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Biomarkers From Late Pregnancy to 6 Weeks Postpartum in HIV-Infected Women Who Continue Versus Discontinue Antiretroviral Therapy After Delivery

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Abstract

Background—Women who use antiretroviral therapy (ART) solely for the prevention of mother-to-child transmission of HIV discontinue postpartum. We hypothesized that women discontinuing ART by 6 weeks postpartum ("discontinuers") would have elevated postpartum inflammatory biomarker levels relative to women remaining on ART postpartum ("continuers").

Methods—Data from HIV-infected pregnant women enrolled in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group P1025 with CD4 counts >350 cells per cubic millimeter before initiating ART or first pregnancy CD4 counts >400 cells per cubic millimeter after starting ART and with available stored plasma samples at >20 weeks of gestation, delivery, and 6 weeks postpartum were analyzed. Plasma samples were tested for highly sensitive C-reactive protein, D-dimer, and interleukin-6. We used longitudinal linear spline regression to model biomarkers over time.

Results—Data from 128 women (65 continuers and 63 discontinuers) were analyzed. All biomarkers increased from late pregnancy to delivery, then decreased postpartum (slopes different from 0, $P < 0.001$). Continuers had a steeper decrease in log D-dimer between delivery and 6 weeks postpartum than discontinuers ($P = 0.002$).

Conclusions—In contrast to results from treatment interruption studies in adults, both ART continuers and ART discontinuers had significant decreases in the levels of D-dimer, highly sensitive C-reactive protein, or interleukin-6 postpartum. Continuation was associated with a more rapid decline in D-dimer levels compared with discontinuation.

Keywords

HIV/AIDS; pregnancy and postpartum; inflammation; antiretroviral therapy

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INTRODUCTION

The treatment guidelines of the United States for HIV-infected adults and adolescents recommend antiretroviral therapy (ART), once initiated, be continued lifelong.[1] The recommended CD4 threshold for initiation of ART in adolescents and adults with HIV infection has evolved over time (<200 to < 350 to <500 cells/mm^3), and ART is now considered for all adolescents and adults, irrespective of CD4 count.[1]

In contrast to treatment guidelines for adolescents and adults,[1] US guidelines for HIV-infected pregnant women incorporate ART as prophylaxis of mother-to-child transmission (MTCT) of HIV and ART as treatment.[2] Historically, pregnant women who met criteria for treatment based on CD4 thresholds were started on ART as soon as possible and continued lifelong, whereas pregnant women who did not meet criteria for treatment were initiated on ART after the first trimester of pregnancy solely for the prevention of MTCT and then discontinued postpartum. As thresholds for initiating ART have increased over time, it has become unclear whether pregnant women with high CD4 counts who have traditionally been started on ART for prophylaxis of MTCT of HIV should continue or discontinue ART postpartum.

Several studies of structured treatment interruption (TI), in which ART was selectively started and stopped in men and nonpregnant women based on CD4 thresholds, have shown excess morbidity and mortality from AIDS and non-AIDS clinical events.[3–5] One of these studies (Strategies for Management of Antiretroviral Therapy or SMART) has demonstrated associations between inflammatory and coagulation biomarkers and clinical outcomes.[6] In this study, a comparison of levels of interleukin-6 (IL-6) and D-dimer at study entry in participants who died and those who survived showed that entry elevations in these markers were associated with a large increase in the likelihood of death, with unadjusted odds ratios for those in the highest quartile compared with the lowest of 8.3 for IL-6 and 12.4 for D-dimer. Adjustment for a variety of factors including age, race, viral load, CD4 count, smoking, body mass index, diabetes, and hepatitis B or C coinfection strengthened these associations. IL-6 and D-dimer increased in discontinuers, particularly in those with virological suppression at entry, and the increases were related to viral load 1 month after discontinuation. These biomarkers were more strongly associated with all-cause mortality than with cardiac death, suggesting that these markers are surrogates of a pathway that is globally detrimental to health. Based on these data, it has been recommended to avoid TI for HIV-infected individuals.[1] It has been argued that extrapolation of findings from TI studies conducted among men and nonpregnant women to pregnant and postpartum women is suboptimal given significant differences in age, overall health status, CD4 nadir levels, and unique physiological drivers of inflammation among this population; however, discontinuation of ART postpartum among women who initiated ART for prevention of MTCT could be considered a unique form of TI because most HIV-infected postpartum women would be expected to restart ART eventually, either for treatment of the woman herself or for transmission prophylaxis during a subsequent pregnancy.

Because of uncertainty surrounding postpartum ART strategy for pregnant women with high nadir CD4 counts, we sought to characterize inflammatory and coagulation biomarkers in pregnant and postpartum women with HIV infection starting ART during pregnancy with pre-ART CD4 counts >350 cells per cubic millimeter or first on ART CD4 count of >400 cells per cubic millimeter and to compare biomarker trajectories in women who continued or discontinued ART after delivery. We also evaluated biomarker levels and associations with subsequent pregnancy and delivery complications and clinical events up to 6 months postpartum. We hypothesized that postpartum ART discontinuation would be associated with marked elevations in biomarkers among discontinuers due to uncontrolled viral

replication and triggering of inflammatory and coagulation pathways and that these elevations in biomarkers would be associated with higher rates of postpartum clinical events resulting from the detrimental end-organ effects of these pathways. We also hypothesized that higher levels of third trimester biomarkers, reflective of higher levels of inflammation and coagulation despite ART, would be associated with subsequent late pregnancy and delivery events.

METHODS

P1025 Protocol

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) P1025 is a prospective cohort study that aims to assess maternal and infant safety and effectiveness of new and existing interventions prescribed for prevention of MTCT of HIV. Starting in 2002, participants aged 13 years from 56 clinical sites in the United States and Puerto Rico were enrolled during pregnancy (8 weeks of gestation) or within 2 weeks of delivery, with follow-up continued until at least 6 months after delivery. The number of antepartum study visits was a maximum of 4 completed at least 4 weeks apart during windows corresponding to 14–20, >20–30, and >30 weeks of gestation to delivery. Postpartum study visits were performed at 6 ± 4 weeks and then at 12 and 24 weeks ± 8 weeks, with a minimum of 4 weeks between visits through 6 months postpartum. Study visits included biologic specimen collection, medical record abstraction, and questionnaire administration for adherence assessment. All women provided written informed consent. Detailed study schedules and evaluations have been described in previously published studies.[7,8]

Study Population and Definitions for This Analysis

The study population for this analysis comprised HIV-infected women enrolled in P1025 during pregnancy who initiated ART during pregnancy (including triple nucleoside combinations), were followed through at least the 6-week postpartum study visit, and had a pre-ART CD4 counts >350 cells per cubic millimeter or first on ART CD4 count of >400 cells per cubic millimeter. Women who had at least 1.5 mL of stored plasma collected at each of 3 time points—late pregnancy (>20 weeks of gestation), delivery (+2 weeks), and 6 weeks postpartum (±4 weeks)—were included in the analysis.

For this manuscript, ART refers to potent 3-drug antiretroviral combinations used in pregnant women for either prophylaxis of MTCT or for treatment. The primary exposure of interest was "ART status," which categorized women into 3 groups according to continuation or discontinuation of ART after delivery: (1) continuers, defined as continuation of ART beyond 6 weeks postpartum and on ART for all 3 biomarker time points; (2) early discontinuers, defined as discontinuation after delivery and before the delivery biomarker measurement; and (3) late discontinuers, defined as discontinuation after delivery and the delivery biomarker measurement, but before the 6-week postpartum measurement. The primary outcomes of interest were biomarkers of inflammation and coagulation: highly sensitive C-reactive protein (hsCRP), IL-6, and D-dimer.

Other important characteristics examined in the analysis included maternal age, race/ethnicity, earliest CD4 count during pregnancy, plasma HIV RNA concentration (viral load) before initiation of ART, CDC clinical classification at entry,[9] ART regimen, complications, and mode of delivery (defined as vaginal delivery, Cesarean section after labor and/or rupture of membranes, and Cesarean section before labor and before rupture of membranes). For the analysis of pregnancy and delivery complications, events included gestational hypertension, gestational diabetes, pre-eclampsia, premature rupture of membranes (<37

weeks), and preterm labor (<37 weeks). For the analysis of postpartum complications, a clinical event was defined as any World Health Organization stage 1–4 diagnosis[10] or any other confirmed clinical diagnosis, including non–AIDS-defining events (defined as liver, kidney, cardiovascular disease, and non–AIDS-associated malignancies).

Biomarker Determination and Validation of D-dimer Measurement From Ethylenediaminetetraacetic Acid Plasma

Samples stored at − 70°C were transported from the IMPAACT repository (Rockville, MD) to Quest Diagnostics (Chantilly, VA) for determination of hsCRP, IL-6, and D-dimer. Testing for hsCRP was performed with nephelometry and testing for IL-6 with a highly sensitive enzyme-linked immunosorbent assay.[11] Because the only validated sample type for D-dimer testing performed at Quest Diagnostics was citrated plasma and stored samples were collected from ethyl-enediaminetetraacetic acid (EDTA) plasma, before study samples were analyzed, a correlation study was performed to compare D-dimer values obtained from citrate and EDTA (performed with STA-R analyzer/immunoturbidimetric method). An excellent correlation between the 2 different sample types was obtained with an R value of 0.99. EDTA plasma samples yielded a slightly higher result in comparison with the citrate plasma samples, with an average bias of 0.1 μg/mL.

Statistical Analysis

Sociodemographic, HIV, and pregnancy characteristics by ART status were compared using χ^2 tests, Kruskal-Wallis tests, or Fisher's exact tests as appropriate. Biomarker distributions and median levels of each biomarker were determined at each time point. Because biomarker measurements at each time point had skewed distributions, all analyses were performed on the natural log transformed values. When the biomarker measurement was below the limit of detection, an imputed value was set to the midpoint between the lower limit of detection and 0 (before transformation).

We expected the biomarker slopes to behave differently before and after delivery and therefore used longitudinal linear regression with a spline knot at time of delivery to model each biomarker over time, where time was calculated from exact dates relative to pregnancy. In all regression analyses, we first fitted models, which allowed the biomarker slopes to differ for each period and according to a given characteristic, and assessed whether slopes differed significantly using an *F* test. If no significant differences were observed, we assessed whether there was an overall difference in biomarker level over time between groups. We compared biomarker slopes by ART status in 2 ways, first across the 3 ART status groups, then between continuers and all discontinuers (early and late discontinuers combined). To explore the possible misclassification of women's ART status postpartum due to nonadherence, we repeated the regression analyses and compared biomarker trajectories between those with viral loads 400 copies per milliliter versus >400 copies per millimeter at 6 weeks postpartum. With n = 50 subjects per group, we had 80% power to detect a medium effect size linear change (0.5 SD). This effect size is in line with that observed by Kuller et al[6] for D-dimer and IL-6 in men and nonpregnant women in the SMART study. We also explored the relationship between biomarker levels over time with age, race/ethnicity, and maternal pregnancy and delivery complication status. In the analysis of pregnancy and delivery complications women were excluded if their first reported complication was before their first biomarker measurement. For postpartum clinical event analysis, we compared the frequency of events by ART group using a χ^2 test. We compared mean biomarker levels in the third trimester and at delivery between those women with and without events up to 6 months postpartum using *t* tests with unequal variance. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). A 2-sided *P* value<0.05 was considered statistically significant.

RESULTS

Size and Characteristics of the Study Population

Of 2057 women enrolled in P1025 as of August 1, 2010, 1549 were enrolled during pregnancy, had delivered, and had been followed through at least 6 weeks postpartum. Of these, 1221 initiated ART during pregnancy. In this group, 307 had antepartum CD4 counts >350 cells per cubic millimeter before initiation of ART. An additional 124 women without pre-ART CD4 measurements had earliest pregnancy CD4 counts >400 cells per cubic millimeter after ART initiation [median weeks on ART before CD4 count: 8.2, interquartile range (IQR): 4.0– 13.9]. Of the 431 women, 128 had   1.5 mL of stored plasma collected at each of the specified time points and were included in the analyses. Characteristics of the 128 women included versus the 303 women excluded due to lack of at least 1 repository sample (166 ART continuers and 137 discontinuers) revealed no significant differences except that the women included were more likely to be on boosted protease inhibitors (PI), whereas those excluded were more likely to be on non-nucleoside reverse transcriptase inhibitors (data not shown).

Of the 128 women studied, 65 were continuers and 63 were discontinuers. Of the 63 discontinuers, 30 stopped after delivery and before the delivery biomarker measurement ("early discontinuers," median duration of ART after delivery of 0 days, IQR: 0–1) and 33 stopped after delivery and after the delivery biomarker measurement and before the 6-week postpartum biomarker measurement ("late discontinuers," median duration of ART after delivery of 13 days, IQR: 3– 21). The first biomarker measurement during pregnancy was taken at a median gestational age of 29 weeks (IQR: 25–34). The delivery measurement was taken within 3 days of delivery in 75% of the group. The final measurement was taken at a median of 6.9 weeks postpartum (IQR: 6.0–7.7).

The baseline characteristics of study participants are shown in Table 1. No statistically significant differences were observed among the 3 ART status groups according to age, race/ethnicity, earliest CD4 count during pregnancy, CDC clinical classification at study entry,[9] or mode of delivery. The median CD4 count was 574 cells per cubic millimeter and 28% of women had earliest pregnancy CD4 counts >700 cells per cubic millimeter. Continuers were more likely to be on a boosted PI regimen during pregnancy ($P = 0.03$) compared with discontinuers. We observed no differences by ART regimen in pretreatment viral load, viral load at time of delivery, or CD4 count at time of delivery.

Biomarker Levels and Trajectories

Median biomarker levels were elevated above the upper limit of the reference range at all time points tested, with highest levels observed at delivery with median hsCRP, D-dimer, and IL-6 of 24.4 mg/L, 2.3 μg/mL, and 4.5 pg/mL, respectively (Fig. 1). All biomarkers increased from late pregnancy to delivery, then decreased postpartum (slopes all significantly different from 0, $P < 0.001$). No significant differences in biomarker trajectories across the 3 ART status groups were observed (Fig. 2).

In the regression analysis combining early and late discontinuers into a single group, continuers had a greater decrease in log D-dimer postpartum than discontinuers (estimated change: – 1.51 versus – 1.13, $P = 0.002$) (Fig. 3).

Of the 77 women with viral load results available at 6 weeks postpartum, 49% had viral loads >400 copies per milliliter [continuers: 30% (n = 13), discontinuers: 74% (n = 25), $P < 0.001$]. No significant differences were observed in biomarker trajectories for hsCRP and IL-6 by viral load. Women with viral loads   400 copies per milliliter had a greater decrease in log D-dimer postpartum compared with those with viral loads >400 copies per milliliter

(estimated change: −1.61 versus −1.20, $P = 0.005$) (Fig. 3). There were differences in D-dimer by age and ethnicity. Women in the highest age quartile (32 years and older) had a higher log D-dimer at all 3 time points compared with younger women (difference = 0.25, $P = 0.02$). Hispanic women had a greater decrease in log D-dimer postpartum than non-Hispanic women (estimated change: − 1.60 versus − 1.19, $P = 0.002$).

Biomarkers and Pregnancy or Delivery Complications

Seventeen women (13% of the study population) had 20 pregnancy or delivery complications. One woman was excluded from this analysis because her first event occurred before her first biomarker measurement. The median time from biomarker collection to complication was 46 days (IQR: 30–75). Women who experienced at least 1 complication had higher levels of IL-6 at all 3 time points and a greater decrease in estimated log IL-6 postpartum (− 1.53 versus − 0.80, $P = 0.007$) compared with women who had no complications. Women who experienced at least 1 complication also had a higher log hsCRP at each time point compared with those with no complications and a higher log D-dimer at each time point, although these differences were not statistically significant (difference = 0.37, $P = 0.09$, and difference = 0.14, $P = 0.36$, respectively) (Fig. 4).

Biomarkers and Complications up to 6 Months Postpartum

Sixteen women had 24 incident postpartum clinical events, but no World Health Organization stage 4 events, significant non–AIDS-defining events, or deaths. No significant increase in the risk of events was observed for ART discontinuers compared with continuers. The most common clinical diagnoses were cervical dysplasia (10 events), bronchitis (4), and pneumonia (3). No significant association was observed between biomarker levels in the third trimester or at delivery and the incidence of postpartum clinical events.

DISCUSSION

Does ART Mediate Markers of Inflammation and Coagulation in Postpartum Women?

In this cohort of HIV-infected women from the United States and Puerto Rico with high CD4 counts, postpartum biomarkers markedly declined among all women, regardless of ART status. Unlike biomarker results from TI studies of nonpregnant women and men with HIV infection, the primary drivers of biomarker levels among our population were pregnancy and delivery. The contribution of inflammation from HIV infection versus pregnancy in our study is unclear because no HIV-uninfected subjects were included. Lack of virological suppression was associated with higher D-dimer levels, supporting the important role of virological suppression in the inflammatory milieu of HIV-infected individuals.

Studies of HIV-uninfected pregnant women show that uncomplicated pregnancy and delivery are characterized by a maternal inflammatory response.[12,13] Elevations in D-dimer also have been described during normal pregnancy and uncomplicated delivery.[14,15] Mikyas et al[16] evaluated serum neopterin, beta-2-microglobulin, tumor necrosis factor alpha, and cell surface activation markers HLA-DR and CD38 on CD8 T cells in 99 HIV-infected women and 46 HIV-uninfected women during pregnancy and up to 6 months postpartum. Evidence of inflammation and cellular immune activation was found in all women at later stages of pregnancy, and the increases in HIV-infected women paralleled those seen in HIV-uninfected women, but at more marked levels. Truong et al[17] also found increased levels of serum activation markers in HIV-infected and -uninfected pregnant women, with a rise postpartum despite various antiretrovirals, although postpartum ART blunted the effect. Taken together, these studies suggest that HIV-infected women experience an inflammatory

response beyond that seen in healthy women with uncomplicated pregnancies. Our study lends support to the hypothesis that ART attenuates postpartum inflammation, with continuation of treatment associated with more rapid declines in postpartum D-dimer levels.

Association of Biomarkers With Subsequent Late Pregnancy and Delivery Complications Among HIV-Infected Women

CRP levels are elevated in healthy HIV-uninfected women with pre-eclampsia,[18] rupture of membranes with chorioamnionitis,[19] and preterm delivery,[20] and elevated CRP at 9–13 weeks of gestation has been shown to be associated with the subsequent development of gestational diabetes.[21] We found an association with IL-6 and pregnancy and delivery complications and a trend toward significance for hsCRP and D-dimer. If confirmed in larger studies, biomarker measurements could be useful for counseling when added to other known risks for adverse pregnancy outcomes (prior history of complications, smoking, hypertension, PI use) to encourage behavior change for modifiable risk factors and inform the need for closer follow-up for those at highest risk of complications.

Biomarkers in Pregnant and Postpartum Women With HIV: Lack of Association With Clinical Events up to 6 Months Postpartum

Controversy exists over whether pregnancy modifies HIV disease in regard to immunologic, virological, and/or clinical outcomes. CD4% seems to remain stable during pregnancy in HIV-infected women.[22–25] Viral loads in women without primary acute infection have also been shown to remain stable during pregnancy in the absence of ART.[23] Additionally, HIV-infected pregnant women do not seem to have an increased risk of virological failure on ART compared with nonpregnant women, regardless of whether they conceive on ART or initiate after pregnancy.[26,27] Therefore, although existing data do not suggest that pregnancy itself accelerates HIV disease progression or that pregnancy increases the risk for virological failure, the potential contribution of a start–stop event or TI to HIV disease progression remains unclear. A recent study evaluated 206 ART-naïve pregnant women with CD4 counts >350 cells per cubic millimeter. No difference in CD4 counts and viral loads was observed over 1 year postpartum regardless of whether women continued or discontinued postpartum antiretrovirals, but more marked $CD8^+$ T-cell immune activation (defined by $CD38^+$ and DR^+) was seen among the 59 women who discontinued antiretrovirals.[28] In this study, the majority of women discontinued zidovudine monotherapy, and only 18 discontinued 3-drug ART postpartum, limiting the power to detect differences among ART continuers and discontinuers, and reducing the generalizability of the results.

Data on poor outcomes after TI have been obtained from men and nonpregnant women in studies across the globe, including 2 studies from Africa, Trivacan and Development of Antiretroviral Therapy in Africa, both stopped early due to an increased rate of morbidity and/or disease progression.[3,5] SMART involved randomization of more than 5000 patients from 33 countries with baseline CD4 counts >350 cells per cubic millimeter (both ART-naïve and on ART), to take therapy continuously or interrupt therapy, with reinitiation for a CD4 decline to <250 cells per cubic millimeter. This trial was also stopped early for a higher risk of serious AIDS-related and non-AIDS events in the TI arm (relative risk: 5.80 and 1.63, respectively).[4] We observed high peak median levels of all 3 biomarkers at delivery, over 4 times the latest median hsCRP level (24.0 versus 5.26 mg/L) observed before death among those who died in the SMART study, and over 3 times the latest D-dimer level (2.3 versus 0.70 μg/mL) observed before death in SMART. Caution must be used in generalizing data from these TI studies to pregnant and postpartum women who are younger and healthier with higher CD4 nadir and a shorter duration of ART exposure. IMPAACT's Promoting Maternal and Infant Survival Everywhere (PROMISE 1077HS) study is an ongoing trial in which women who do not meet criteria for long-term ART (by country-

specific guidelines) are randomized to continue or discontinue ART postpartum. Pending data from this trial, information is needed that can help to identify women with high CD4 counts who would most benefit from ART continuation postpartum.

Study Limitations and Weaknesses

Our study has several important limitations. Because the study population did not include HIV-uninfected women, we cannot comment on the contribution of HIV to absolute elevations in biomarkers. Approximately 70% of P1025 participants were excluded from our analysis due to missing samples, and although we did not detect differences other than ART regimen, we cannot exclude the possibility of other unmeasured differences between participants who did versus did not have plasma stored during the study. Additionally, of those women included, we do not have complete data on reasons for continuation versus discontinuation. Therefore, it is possible that women who continued ART in our sample may have been different, either clinically (ie, sicker) or in other ways (providers, insurance, social issues) than those who discontinued. Early in our analysis, we recognized that a subset of ART continuers were not virologically suppressed at 6 weeks postpartum and therefore evaluated groups using viral load data. This analysis was limited to the 77 women who had viral load data and may have been underpowered to detect differences in IL-6 and hsCRP and biased by the large amount of data missing from the analysis. Finally, preconception biomarker data and long-term data on biomarkers and clinical events are important to our understanding of inflammation in women during pregnancy and postpartum but were not collected in our study.

CONCLUSIONS

In contrast to results from TI studies in men and nonpregnant women, both ART continuers and ART discontinuers in this population of women with high nadir CD4 counts had significant decreases in the levels of D-dimer, hsCRP, and IL-6 postpartum. We did find a significantly more rapid decline in D-dimer levels in postpartum ART continuers compared with discontinuers and among those in whom viral loads were 400 copies per milliliter at 6 weeks postpartum. We found a significant association between IL-6 and subsequent pregnancy and delivery complications, but no significant associations between biomarker levels and AIDS and non–AIDS-defining clinical events up to 6 months postpartum. Future studies should evaluate preconception biomarker levels and incorporate longer postpartum follow-up to better characterize associations between biomarkers, ART status, and clinical events. Questions about use of ART in postpartum women must be answered through direct, carefully planned, randomized trials that inform clinical decision making for this unique subset of the HIV-infected population.

Acknowledgments

Appendix

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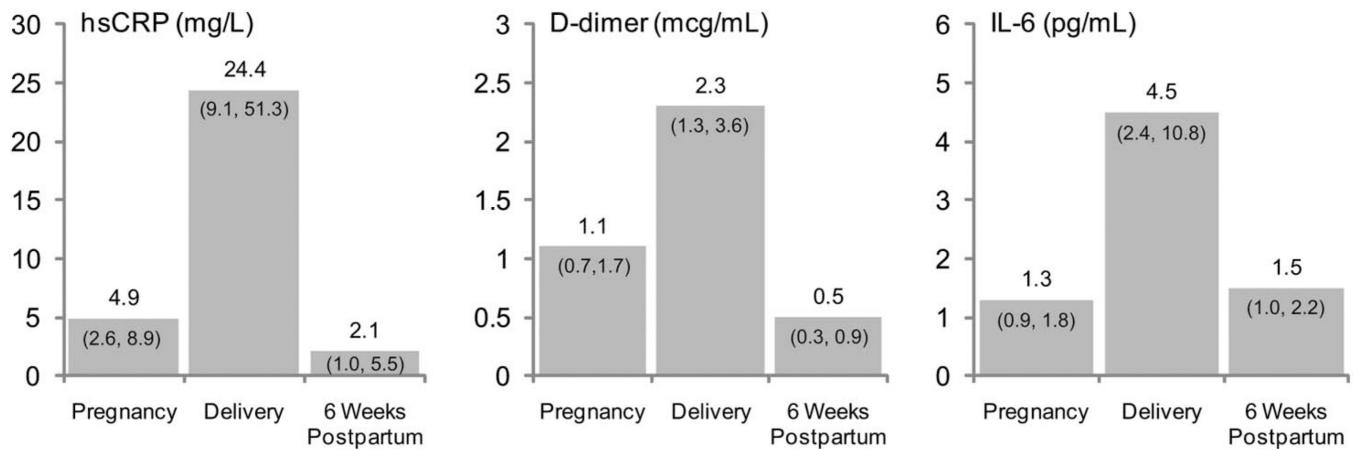**FIGURE 1.**
Median (Q1, Q3) biomarker levels. All biomarker levels were highest at time of delivery, then decreased postpartum to a level comparable with or lower than the level during pregnancy. Quest reference range: (1) hsCRP: >3–10 mg/L is considered high risk and <1 mg/L low risk; (2) D-dimer upper limit of normal is 0.50 μg/mL; (3) IL-6 (highly sensitive) lower limit of detection is −0.31pg/mL. Data gathered from http:// www.questdiagnostics.com/testcenter and http://www.specialtylabs.com/clients/gbmc/ details.asp?id=S51587&spt=true.
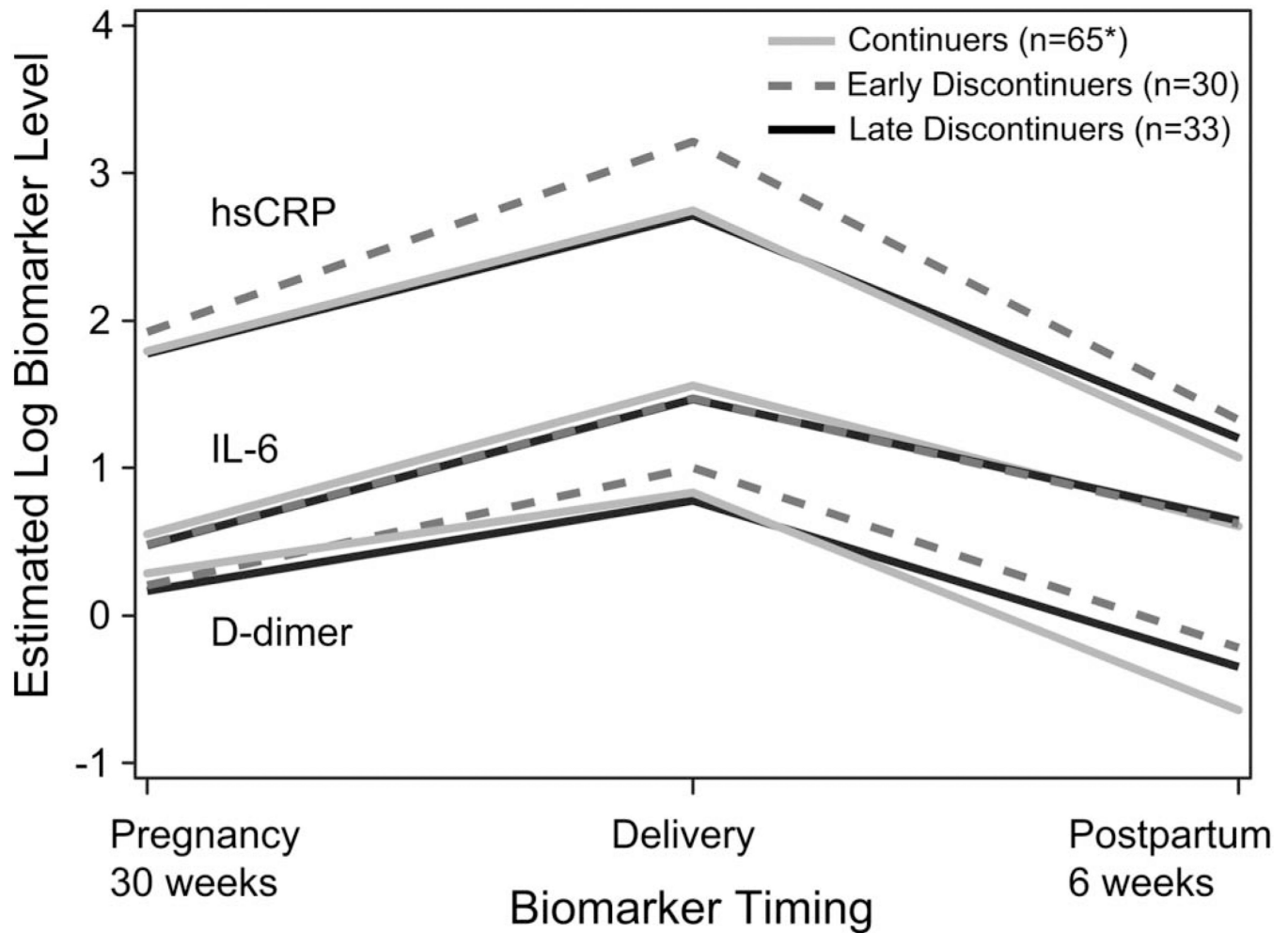
FIGURE 2.
Estimated log biomarker trajectories by ART status group. Displays predicted values at selected time points from longitudinal regression models. All biomarkers increased from the third trimester of pregnancy to delivery and decreased by 6 weeks postpartum to levels below those seen in pregnancy. *One woman was missing the D-dimer measurements.
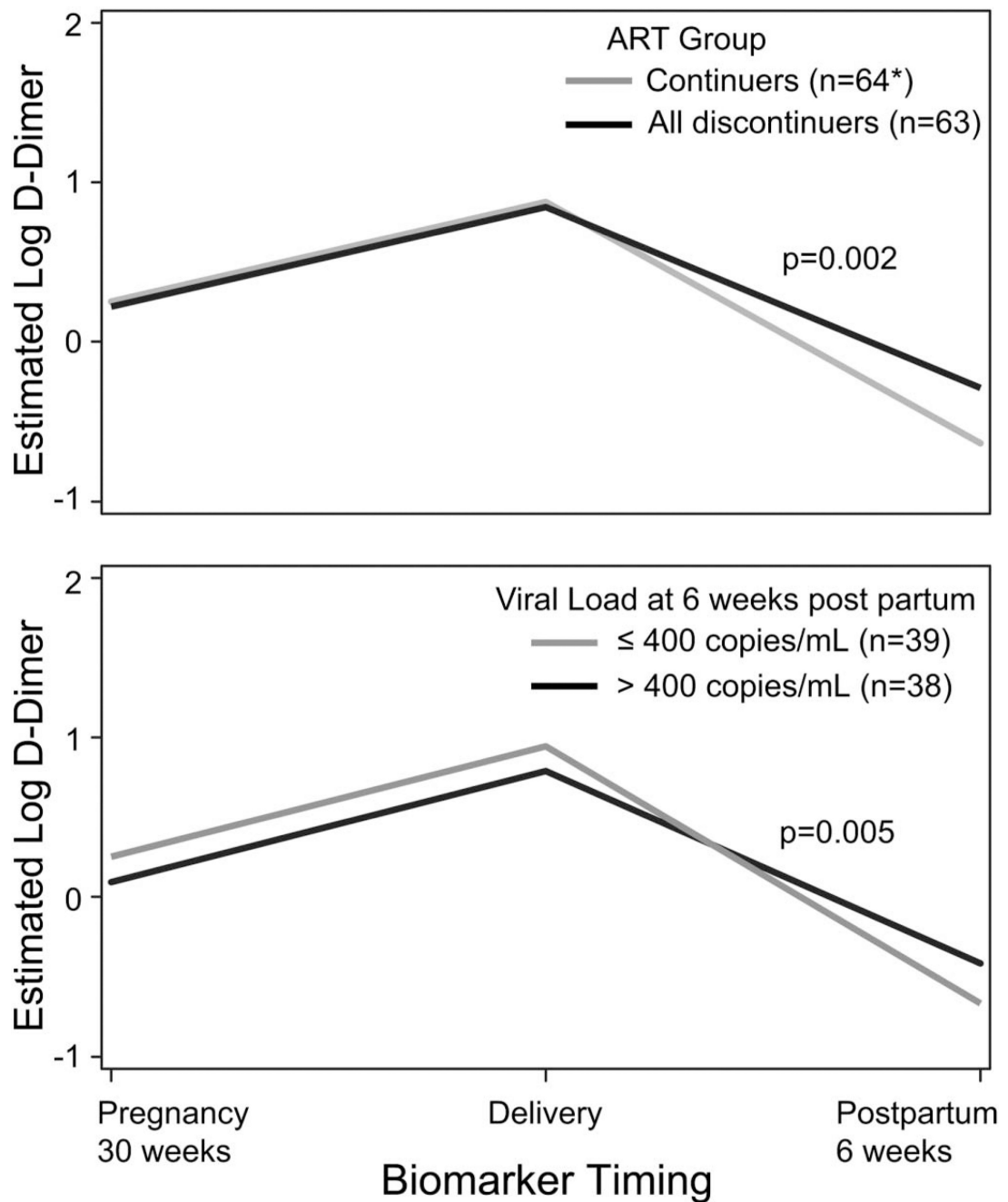
FIGURE 3.
Estimated log D-dimer trajectory by ART status and viral load at 6 weeks postpartum.
Displays predicted values at selected time points from longitudinal regression models. D-dimer levels were significantly higher among women when early and late discontinuers were combined into 1 group (above) and in women with viral loads greater than 400 copies per milliliter (below). *One woman was missing the D-dimer measurements. Viral load at 6 weeks postpartum was only available in 77 women (43 continuers and 34 discontinuers).
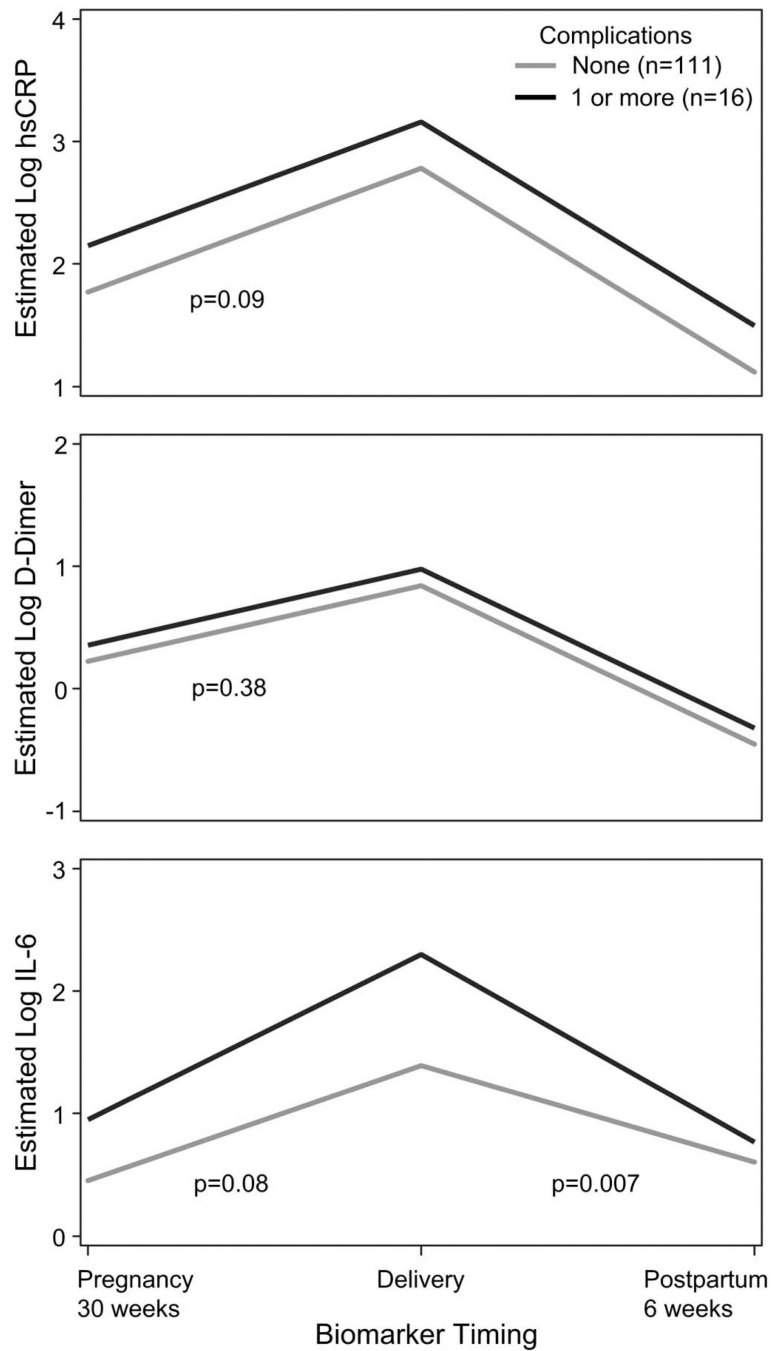
FIGURE 4.
Biomarker trajectories in women with and without pregnancy/delivery complications. Displays predicted values at selected time points from longitudinal regression models. IL-6 trajectory was significantly different in women who experienced at least 1 pregnancy/ delivery complication compared with those who did not. At each time point, D-dimer and hsCRP levels were higher in women who experienced at least 1 pregnancy/delivery complication compared with those who did not, but these differences were not statistically significant.

TABLE 1

Characteristics of Women by ART Status Group

| | | ART Group | | | |
| | | Discontinuers | | | |
Characteristic	Continuers N = 65	Early, N = 30	Late, N = 33	Total, N =128	P
Age (yrs), n (%)					
13–24	21 (32)	15 (50)	13 (39)	49 (38)	0.14[*]
25–30	17 (26)	8 (27)	13 (39)	38 (30)	
31+	27 (42)	7 (23)	7 (21)	41 (32)	
Race/ethnicity, n (%)					
Black non-Hispanic	31 (48)	22 (73)	20 (61)	73 (57)	0.20[*]
Hispanic	26 (40)	6 (20)	9 (27)	41 (32)	
White non-Hispanic/other	8 (12)	2 (7)	4 (12)	14 (11)	
Earliest CD4 count during pregnancy (cells/mm^3), n (%)					
Median (Q1, Q3)	540 (478, 670)	568 (467, 719)	663 (524, 773)	574 (478, 720)	0.17[†]
350–399	1 (2)	2 (7)	2 (6)	5 (4)	0.21[‡]
400–499	21 (32)	8 (27)	6 (18)	35 (27)	
500–599	19 (29)	7 (23)	4 (12)	30 (23)	
600–699	10 (15)	5 (17)	7 (21)	22 (17)	
700+	14 (22)	8 (27)	14 (42)	36 (28)	
Pre-ART viral load during pregnancy (copies/mL), n (%)[§]					
400	8 (20)	6 (24)	7 (26)	21 (23)	0.05[*]
401–1000	4 (10)	3 (12)	6 (22)	13 (14)	
1001–10,000	9 (22)	10 (40)	11 (41)	30 (32)	
>10,000	20 (49)	6 (24)	3 (11)	29 (31)	
CDC clinical classification at entry, n (%)					
A	58 (89)	28 (93)	33 (100)	119 (93)	0.25[‡]
B	3 (5)	2 (7)	0 (0)	5 (4)	
C	4 (6)	0 (0)	0 (0)	4 (3)	

Characteristic	Continuers N = 65	ART Group		Total, N =128	P
		Discontinuers			
		Early, N = 30	Late, N = 33		
Initial ART regimen during pregnancy, n (%)[//]					
2 NRTIs + 1 NNRTI	2 (3)	0 (0)	2 (6)	4 (3)	0.08[†]
2 NRTIs + 1 PI	16 (25)	9 (30)	5 (15)	30 (23)	
2 NRTIs + 1 boosted PI	39 (60)	16 (53)	14 (42)	69 (54)	
3 NRTIs	8 (12)	5 (17)	12 (36)	25 (20)	
Mode of delivery, n (%)					
Vaginal	32 (49)	16 (53)	17 (52)	65 (51)	0.78[*]
Cesarean section after labor and/or rupture of membranes	10 (15)	7 (23)	6 (18)	23 (18)	
Cesarean section before labor and before rupture of membranes	23 (35)	7 (23)	10 (30)	40 (31)	

[*] Chi square test; comparison for all 3 groups (continuers, early discontinuers, and late discontinuers).

[†] Kruskal–Wallis test; comparison for all 3 groups (continuers, early discontinuers, and late discontinuers).

[‡] The Fisher exact test; comparison for all 3 groups (continuers, early discontinuers, and late discontinuers).

[§] Pre-ART viral load was unavailable in n = 35 women.

[//] Classified by first regimen during pregnancy; 102 women (80%) were only on 1 regimen during pregnancy, 23 (18%) were on 2 regimens, and 3 (2%) were on 3 or 4 regimens during pregnancy.

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.