significantly associated with the outcome ($P \leq .05$) or deemed to be of clinical importance.

Selection bias regarding factors associated with becoming pregnant was addressed via a propensity-adjusted method [15]. The propensity score of the estimated probability of becoming pregnant was derived from a logistic regression model that predicted the occurrence of pregnancy on the basis of several factors: age, race, marital status, baseline CD4⁺ lymphocyte count >200 cells/mm³, baseline HIV-1 RNA level $>10,000$ copies/mL, durable virologic suppression, HAART duration, non-HAART ART duration, mean number of patient encounters per year, mean number of nutrition consults per year, receipt of nutritional supplementation, and history of substance abuse.

Another method used to adjust for differences between pregnant and nonpregnant women was a matched-pair analysis in which 1 nonpregnant woman was matched to 1 pregnant woman (1 : 1 match). Subjects were matched according to date of cohort entry (± 6 months), baseline CD4⁺ lymphocyte count (± 100 cells/mm³), receipt of HAART, and age at study entry (± 5 years). A list of nonpregnant women who matched on all criteria was generated for each pregnant woman, and the nonpregnant woman with the closest date of cohort entry was chosen. When a previously matched nonpregnant woman was the only match for a pregnant woman, the previously matched pregnant woman was reassigned to the nonpregnant woman with the next closest date of cohort entry. Multivariate Cox proportional hazards models of HIV disease progression were performed separately for time before the pregnancy event (defined as live birth, abortion, stillbirth, or ectopic pregnancy) and time after the pregnancy event. The date of the pregnancy event in the pregnant woman was also used for the matched nonpregnant pair.

$P \leq .05$ (2-tailed) was considered to indicate statistical significance. Stata SE (version 8.2; Stata Corporation) and SPSS (version 14; SPSS) were used for statistical analyses.

RESULTS

Patient characteristics. We identified 759 women who met the inclusion criteria, of whom 139 (18%) had at least 1 pregnancy during follow-up. There were 174 pregnancies during the study period; 30 women had 2 pregnancies and 5 women had 3 pregnancies. Among the 139 index pregnancies, there were 124 live births, 9 spontaneous abortions, 3 elective abortions, 2 stillbirths, and 1 ectopic pregnancy.

Clinical and demographic characteristics of the cohort are shown in [table 1](#). Compared with nonpregnant women, pregnant women were younger and had higher median baseline CD4⁺ lymphocyte counts and lower median baseline HIV-1 RNA levels. HAART was received by 540 women (71%); 75 women (10%) received non-HAART ART only. All pregnant women received ART. Pregnant women were more likely than nonpregnant women to receive HAART, but, among women who received HAART, treatment duration was comparable for pregnant and nonpregnant women. Pregnant women were also more likely to achieve durable

virologic suppression. Duration of follow-up was longer for pregnant women.

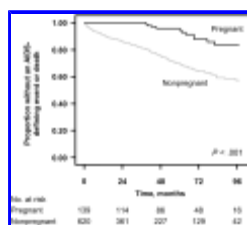
Table 1. Clinical and demographic characteristics of the study patients, by pregnancy status.

Subjects were assessed for other clinical factors potentially associated with disease progression ([table 1](#)). Pregnant women had higher rates of clinic attendance than nonpregnant women and were more likely to receive nutritional consults and supplements. Pregnant women were less likely to have intravenous drug use as a risk factor for HIV acquisition.

Risk of disease progression. Outcomes by pregnancy status are shown in [table 2](#). The AIDS-defining events in pregnant women were *Candida* esophagitis, cytomegalovirus retinitis, disseminated cryptococcosis, lymphoma, wasting syndrome, *Pneumocystis jiroveci* pneumonia (3), and recurrent bacterial pneumonia (2).

Table 2. Outcomes in study patients, by pregnancy status.

In Kaplan-Meier analysis, pregnant women were less likely to progress to an AIDS-defining event or death than nonpregnant women ($P < .001$, log-rank test) ([figure 1](#)). Results of univariate Cox proportional hazards analysis of predictors of clinical disease progression are displayed in [table 3](#). Baseline CD4⁺ lymphocyte count >200 cells/mm³, HAART duration, non-HAART ART duration, durable virologic suppression, and pregnancy were all associated with a lower risk of progression to an AIDS-defining event or death; baseline HIV-1 RNA level $>10,000$ copies/mL and increased age were associated with a higher risk of disease progression. Although other clinical variables were evaluated, only receipt of prenatal vitamins or any nutritional supplement significantly affected disease progression.



(40 kB)

Figure 1. Kaplan-Meier survival curve of progression to a new AIDS-defining event or death among the overall cohort, by pregnancy status. The nos. of pregnant and nonpregnant women at risk during each interval are given below the graph.

Table 6. Results of multivariate Cox proportional hazards models for progression to an AIDS-defining event or death among 81 matched pairs of pregnant and nonpregnant women.

In Cox proportional hazards analyses in which the end point was either an AIDS-defining event alone or death alone, the event rate remained significantly lower in pregnant women ($P = .003$ for AIDS-defining event only and $P < .001$ for death only). In multivariate models that assessed progression to death only, pregnancy was protective after adjusting for CD4⁺ lymphocyte count, HIV-1 RNA level, age, and durable virologic suppression (HR, 0.28 [95% CI, 0.10–0.78]; $P = .02$). The risk of AIDS-defining events alone was lower in pregnant women than in nonpregnant women, but the difference was not statistically significant (HR, 0.55 [95% CI, 0.27–1.11]; $P = .10$).

Cox proportional hazards models were then constructed in which follow-up for pregnant women began at the end of pregnancy rather than after the first clinic visit. Pregnant women were less likely to experience disease progression after controlling for age, durable virologic suppression, and CD4⁺ lymphocyte count and HIV-1 RNA level at the end of pregnancy (HR, 0.47 [95% CI, 0.22–0.99]; $P = .047$).

Women with >1 pregnancy during follow-up tended to have a lower risk of disease progression than women with 1 pregnancy. This was demonstrated in Kaplan-Meier analyses ($P = .08$, log-rank test) and multivariate Cox proportional hazards models that controlled for CD4⁺ lymphocyte count, HIV-1 RNA level, age, and durable virologic suppression (HR, 0.16 [95% CI, 0.02–1.38]; $P = .1$).

In analyses limited to women <45 years old, results of univariate analyses of clinical disease progression were essentially unchanged. In multivariate Cox proportional hazards models, the lower risk of disease progression in pregnant women was similar to that in the full cohort (HR, 0.36 [95% CI, 0.19–0.69]; $P = .002$).

When the cohort was subdivided according to baseline CD4⁺ lymphocyte count, the difference in disease progression between pregnant and nonpregnant women was most pronounced among women with CD4⁺ lymphocyte counts between 201 and 350 cells/mm³ ($P = .01$) (figure 2). Similarly, Kaplan-Meier curves demonstrated significant survival differences between pregnant and nonpregnant women when the baseline CD4⁺ lymphocyte count was between either 201 and 350 or 351 and 500 cells/mm³ but not when <200 or >500 cells/mm³ ($P = .10$ for <200 cells/mm³, $P = .01$ for 201–350 cells/mm³, $P = .03$ for 351–500 cells/mm³, and $P = .12$ for >500 cells/mm³, log-rank test) (data not shown).

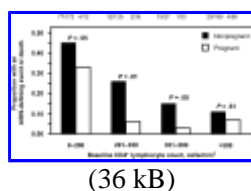


Figure 2. Proportion of women progressing to a new AIDS-defining event or death, by pregnancy status and baseline CD4⁺ lymphocyte count. The no. of women with an event and the no. at risk in each CD4⁺ lymphocyte count stratum are provided above each bar. Sample sizes are less than the overall cohort because of missing data on

baseline CD4⁺ lymphocyte counts for 7 nonpregnant women and 1 pregnant woman. *P* values were determined by Fisher's exact test.

DISCUSSION

In this observational cohort study of HIV-infected women during the HAART era, pregnancy was associated with a significantly lower risk of clinical disease progression. There were several differences in baseline characteristics between pregnant and nonpregnant women: pregnant women were younger, had higher median CD4⁺ lymphocyte counts and lower median HIV-1 RNA levels at baseline, and were more likely to receive HAART. Nonetheless, the decreased risk of disease progression associated with pregnancy persisted after controlling for age, baseline CD4⁺ lymphocyte count and HIV-1 RNA level, HAART duration, non-HAART ART duration, and durable virologic suppression.

It is not possible to study the effect of pregnancy on HIV disease progression in a randomized clinical trial, thus necessitating the use of observational cohort data. However, all observational studies are potentially subject to the effects of confounding variables, both measured and unmeasured. It has been noted that healthier HIV-infected women are more likely to become pregnant [16]. To address this difference in the likelihood of pregnancy and account for the lack of randomization of pregnancy, we constructed Cox models that included a propensity score for pregnancy. We also performed analyses in which pregnant and nonpregnant women were matched on key clinical criteria, including time of entry into care. To avoid "immortal time" bias in pregnant women (e.g., when time before pregnancy is credited toward disease-free survival after pregnancy), we assessed the pregnant and nonpregnant matched pairs after the pregnancy event [17, 18]. Pregnancy remained consistently associated with a lower risk of disease progression even after the above adjustments were made (tables 4 and 6). However, it should also be noted that, in the matched-pair analysis before the pregnancy event, pregnant women had better outcomes than nonpregnant women (table 6). Although this could be because the months of pregnancy before the pregnancy event provided benefit, it may also be that the healthier immune status of pregnant women also contributed to the improved outcome. Additional studies are needed.

In analyses comparing disease progression in women with 1 pregnancy versus >1 pregnancy, we detected a trend toward a decreased risk of disease progression in women with multiple pregnancies. This difference did not reach statistical significance, likely because of the small number of women with multiple pregnancies in our cohort. This apparent dose-response relationship, however, also supports a possible protective effect of pregnancy on disease progression. These findings are consistent with those from a study in 1282 HIV-infected US women, which reported a small but statistically significant survival advantage in women with 2 pregnancies compared with those with 1 pregnancy [12]. That study was limited by the absence of nonpregnant women and the low prevalence of HAART use (14%), but another study in 82 HIV-infected Ugandan women also found that women with multiple pregnancies survived longer than women with 1 pregnancy [19]. Moreover, studies of the long-term effects of childbearing in healthy HIV-uninfected populations have demonstrated either lower mortality in parous than nulliparous women [20] or a U-shaped

curve with higher mortality in women who were nulliparous or had at least 3 births [21]. Given the absence of an association between pregnancy and decreased HIV disease progression in pre-HAART-era studies [6–11], our findings during the HAART era suggest that a beneficial interaction between HAART and pregnancy could be responsible for the superior outcome in parous women. This deserves further study.

Interestingly, pregnancy appeared to influence outcome maximally in women with baseline CD4⁺ lymphocyte counts between 200 and 500 cells/mm³. This suggests that, although high and low CD4⁺ lymphocyte levels are of overriding importance in determining the course of HIV disease, pregnancy appears to exert its greatest influence in women with intermediate CD4⁺ lymphocyte counts.

Because durable virologic suppression, substance abuse, nutritional supplements, and clinic attendance rate may affect the course of HIV disease and differed between pregnant and nonpregnant women, they were potential explanations for a protective effect of pregnancy. As in other prenatal HIV clinics, pregnant women in our clinic had intensive health care intervention, including regularly scheduled visits with a health care provider, nutritionist, and social worker as well as nutritional supplementation and adherence counseling. Of these clinical variables, only durable virologic suppression was significantly associated with disease progression in multivariate analyses; adjustment for this factor did not obviate the beneficial effect of pregnancy.

Given the beneficial effect of pregnancy on disease progression despite several methods to control for confounding factors, one must entertain possible physiologic explanations. Characterization of fluctuations in the T lymphocyte profile in HIV-infected women during pregnancy have yielded inconsistent results: it has been variously reported that CD4⁺ lymphocyte levels decline during pregnancy without postpartum recovery [3], are stable during pregnancy [22], or increase steadily throughout pregnancy before decreasing to baseline during the first postpartum year [23]. HIV-1 RNA levels are stable during pregnancy but may rebound during the early postpartum period [24], possibly because of decreased postpartum adherence to ART or because of reversal of decreased viral reproduction and/or increased clearance that may occur during pregnancy. A survival benefit associated with pregnancy may be related to the complex set of immunologic changes during gestation, particularly in cytokine levels. Pregnancy is associated with a shift from Th1 to Th2 dominance; Th2-associated cytokines play key roles in the successful maintenance of pregnancy [25]. It may be that the dominant Th2 immune response that arises during the gestational period provides a survival advantage through immunological activation during this relatively short period. Taken together, there may be a biological mechanism by which pregnancy could impede HIV disease progression, but further study is needed.

Several limitations must be considered in addition to those noted above. Data on adherence to ART were not available. Durable virologic suppression, however, is a marker of adherence [26–28] and was assessed in all women with at least 2 HIV-1 RNA measurements. The systematic chart review that incorporated patient and provider reports of ART use also provided a rough assessment of adherence. Follow-up duration was significantly longer for pregnant women than for nonpregnant women. Fewer AIDS-defining events, however, were likely ascertained in nonpregnant women than had follow-up time been equivalent to that of

pregnant women. Thus, the difference in event rates between the 2 groups was likely underestimated, not overestimated. We were unable to distinguish non–AIDS-related deaths from AIDS-related deaths. Although this might have affected our results, the risk of HIV disease progression was lower in pregnant women even when assessing only AIDS-defining events.

Our data suggest that, in a setting with high rates of HAART use, pregnancy is independently associated with a decreased risk of HIV disease progression. Further investigation into the responsible underlying biological mechanisms is warranted, particularly the interaction between ART and the immunological changes that occur during pregnancy.

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