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Postpartum Viral Load Rebound in HIV-1–Infected Women Treated with Highly Active Antiretroviral Therapy: AIDS Clinical Trials Group Protocol A5150

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Abstract

Background—Pregnancy may lead to increases in HIV-1 RNA levels postpartum. The AIDS Clinical Trials Group (ACTG) A5150 study was designed to characterize the incidence of viral load rebound during the immediate 24 weeks postpartum and explore factors associated with viral load rebound.

Methods—We enrolled pregnant women in the United States who were ≥ 13 years of age, between 22 to 30 weeks gestation, and who planned to be on stable highly active antiretroviral therapy (HAART) for ≥ 8 weeks predelivery and to continue this therapy after delivery for the duration of the study. Choice of antiretrovirals (ARVs) was determined by the primary HIV provider. Viral load rebound was defined as an increase of $\geq 0.7 \log_{10}$ (5-fold) from the average of

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the weeks 34 and 36 gestation viral loads to week 24 postpartum or an absolute increase to >500 copies/mL for those with viral load <50 copies/mL.

Results—Eighty-four women enrolled for postpartum follow-up. Sixty-three had follow-up and viral load obtained through week 24 postpartum. Overall, 18/63 (28.6%; 95% confidence interval [CI], 17.9–41.4) met criteria for viral load rebound. Nineteen of the 63 women made changes or discontinued their ARV regimen prior to week 24 postpartum. For those who remained on stable ARVs, rebound occurred in 8/44 (18.2%; 95% CI, 8.2–32.7) compared with 10/19 (52.6%; 95% CI, 28.9–75.5) who did not remain on a stable ARV regimen.

Conclusions—In the early postpartum period, HIV-1–infected women commonly have increases in viral load. Unplanned changes in ARV regimens and discontinuations of treatment are frequent.

Keywords

HIV-1 viral load; lopinavir; nelfinavir; pharmacokinetics; pregnancy; ritonavir

Pregnancy is not associated with HIV-1 disease progression as defined by immunologic or clinical deterioration.^{1–6} However, data suggest that increases in viral load occur in the early postpartum period.^{7–9} The Ariel Project, conducted prior to the use of highly active anti-retroviral therapy (HAART), showed a significant average 6 copies/mL per day rise in viral load and a decline in CD4+ lymphocytes among 198 mothers in the 6 months after delivery.⁷ The 29 women who never received zidovudine also had a significant increase in viral load during the initial 24 weeks postpartum ($P = .02$), suggesting this finding was not solely due to loss of zidovudine activity. More recent studies examined HAART in pregnant women. Data from Pediatric AIDS Clinical Trials Group (PACTG) protocols 353, 354, 358, and 386, which were phase 1 pharmacokinetic studies of nelfinavir-, ritonavir-, indinavir-, and saquinavir-based regimens conducted in pregnant women, indicate that postpartum viral load rebound is a common phenomenon. Combining the 4 studies, 38/47 (81%) women had less than 400 copies/mL at delivery, 20/30 (67%) had less than 400 copies/mL at 6 weeks postpartum, and only 19/40 (47%) had less than 400 copies/mL at 12 weeks postpartum.^{10–13}

Many factors are likely to play a role in the viral load rebound that was reported postpartum. We hypothesized that both physiologic changes of pregnancy and decreased adherence following delivery could contribute to viral load rebound. Recent publications have shown that adherence to HAART is lower in the postpartum period than antepartum.^{14,15} Development of viral resistance could be a potential consequence of such changes in behavior or physiology postpartum and could result in an increased plasma viral load. ACTG A5150 was designed to examine these factors prospectively.

METHODS

Study Population and Design

The AIDS Clinical Trials Group (ACTG) Protocol A5150 was a multicenter, prospective, observational study designed to characterize the incidence, magnitude, and consequences of postpartum viral load rebound and explore factors associated with viral load rebound during the initial 24 weeks postpartum in HIV-1–infected pregnant women who remained on or initiated antiretroviral (ARV) therapy during pregnancy and who planned to remain on therapy after delivery.

Women ≥ 13 years with singleton pregnancy between 22 and 30 weeks gestation were eligible to enter the study if they planned to be on a stable HAART regimen for at least 8

weeks prior to delivery and to continue HAART postpartum. HAART was defined as any 2 nucleoside analogues (NRTI) combined with either a non-nucleoside analogue (NNRTI) or a protease inhibitor (PI) or any NNRTI with lopinavir/ritonavir. Other infrequently used regimens that were classified as HAART included zidovudine/lamivudine/abacavir, zidovudine/lamivudine/didanosine, lopinavir/ritonavir/lamivudine, saquinavir/ritonavir/lamivudine, and abacavir/nelfinavir/saquinavir. Choice of ARV medications was determined by each woman's primary HIV care provider who remained responsible for her clinical management throughout the study.

The baseline third trimester viral load from which rebound was determined was calculated as the average $\log_{10}$ viral load of gestational weeks 34 and 36, with a value <50 set to 50 copies/mL. To remain in the study for postpartum follow-up, women had to have been on stable HAART for at least 4 weeks prior to delivery of a live infant, have a baseline third trimester viral load measurement, and achieve a viral load of $<5,000$ copies/mL by delivery. Stable ARV was defined as no change in the number (increase or decrease) of NNRTI, NRTI, or PIs lasting more than 7 days during the period 4 weeks before delivery to the week 24 postpartum viral load measurement, with the exception of in-class substitutions for toxicity, use of intravenous (IV) zidovudine during labor and delivery, or any regimen change limited to ± 3 days of delivery.

Postpartum follow-up visits occurred at 2, 6, 12, and 24 weeks after delivery. For a subset of women who enrolled early in the study period, follow-up was scheduled up to 96 weeks postpartum. Due to slower than expected accrual, the study was closed to accrual and follow-up was truncated to 24 weeks of postpartum follow-up.

Self-reported adherence was measured by a standard validated ACTG questionnaire at study entry, 34 and 36 weeks gestation, delivery, and all postpartum visits.¹⁶ The 2 measures analyzed to assess adherence included the number of doses missed over the past 4 days and the estimation of the last time a dose was missed categorized as never skip medications, more than 3 months ago, 1 to 3 months ago, 2 to 4 weeks ago, 1 to 2 weeks ago, or within the past week.

Plasma HIV-1 RNA levels were measured with the Roche Amplicor HIV-1 Monitor (Version 1.5; Roche Diagnostic Systems, Inc, Branchburg, New Jersey, USA) (lower limit of quantification detection 50 copies/mL) at a central reference laboratory (Johns Hopkins University Hospital, Baltimore, Maryland, USA). Standard population sequencing for HIV resistance was performed at the University of Washington Clinical Virology Laboratory using an independently validated, Virology Quality Assessment (VQA)-certified assay on all available plasma specimens at the time of virologic failure.^{17,18} The numbers of resistant drug genotypes (class-specific resistance) were estimated using the Stanford University database (HIVDB.stanford.edu; version 6.0.1) and the results reported as the genotypic susceptibility score. Values assigned for degree of resistance of each ARV drug the woman was receiving, except for boosted ritonavir, were 0 for high-level resistance, 0.5 for intermediate or low-level resistance, and 1 for potential low-level resistance or no resistance.^{19,20} The total genotypic susceptibility score was the sum of the values assigned for each ARV in their regimen, thus 3-drug regimens would typically range from 0 (complete resistance) to 3 (potential low/no resistance).

HIV-1 infection status was determined retrospectively in the newborn infants when possible. The study was approved at the local institutional review board for all participating sites, and written informed consent was obtained from all women.

The primary study endpoint was the development of viral load rebound at 24 weeks postpartum compared with the third trimester value. Rebound was defined as an increase of

0.7 log₁₀ copies/mL or more. If the third trimester viral load was <50 copies/mL, rebound was defined as a rise to ≥500 copies/mL. The study's primary objective was to estimate the probability of developing viral load rebound. Secondary endpoints included development of viral rebound at each of 6 and 12 weeks postpartum, as well as cumulatively during the first 24 weeks postpartum. Because we anticipated differences in the development of viral load rebound by ARV experience, we compared viral load rebound by whether in their current pregnancy women were on their initial HAART regimen or on a subsequent, noninitial, regimen.

This study was reviewed administratively 3 times by a study monitoring committee appointed in accordance with ACTG operating procedures. At the first and second review, concern was voiced about slow accrual and high loss to follow-up prior to the first postpartum visit. Subsequent to the second review, the ACTG Scientific Agenda Steering Committee directed the team to close the study to accrual and truncate follow-up to postpartum week 24 for remaining women.

Statistical Analysis

The Clopper-Pearson method-based 95% confidence interval (CI) was calculated on the probability of viral load rebound at week 24. This study aimed to have data available at postpartum week 24 on 104 women in order to yield confidence intervals on the probability of viral load rebound of a width of 0.20 or smaller.

Logistic regression modeling with exact methods was used to assess in an exploratory fashion the association of antepartum/delivery subject characteristics as well as early (week 6) postpartum values for plasma HIV-1 RNA level, CD4 cell count, ARV use, and adherence with postpartum week 24 viral load rebound. The secondary endpoint of cumulative viral load rebound by postpartum week 24 was summarized with a Kaplan-Meier-based survival probability estimate.

Analyses were performed using SAS version 9 (SAS Inc, Cary, North Carolina, USA) and S-plus version 6 (Insightful Corp, Seattle, Washington, DC). Reported 2-sided *P* values and confidence interval levels are nominal.

RESULTS

One hundred twelve women were enrolled between December 23, 2002 and May 13, 2005. Twenty-eight women did not enter postpartum follow-up. Eighteen were ineligible for postpartum follow-up due to premature delivery such that no baseline (third trimester) viral load could be calculated (*n* = 10), fetal demise (*n* = 1), viral load ≥5,000 copies/mL near delivery (*n* = 4), or change in ARV therapy (*n* = 3). The other 10 did not enter postpartum follow-up for technical reasons: they were unable to come to clinic/missed postpartum entry visit time window (*n* = 7) or withdrew consent (*n* = 3).

Age, CD4 cell count, weight, gestational age, number of prior pregnancies, and history of prior AIDS-defining conditions at study entry did not differ significantly between those who did and did not enter postpartum follow-up (Table 1). However, a significantly larger proportion of women without postpartum follow-up reported a history of premature delivery (25% vs 4.8%; *P* = .01), and their median study entry plasma HIV-1 RNA level was higher (2.1 log₁₀ vs 1.7 log₁₀; *P* = .02). At delivery, the 84 women who were followed postpartum were on 29 different ARV regimens with the most common being zidovudine/lamivudine plus nelfinavir (*n* = 19), zidovudine/lamivudine plus nevirapine (*n* = 12), and zidovudine/lamivudine plus lopinavir/ritonavir (*n* = 8). Four or fewer women were on each of the other ARV regimens.

Postpartum Follow-Up

Of the 84 women who registered for postpartum follow-up, 12 withdrew from study follow-up prior to the primary endpoint at postpartum week 24 for reasons of loss to follow-up (4), subject decision (4), unable to attend clinic (2), no longer taking ARV (1), and moved (1). Of the 72 women with week 24 postpartum follow-up, viral load values were available on 63 and missing on 9 due to missed visits (8 women) or invalid assay result (1 woman). These 63 women comprise the dataset for our primary endpoint. Baseline characteristics are detailed for these 63 women as well as the subset of 44 women who remained on stable ARVs through week 24 postpartum (Table 1).

Eighteen women (18/63; 28.6%; 95% CI, 17.94–41.4) met criteria for viral load rebound (Table 2). In sensitivity analyses where missing viral load equals rebound, the estimated probability of rebound was 46.4% (95% CI, 35.5–57.7; 21 values imputed); using the last-value-carried forward, this probability estimate was 27.4% (95% CI, 18.2–38.2). The probability of viral load rebound did not differ significantly by whether women were on their initial HAART regimen, as 14 of 46 (30.4%; 95% CI, 17.7–45.8) women on initial HAART rebounded and 4 of 17 (23.5%; 95% CI, 7.0–49.9) of ARV-experienced women rebounded ($P = .76$).

For the 63 women with postpartum week 24 viral load data in univariate logistic regression (exact method) analysis, only postpartum week 6 HIV-1 RNA and race/ethnicity were significantly associated with viral load rebound where non-black women had a higher odds of viral load rebound than black women ($P = .03$; estimated odds ratio [OR] 4.00; 95% CI, 1.13–19.02) (Table 3). Overall, 3 out of 23 black women, 9 out of 26 Hispanic women, and 6 out of 14 white/other race/ethnicity women met criteria for viral load rebound at 24 weeks postpartum. In a sensitivity analysis, when race/ethnicity was categorized as Hispanic versus non-Hispanic, this association was no longer significant (non-Hispanic vs Hispanic [reference]: OR 1.64; 95% CI, 0.54–5.0; $P = .38$). This observed association between race/ethnicity with virologic rebound may be confounded by the subjects' clinical research site. While 13 of the 17 sites enrolled between 1 and 3 black women, 2 sites enrolled 73.1% (19) of the 26 Hispanic women. At these 2 sites, only 2 out of 19 Hispanic women with HIV-1 RNA data at week 24 met criteria for viral load rebound. Women not enrolled at these 2 sites were 5.85 times more likely to develop postpartum viral load rebound than those enrolled at these 2 sites (95% CI, 1.43–39.81, post hoc analysis). Additionally 16/23 (70%) of postpartum enrollees from these 2 sites remained on stable ARVs through week 24 versus 28/61 (46%) from other sites ($P = .08$, Fisher exact test). When both race/ethnicity (non-black vs black) and HIV RNA at postpartum week 6 ($n = 58$) were included in 1 model, estimates remained similar but race/ethnicity was no longer significant albeit still showing a trend for an association (non-black vs black [reference] race/ethnicity: OR 3.85; 95% CI, 0.99–19.66; $P = .07$; >50 vs ≤ 50 [reference] at week 6 postpartum visit: OR 4.07; 95% CI, 1.21–14.80; $P = .03$).

Although women who entered the study planned to continue ARV therapy after delivery and all women were encouraged to avoid ARV changes or discontinuations through 24 weeks postpartum, a greater number of women changed or discontinued ARV therapy than expected. Only 44 (69%) of the 63 women with a viral load measurement at 24 weeks postpartum remained on stable ARVs during this time period. Remaining on stable therapy was associated with being black non-Hispanic versus other (OR 4.44; 95% CI, 1.26–21.09; $P = .02$), older age (per 10 years older: OR 0.33; 95% CI, 0.12–0.84; $P = .02$), and better third trimester adherence (100% vs $<100\%$: OR 6.85; 95% CI, 2.04–25.34; $P < .01$).

Eight of the 44 women on stable ARVs through week 24 postpartum (18.2%; 95% CI, 8.2–32.7) met criteria for viral load rebound (Table 2). Those with a postpartum week 6 HIV-1

RNA >50 copies/mL (vs ≤50 copies/mL) had significantly higher odds of rebound at week 24 postpartum (estimated OR 16.5; 95% CI, 1.64–861.1; $P = .01$; Table 3). Six of 14 women with postpartum week 6 HIV-1 RNA value >50 copies/mL had viral load rebound at week 24 postpartum compared with 1 of 25 with postpartum week 6 HIV-1 RNA ≤50 copies/mL. As a group, only 28 of 44 (63.6%) women on stable therapy had a viral load of ≤50 copies/mL at 24 weeks postpartum. None of the other 18 covariates analyzed univariately showed a significant association with week 24 postpartum viral load rebound while on stable ARV ($P > .08$). Multivariable analyses were not performed due to the small event number.

Ten of the 19 (52.6%; 95% CI, 28.9–75.5) women who did not remain on a stable ARV therapy regimen after entry for postpartum follow-up had viral load rebound at week 24 postpartum (Table 2). All 10 rebounders had discontinued their ARV therapy: 4 per their request at 4.7, 13.3, 14.9, and 15.9 weeks postpartum, 3 per physician request at 14, 14.4, and 18 weeks postpartum, and 1 each for social issues, hepatotoxicity to zidovudine/lamivudine and nelfinavir, and nausea due to subsequent pregnancy. In general, the participant and physician decisions to stop medication seemed dependent on a stable CD4 and difficulty with adherence to the medication regimen and/or clinical follow-up.

We were able to successfully perform genotypic resistance testing on 15 of the 18 rebounders. Two women's samples were not amplifiable (HIV-1 RNA 2,550 copies/mL and 4,162 copies/mL) and one woman's sample was lost (Table 2). Of the 7 rebounders with genotypic resistance data on stable ARVs at the time of rebound, 3 had a genotypic susceptibility score of ≤1 compared with none of the 8 rebounders on unstable ARVs. In total, 8/15 rebounders had a genotypic susceptibility score of <3. The median time from discontinuing ARVs to the week 24 postpartum genotypic resistance assay sample date for the 8 rebounders on unstable ARVs was 9.7 weeks (range, 2.5 to 20.9).

For the secondary endpoint of cumulative viral load rebound, 27 of the 84 women who entered postpartum follow-up had viral load rebound between postpartum week 2 and 24 (estimated probability of remaining free of viral load rebound, 63.4%; 95% CI, 51.1–73.4). Nine women who had viral load rebound at 2, 6, or 12 weeks postpartum were not counted as viral load rebounders in the cross-sectional week 24 postpartum primary endpoint because 5 ended the study follow-up prematurely and 4 had a decline in viral load to <200 copies/mL (only 1 to <50 copies/mL) by week 24 postpartum. At week 6 postpartum, 10 of 74 (13.5%; 95% CI, 6.7–23.5) women with data had viral load rebound; at week 12 postpartum, 8 of 65 (12.3%; 95% CI, 5.5–22.8) with data had viral load rebound.

Among the 64 women with baseline and week 24 postpartum CD4 cell count data, the median (minimum, maximum) increase in CD4 cell count was +84 cells/mm³ (range, −304 to 915) and the median increase in CD4% was +1% (range, −13.5 to 25.5). For the 44 women who were on stable HAART at week 24 postpartum, the median changes in CD4 and CD4% were +103.5 (range, −304 to 915) cells/mm³ and +1.5 (range, −8 to 25.5), respectively. For the 19 women who were not on stable HAART at week 24 postpartum, the median changes in CD4 and CD4% were +49.5 (range, −276 to 330) cells/mm³ and +3 (range, −13.5 to 18), respectively.

Adherence Analysis

In cross-sectional analysis, the proportions of women with data who reported “no missed doses in the last 4 days” and “never skip medications” were lower at weeks 6 and 12 postpartum compared with the third trimester (Table 4). The sample size reporting adherence measures decreased from 83 to 53 women at 24 weeks postpartum. There was no obvious difference in week 24 postpartum adherence reported by women who were on their initial HAART regimen versus those on a subsequent regimen during the pregnancy; 30/38

(79%) on their initial HAART regimen reported no missed doses within the past 4 days versus 12/15 (80%) on a subsequent regimen. Week 6 postpartum adherence, as measured by 100% adherence versus < 100% adherence or by never missed ARVs versus missed ARVs, was not significantly associated with week 24 postpartum viral load rebound (Table 3). We found no significant evidence of the median change in adherence being different from zero for the continuous outcome of change in 4-day recall adherence when considering change from third trimester to week 6 postpartum, week 24 postpartum, or change from week 6 to week 24 postpartum (signed rank test, $P \geq .12$). We did find that women who reported that they had missed taking their ARVs at least once during the third trimester had significantly increased odds of missing their postpartum week 24 visit (ever vs never skip [reference]: estimated OR 2.92; 95% CI, 1.03–9.15; $P = .04$; 20 events).

Infant HIV-1 infection status was collected retrospectively but could not be obtained for all children. For the 84 women who registered to postpartum follow-up, 73 infants were known to be HIV uninfected and 11 had unknown status.

DISCUSSION

Our study is the first to prospectively characterize and assess factors associated with viral load changes postpartum. Of the 84 women who entered the postpartum follow-up period, 63 women had a viral load available at 24 weeks postpartum. Of these women, 28.6% (18/63) met criteria for viral load rebound at week 24 postpartum consistent with a true rebound probability of 17.9% to 41.4%, based on a 95% CI. It is likely that this is an underestimation of the proportion with viral load rebound, because women who reported missing ARV doses during the third trimester were significantly more likely to miss their week 24 postpartum visit. In the missing equals rebound sensitivity analysis for viral load rebound, the estimated probability increases to 46.4%, consistent with a true probability of 36% to 58% based on the 95% CI.

We were surprised that of the 84 women who entered postpartum follow-up, only 44 women (52%) with an RNA measurement at week 24 postpartum remained on stable ARVs. This group represented the population for which the study was designed to characterize the incidence of postpartum viral load rebound and explore reasons for rebound. Not surprisingly, these women had a lower frequency of viral load rebound at that timepoint (8/44; 18%; 95% CI, 8.2–32.7) compared with the 19 women with data who had changed or discontinued their ARVs prior to the week 24 postpartum HIV-1 RNA measurement (10/19; 53%; 95% CI, 28.9–75.5). Of these 19 women, all 10 rebounders had stopped their ARVs; of the 9 women who did not rebound, 1 had discontinued ARVs, 4 had temporarily held, and 4 had changed their ARV regimen prior to their postpartum week 24 measurement. Although we did not demonstrate an association between 4-day recall or last time a dose was missed with the development of postpartum viral load rebound, we did find that better third trimester adherence was associated with remaining on stable ARVs.

Among the variables analyzed, only week 6 postpartum viral load was associated with viral load rebound at week 24 postpartum for women remaining on stable ARV. The ability to identify factors that are independently associated with viral load rebound is limited due to the small event number. The most important antepartum factors identified a priori were third trimester RNA level, adherence, substance abuse, grade 3 or higher events, and CD4 cell count. Week 6 postpartum RNA and adherence were identified as the most important postpartum factors.

In our analysis of the 63 women who had week 24 postpartum viral load data, we were intrigued that black women had a lower rate of viral load rebound than other women. The

observed association between race/ethnicity with virologic rebound was difficult to interpret because of the concurrent association of race/ethnicity with enrollment at specific clinical research sites. We postulate that sites with the ability to provide coordinated care to the mother and baby postpartum in 1 location with adequate support staff, similar to the 2 sites in our study who had low frequency of viral load rebound and enrolled primarily Hispanic women, are more likely to be successful at maintaining adherence and minimizing the risk of viral load rebound postpartum. Genotypic resistance did not appear to explain viral rebound at week 24 postpartum in 7 of the 15 rebounders that we could test (genotypic sensitivity score [GSS] = 3 at rebound). Two of the 7 rebounders on stable ARVs had a GSS score of 3, suggesting a fully active regimen. These resistance data further suggest the role of nonadherence in postpartum viral load rebound.

Given that women who enrolled were anticipated to remain on ARVs postpartum and were encouraged to avoid elective ARV changes until after 24 weeks postpartum, we were surprised at the high rate of study dropout and ARV modifications/discontinuations that occurred. The resulting relatively lower than anticipated sample size for our week 24 viral load rebound endpoint limited precise estimation and the ability to detect associations, and consequently this study was more descriptive in nature.

Discontinuation of HAART can be considered an extreme form of nonadherence. The Women's Interagency HIV Study (WIHS) cohort demonstrated that HAART discontinuation resulted in large declines in CD4 cell counts and HIV-1 RNA increases.²¹ Of the 1,058 out of 1,072 HIV-1-infected women who initiated HAART between October 1994 and September 1999 and were still on HAART after October 1996, 223 (21.1%) discontinued all ARVs by September 1999. Side effects were the most frequently cited reason for stopping therapy. Currently recommended ARV regimens during pregnancy are associated with more toxicity (similar to regimens commonly used in the late 1990s) than currently recommended regimens outside of pregnancy.²³ This may contribute to treatment discontinuations and adherence issues. ARV adherence in our study was lower than previously reported in nonpregnant treatment-naïve trials using similar regimens. Another ACTG study, A5142, compared 3 regimens for initial therapy, efavirenz plus 2 NRTIs, lopinavir-ritonavir plus 2 NRTIs, and lopinavir-ritonavir plus efavirenz.²² At week 12, 405 of 657 (62%) reported having missed no doses since study entry with no significant differences by study treatment arm. This corresponds to our category of "never skip medications," which ranged from 36% to 47% for the 84 women who entered postpartum follow-up.

Several studies, including ours, have demonstrated that the early postpartum period is a vulnerable time associated with high rates of nonadherence, medication interruptions, and medication changes and discontinuations. From March 2001 to June 2005, the Women and Infants Transmission Study (WITS) found that antiretroviral therapy adherence was better during pregnancy than 6 months postpartum (OR 2.26).¹⁵ Sixty-one percent (188/309) of women reported complete adherence during the third trimester compared with 44% (97/220) at the 6 month postpartum visit. Compared with the third trimester, postpartum women are seen less often and there are fewer opportunities to reinforce adherence. After delivery, women may focus on their infant and neglect their own health care. Among women enrolled in PACTG 1025 from August 2002 to July 2005, 75% (344/455) self-reported perfect adherence defined as no missed doses in the 4 days before the study visit closest to and before delivery.¹⁴ This rate decreased postpartum to 185/284 (65%) at 6 weeks postpartum, 76/118 (64%) at 24 weeks postpartum, and 42/64 (66%) at 48 weeks postpartum ($P < .01$).

Additional planned pharmacokinetic and immunologic analyses may shed further insight into viral load increases postpartum. However, adherence and treatment discontinuation are

likely to remain key factors accounting for these viral load increases. Multiple studies have now shown that the postpartum period is associated with worse virologic outcome and adherence. We found that, among women who during pregnancy were deemed appropriate candidates to continue ARVs in the postpartum period, women who stayed on stable ARV therapy postpartum did better virologically than those who did not. Thus, future efforts should be devoted toward finding ways to improve the maintenance of ARV therapy in the postpartum period.

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Table 1

Baseline characteristics

Characteristic	Total subjects (N=112)			With week 24 viral load data		
	Not entered into PP follow-up (n=28)	Entered into PP follow-up (n=84)	Total (N=63)	Subjects on stable HAART (n=44)	Subjects not on stable HAART (n=19)	
Age, years	28	84	63	44	19	
	29 (27, 34)	30.5 (26, 34)	31 (26, 35)	32 (27, 35)	26 (23, 32)	
Race/ethnicity	3 (11%)	14 (17%)	12 (19%)	5 (11%)	7 (37%)	
White non-Hispanic	18 (64%)	35 (42%)	23 (37%)	20 (45%)	3 (16%)	
Black non-Hispanic	6 (21%)	31 (37%)	26 (41%)	18 (41%)	8 (42%)	
Hispanic (regardless of race)	1 (4%)	4 (5%)	2 (3%)	1 (2%)	1 (5%)	
Other	28	84	63	44	19	
Gestational age at study entry	27.8 (24.5, 29.0)	27 (25, 29)	27 (25, 29)	27 (25, 29)	28 (25, 29)	
Median (Q1, Q3)	28	84	63	44	19	
No. of prior pregnancies	2.5 (1, 4)	2 (1, 3)	2 (1, 3)	2 (1, 3)	1 (1, 3)	
Median (Q1, Q3)	21 (75%)	80 (95%)	60 (95%)	42 (95%)	18 (95%)	
History of premature delivery	7 (25%)	4 (5%)	3 (5%)	2 (5%)	1 (5%)	
Yes	26	83	62	43	19	
CD4 count at study entry, cells/mm ³	337 (197, 564)	389 (275, 594)	463 (285, 642)	481 (275, 658)	389 (296, 607)	
Median (Q1, Q3)	14 (50%)	36 (43%)	25 (40%)	17 (39%)	8 (42%)	
<350	12 (43%)	47 (56%)	37 (59%)	26 (59%)	11 (58%)	
≥350	2 (7%)	1 (1%)	1 (2%)	1 (2%)	0 (0%)	
Missing	26	82	62	43	19	
HIV-1 RNA at Log ₁₀ study entry, copies/mL	2.1 (1.7, 3.0)	1.7 (1.7, 2.3)	1.7 (1.7, 2.2)	1.7 (1.7, 2.1)	1.9 (1.7, 2.8)	
Median (Q1, Q3)	7 (25%)	45 (54%)	36 (57%)	27 (61%)	9 (47%)	
≤50	19 (68%)	37 (44%)	26 (41%)	16 (36%)	10 (53%)	
>50	2 (7%)	2 (2%)	1 (2%)	1 (2%)	0 (0%)	
Missing	26 (93%)	76 (90%)	58 (92%)	39 (89%)	19 (100%)	
History of prior AIDS-defining illness at study entry	2 (7%)	8 (10%)	5 (8%)	5 (11%)	0 (0%)	
Yes	18 (64%)	56 (67%)	39 (62%)	28 (64%)	11 (58%)	
Highest education level						
≤11th grade						

Characteristic	Total subjects (N=112)			With week 24 viral load data		
	Not entered into PP follow-up (n=28)	Entered into PP up (n=84)	Total (N=63)	Subjects on stable HAART (n=44)	Subjects not on stable HAART (n=19)	
Log ₁₀ HIV-1 RNA at 3rd trimester, copies/mL	High school +	10 (36%)	28 (33%)	24 (38%)	16 (36%)	8 (42%)
	n	-	84	63	44	19
	Median (Q1, Q3)		1.7 (1.7, 1.7)	1.7 (1.7, 1.8)	1.7 (1.7, 1.7)	1.7 (1.7, 2.8)
3rd trimester CD4 count, cells/mm ³	≤50	-	61 (73%)	47 (75%)	34 (77%)	13 (68%)
	>50	-	23 (27%)	16 (25%)	10 (23%)	6 (32%)
	n	-	82	62	43	19
3rd trimester >grade 3 lab./sign/symp.	Median (Q1, Q3)	-	418 (295, 588)	448.3 (299.0, 608.5)	447.5 (285, 602)	480.5 (299, 630)
	<350	-	30 (36%)	22 (35%)	15 (34%)	7 (37%)
	≥350	-	54 (64%)	41 (65%)	29 (66%)	12 (63%)
Type of delivery	Yes	-	13 (15%)	13 (21%)	11 (25%)	2 (11%)
	No	-	50 (60%)	50 (79%)	33 (75%)	17 (89%)
	Missing	-	21 (25%)	0 (0%)	0 (0%)	0 (0%)
IV ZDV at delivery	Vaginal	-	37 (44%)	28 (44%)	19 (43%)	9 (47%)
	Cesarean	-	47 (56%)	35 (56%)	25 (57%)	10 (53%)
	Yes	-	68 (81%)	54 (86%)	37 (84%)	17 (89%)
On initial ARV at delivery	No	-	16 (19%)	9 (14%)	7 (16%)	2 (11%)
	Yes	-	61 (73%)	46 (73%)	31 (70%)	15 (79%)
	No	-	23 (27%)	17 (27%)	13 (30%)	4 (21%)
PP week 6 log ₁₀ HIV-1 RNA, copies/mL	n	-	74	58	39	19
	Median (Q1, Q3)	-	1.7 (1.7, 2.2)	1.7 (1.7, 2.2)	1.7 (1.7, 1.9)	1.7 (1.7, 2.3)
	≤50	-	45 (54%)	37 (59%)	25 (57%)	12 (63%)
PP week 6 CD4 count, cells/mm ³	>50	-	29 (35%)	21 (33%)	14 (32%)	7 (37%)
	Missing	-	10 (12%)	5 (8%)	5 (11%)	0 (0%)
	n	-	72	58	39	19
PP week 6 CD4 count, cells/mm ³	Median (Q1, Q3)	-	560.5 (368.0, 765.5)	590 (376, 752)	619 (376, 792)	577 (332, 739)
	<350	-	16 (19%)	13 (21%)	8 (18%)	5 (26%)
	≥350	-	56 (67%)	45 (71%)	31 (70%)	14 (74%)

Characteristic	Total subjects (N=112)		With week 24 viral load data		
	Not entered into PP follow-up (n=28)	Entered into PP follow-up (n=84)	Total (N=63)	Subjects on stable HAART (n=44)	Subjects not on stable HAART (n=19)
PP week 6 adherence 1	Missing	12 (14%)	5 (8%)	5 (11%)	0 (0%)
	<100%	25 (30%)	20 (32%)	11 (25%)	9 (47%)
	100%	49 (58%)	39 (62%)	30 (68%)	9 (47%)
	Missing	10 (12%)	4 (6%)	3 (7%)	1 (5%)
PP week 6 adherence 2	Never miss	29 (35%)	27 (43%)	21 (48%)	6 (32%)
	Other	45 (54%)	32 (51%)	20 (45%)	12 (63%)
	Missing	10 (12%)	4 (6%)	3 (7%)	1 (5%)
Sites post hoc ^a	Site 1, site 2	23 (27%)	21 (33%)	16 (36%)	5 (26%)
	Other sites (n=18)	61 (73%)	42 (67%)	28 (64%)	14 (74%)

Note: Values shown are n (%) unless otherwise indicated. IV ZDV = intravenous zidovudine; ARV = antiretroviral; PP = postpartum.

^aTwo sites that enrolled a large number of Hispanic women (19 out of 21) and also had only 2 virologic failures among 21 women.

Viral load and genotypic susceptibility score for women who developed rebound at 24 weeks postpartum

Table 2

Group (N=63)	Median log ₁₀ HIV-1 RNA at 24 wks PP (range)	Median HIV-1 RNA rise from third trimester baseline (range)	HIV-1 RNA <50 copies/mL at baseline (34/36 week gestation)	Total genotypic susceptibility score	
				Score	No. with score
All rebounders (n = 18)	3.86 (3.19–4.6)	1.77 (0.95–2.84)	11/18 (61%)		(n = 15)
				0.5–1	3
				1.5–2	3
				2.5	2
				3	7
Rebounders on stable ARV (n = 8)	3.85 (3.19–4.4)	1.7 (0.95–2.29)	4/8 (50%)		(n = 7)
				0.5–1	3
				1.5–2	2
				2.5	0
				3	2
Rebounders on unstable ARV (n = 10)	3.95 (3.34–4.6)	1.86 (0.98–2.84)	7/10 (70%)		(n = 8)
				0.5–1	0
				1.5–2	1
				2.5	2
				3	5

Note: PP = postpartum; ARV = antiretroviral.

Logistic regression results for week 24 viral load rebound for women with week 24 viral load data

Table 3A

Covariate	Level (1st is reference group)	Est. OR (95% CI, exact)	With week 24 viral load data (n=63)		
			Exact P value	No. [no. (%) with rebound in ref. group]	No. [no. (%) with rebound in comp. group]
Race/ethnicity	Black vs other	4.00 (1.13, 19.02)	0.03	23 [3(13.0)]	40 [15(37.5)]
Age	per 10 years	1.26 (0.50, 3.25)	0.63	—	—
Age (categorical)	≤24 vs >24 years	1.00 (0.28, 4.12)	1.00	14 [4(28.6)]	49 [14(28.6)]
History of IV drug use	Never vs ever	1.28 (0.17, 7.26)	0.79	57 [16(28.1)]	6 [2(33.3)]
Education	High school+ vs ≤11th grade	1.45 (0.47, 4.43)	0.51	39 [10(25.6)]	24 [8(33.3)]
Prior pregnancies	No vs yes	1.73 (0.38, 12.31)	0.50	10 [2(20.0)]	53 [16(30.2)]
Time since first HIV diagnosis	per year	0.96 (0.85, 1.08)	0.54	—	—
Prior AIDS defining illness at entry	No vs yes	0.60 (0.03, 4.46)	0.65	58 [17(29.3)]	5 [1(20.0)]
Gestation week at delivery	per week	1.41 (0.96, 2.16)	0.08	—	—
3rd trimester HIV-1 RNA	≤50 copies/mL vs >50 copies/mL	2.55 (0.76, 8.52)	0.13	47 [11(23.4)]	16 [7(43.8)]
3rd trimester CD4 count	per 100 cells/mm ³	1.01 (0.79, 1.28)	0.92	—	—
3rd trimester CD4 count (categorical)	≥350 cells/mm ³ vs <350 cells/mm ³	1.27 (0.40, 3.93)	0.68	41 [11(26.8)]	22 [7(31.8)]
3rd trimester ≥grade 3 lab./sign/symp.	No vs yes	1.78 (0.47, 6.37)	0.39	50 [13(26.0)]	13 [5(38.5)]
Type of delivery	Vaginal vs cesarean	1.00 (0.33, 3.07)	1.00	28 [8(28.6)]	35 [10(28.6)]
IV ZDV at delivery	Yes vs no	1.30 (0.25, 5.63)	0.74	54 [15(27.8)]	9 [3(33.3)]
On initial ARV at delivery	Yes vs no	1.42 (0.42, 5.74)	0.59	17 [4(23.5)]	46 [14(30.4)]
3rd trimester adherence 1	100% vs <100%	2.48 (0.74, 8.30)	0.14	46 [11(23.9)]	16 [7(43.8)]
3rd trimester adherence 2	Never miss vs other	1.44 (0.48, 4.41)	0.51	35 [9(25.7)]	27 [9(33.3)]
PP week 6 HIV-1 RNA	≤50 copies/mL vs >50 copies/mL	3.90 (1.21, 13.33)	0.02	37 [7(18.9)]	21 [10(47.6)]
PP week 6 CD4 count	per 100 cells/mm ³	0.90 (0.71, 1.10)	0.33	—	—
PP week 6 CD4 count (categorized)	<350 vs ≥350 cells/mm ³	1.72 (0.45, 6.25)	0.42	45 [12(26.7)]	13 [5(38.5)]
PP week 6 adherence 1	100% vs <100%	1.24 (0.36, 4.07)	0.72	39 [10(25.6)]	20 [6(30.0)]
PP week 6 adherence 2	Never miss vs other	1.59 (0.50, 5.41)	0.43	27 [6(22.2)]	32 [10(31.3)]

Note: Age, time since first HIV-1 diagnosis, gestation week at delivery, and CD4 cell count were analyzed on a continuous scale, unless otherwise mentioned. NA = The logistic regression analysis could not be performed as all events fell into one group among those on stable ARV through week 24 postpartum. ARV = antiretroviral; OR = odds ratio; PP = postpartum.

Logistic regression results for week 24 viral load rebound for women with week 24 viral load data on stable ARV therapy at week 24

Table 3B

Covariate	Level (1st is reference group)	Est. OR (95% CI, exact)	On stable ARV at week 24 (n=44)		
			Exact P value	No. [no. (%) with rebound in ref. group]	No. [no. (%) with rebound in comp.group]
Race/ethnicity	Black vs other	1.48 (0.24,10.97)	0.92	20 [3(15.0)]	24 [5(20.8)]
Age	per 10 years	2.65 (0.63,13.61)	0.20	—	—
Age (categorical)	≤24 vs >24 years	NA	NA	NA	NA
History of IV drug use	Never vs ever	NA	NA	NA	NA
Education	High school + vs ≤11th grade	1.06 (0.14, 6.53)	1.00	28 [5(17.9)]	16 [3(18.8)]
Prior pregnancies	No vs yes	1.39 (0.13, 73.47)	1.00	7 [1(14.3)]	37 [7(18.9)]
Time since first HIV diagnosis	per year	0.92 (0.74, 1.11)	0.44	—	—
Prior AIDS defining illness at entry	No vs yes	1.14 (0.02, 14.19)	1.00	39 [7(17.9)]	5 [1(20.0)]
Gestation week at delivery	per week	1.75 (0.94, 3.70)	0.08	—	—
3rd trimester HIV-1 RNA	≤50 copies/mL vs >50 copies/mL	4.77 (0.69, 34.38)	0.13	34 [4(11.8)]	10 [4(40.0)]
3rd trimester CD4 count	per 100 cells/mm ³	0.86 (0.57, 1.22)	0.45	—	—
3rd trimester CD4 count (categorical)	≥350 cells/mm ³ vs <350 cells/mm ³	2.23 (0.35, 14.43)	0.51	29 [4(13.8)]	15 [4(26.7)]
3rd trimester ≥grade 3 lab./sign/symp.	No vs yes	3.98 (0.59, 27.69)	0.18	33 [4(12.1)]	11 [4(36.4)]
Type of delivery	Vaginal vs cesarean	1.32 (0.22, 9.84)	1.00	19 [3(15.8)]	25 [5(20.0)]
IV ZDV at delivery	Yes vs no	2.03 (0.16,16.72)	0.75	37 [6(16.2)]	7 [2(28.6)]
On initial ARV at delivery	Yes vs no	1.31 (0.19,15.29)	1.00	13 [2(15.4)]	31 [6(19.4)]
3rd trimester adherence 1	100% vs <100%	NA	NA	NA	NA
3rd trimester adherence 2	Never miss vs other	NA	NA	NA	NA
PP week 6 HIV-1 RNA	≤50 copies/mL vs >50 copies/mL	16.50 (1.64, 861.1)	0.01	25 [1(4.0)]	14 [6(42.9)]
PP week 6 CD4 count	per 100 cells/mm ³	0.78 (0.52, 1.07)	0.14	—	—
PP week 6 CD4 count (categorized)	<350 vs ≥350 cells/mm ³	3.87 (0.43, 32.20)	0.27	31 [4(12.9)]	8 [3(37.5)]
PP week 6 adherence 1	100% vs <100%	0.41 (0.01, 4.10)	0.76	30 [6(20.0)]	11 [1(9.1)]
PP week 6 adherence 2	Never miss vs other	0.36 (0.03, 2.61)	0.45	21 [5(23.8)]	20 [2(10.0)]

Note: Age, time since first HIV-1 diagnosis, gestation week at delivery, and CD4 cell count were analyzed on a continuous scale, unless otherwise mentioned. NA = The logistic regression analysis could not be performed as all events fell into one group among those on stable ARV through week 24 postpartum. ARV = antiretroviral; OR = odds ratio; PP = postpartum.

Cross-sectional, self-reported adherence over time for the 84 women who entered postpartum follow-up and for the 44 women who were on stable HAART through week 24 postpartum and had week 24 RNA data

Table 4

	n	3rd trimester	PP week 2	PP week 6	PP week 12	PP week 24
No missed doses last 4 days	84	60/83 (72%)	57/75 (76%)	49/74 (66%)	43/61 (70%)	42/53 (79%)
	44	37/43 (86%)	33/40 (83%)	30/41 (73%)	29/37 (78%)	34/44 (77%)
Never skip medications	84	47%	47%	39%	36%	43%
	44	67%	60%	51%	49%	43%
Last missed dose occurred within past week	84	19%	20%	27%	28%	17%
	44	2%	13%	24%	19%	16%

Note: PP = postpartum; HAART = highly active antiretroviral therapy.