Perinatal Depressive Symptoms, Human Immunodeficiency Virus (HIV) Suppression, and the Underlying Role of Antiretroviral Therapy Adherence: A Longitudinal Mediation Analysis in the IMPAACT P1025 Cohort

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Background. Women with HIV have higher risk of depressive symptoms in the perinatal period. Evidence on how perinatal depressive symptoms affect viral suppression (VS) and adherence to antiretroviral therapy (ART) remains limited.

Methods. Perinatal depressive symptoms were assessed using 6 items from the AIDS Clinical Trials Group (ACTG) Quality of Life questionnaire. VS (viral load <400 copies/mL) was the outcome. Adherence was defined as no missed dose in the past 1–4 weeks using the ACTG Adherence Questionnaire. Generalized mixed-effects structural equation models estimated the association of depressive symptoms on VS and the mediating role of ART adherence among women enrolled in the IMPAACT P1025 Perinatal Core Protocol (2002–2013).

Results. Among 1869 participants, 47.6% were 21–29 years, 57.6% non-Hispanic Black. In the third trimester, the mean depressive symptoms score was 14.0 (±5.2), 68.0% had consistent adherence, and 77.3% achieved VS. At 6 months postpartum, depressive symptoms declined while adherence and VS fell to 59.8% and 53.0%, respectively. In the fully adjusted model, a 1-SD increase in depressive symptoms was associated with a 3.8-percentage-point (95% CI: −5.7, −1.9) decline in VS. This effect is the sum of the indirect effect of depressive symptoms on VS via ART adherence (−0.4; 95% CI: −.7, −.2) and the direct effect through other pathways (−3.4; −5.2, −1.5). The decline in adherence driven by depressive symptoms accounted for ≥11% of the total negative effect of depressive symptoms on VS.

Conclusions. Perinatal depressive symptoms were associated with decreased adherence and VS, highlighting the need to screen for, diagnose, and treat perinatal depression to optimize maternal outcomes.

Clinical Trials Registration. NCT00028145.

Keywords. women with HIV; perinatal period; depressive symptoms; ART adherence; viral suppression.

Depressive symptoms increase during pregnancy and the postpartum period, particularly for women living with human immunodeficiency virus (HIV) [1]. Perinatal depression is associated with adverse birth outcomes, including preterm birth and low birth weight [2], and adverse maternal outcomes such as pre-eclampsia and emergency cesarean delivery [3, 4]. For women living with HIV, however, the association between perinatal depressive symptoms and viral suppression (VS) at delivery and postpartum is less clear. Maternal VS can preserve maternal immune function and minimize the risk of perinatal HIV transmission [5]. Yet, the majority of studies examining the association between perinatal depression and VS were conducted outside the United States [6–8] where antiretroviral therapy (ART) is not as readily available and contextual factors differ from those in the United States. Studies from the United States have been

cross-sectional and have found inconsistent associations between perinatal depression, ART adherence, and VS [9, 10].

Using longitudinal data from the International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPAACT) Perinatal Core Protocol, P1025 prospective cohort study, we evaluated the associations of depressive symptoms with VS during the perinatal period, as well as the extent to which ART adherence mediates these associations, controlling for relevant demographic, clinical, and behavioral confounders. We hypothesized that depressive symptoms would be associated with poorer ART adherence and a lower likelihood of perinatal VS.

METHODS

IMPAACT P1025 Cohort

IMPAACT P1025 is a multicenter observational US study created to evaluate the safety and effectiveness of ART and other interventions intended to prevent perinatal HIV transmission. Methods for P1025 have been previously described [11]. The P1025 study population includes women living with HIV, age 13 years and older, with a viable pregnancy of 8 weeks or greater gestation who enrolled during pregnancy or immediately postpartum between 2002 and 2013 (n = 2756 mother–infant pairs followed for up to 1 year postpartum, with follow-up closing in 2013).

Study Sample and Inclusion Criteria

We evaluated changes from the prenatal to postpartum period in the relationship of depressive symptoms to ART adherence and VS. Accordingly, we excluded women who enrolled at delivery (n = 844) and those with missing data on basic demographic and HIV variables (n = 43), producing a final sample of 1869 women. If mothers had multiple pregnancies during the study, we analyzed data from only their first P1025-enrolled pregnancy. All sites had institutional review board approval and women provided written informed consent prior to participation.

Longitudinal Design

We classified all available longitudinal data into 7 observation periods: first, second, and third trimester; delivery (±14 days around delivery); and 1–3 months, 3–6 months, and 6–12 months postpartum. We limited our primary longitudinal regression analyses to the 4 periods with greatest enrollment (Supplementary Tables 1 and 2), namely the following: third trimester, delivery, 1–3 months postpartum, and 3–6 months postpartum. In secondary analyses, we added available data from the second trimester and accounted for the timing of study entry whenever applicable. In this study, we use the term perinatal to refer to the third trimester up to 6 months postpartum.

Measures

Main study variables include VS (outcome), depressive symptoms (exposure), and ART adherence (mediator), all measured longitudinally. Within each observation period, most participants (81%) had their depressive symptoms and adherence measurements temporally preceding their viral load (VL) measurement date. Measurements of ART adherence and depressive symptoms were often collected on the same date, however.

Viral Suppression

Viral suppression, obtained via medical chart abstraction, was defined as having a VL less than 400 copies/mL to account for differences in laboratory cut points and maintain consistency over the study period.

Depressive Symptoms

Participants completed the AIDS Clinical Trials Group (ACTG) SF-21 Quality of Life interview [12, 13]. This 21-item questionnaire encompasses validated subscales for domains relevant to mood disorders, including mental health, cognitive functioning, and fatigue [14–16]. We selected 6 items assessing the past-month frequency of depressive symptoms (ranging from 1 = "none of the time" to 6 = "all of the time," with a possible total score of 6 to 36, with higher scores indicating more symptoms). Selected items were consistent with *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-V), criteria for major depressive disorder [17] and included 2 mood items ("Have you felt down-hearted and blue?"; reverse-coded "Have you been a happy person?"); 2 items related to diminished ability to think or concentrate ("Did you have difficulty reasoning or problem solving?"; "Did you have trouble keeping your attention on any activity for long?"); and 2 items related to fatigue/loss of energy (reverse-coded "Did you have enough energy to do the things you wanted to do?"; "Did you feel tired?"). While fatigue/loss of energy are likely symptoms of pregnancy as well, prior research establishes that these symptoms remain substantial indicators of depression among pregnant women, both in the prenatal and postnatal periods [18, 19]. The 6 items formed a single-factor solution in a principal components analysis, explaining 47% of the variance with good internal consistency (Cronbach's α = 0.78). We converted depressive symptoms scores to z scores with a mean of zero and a standard deviation (SD) of 1 to facilitate modeling and interpretation.

ART Adherence

The P1025 cohort study assessed self-reported adherence using the ACTG Adherence Questionnaire [20]. Throughout the study, however, participants most consistently completed the "last-missed-dose" component of the ACTG Adherence Questionnaire, asking when they last missed ART doses (1–2, 2–4, >4 week ago, or never). While it does not capture the multidimensional nature of adherence, the "last-missed-dose" measure uniquely and reliably captures longer-term adherence behavior [21]. We categorized those who reported not

missing a dose in the last 4 weeks or less (compared with those who skipped a dose in the last 1–4 weeks) as having consistent adherence.

Potential Confounders

We considered demographic, clinical, and substance-use factors as potential confounders of the associations among depressive symptoms, adherence, and VS. Demographic variables included age at enrollment, race/ethnicity (non-Hispanic Black/African American, non-Hispanic White/other races, and Hispanic/Latino), and education (<high school diploma, high school diploma/GED, any college). Clinical variables included number of previous pregnancies, trimester of entry into prenatal care, whether HIV diagnosis was made before or during pregnancy, years living with HIV, and calendar year of delivery (to account for changes in relevant clinical practice guidelines, particularly with respect to ART prescription). Substance use included time-varying any use since the start of pregnancy of each of the following: alcohol, tobacco, marijuana, or other controlled/illicit substances (ie, cocaine, heroin, amphetamines, methamphetamine, barbiturates, ecstasy, or prescription opioids).

Statistical Analysis
#### Missing Data

Supplementary Table 3 gives a complete picture of the extent of missing data in the current study sample (N = 1869). Excluded observations due to incomplete data were more likely from participants who were younger, non-Hispanic Black, started prenatal care later in pregnancy, and enrolled in the study in 2006–2009, relative to those included in the current study (Supplementary Table 4). Education and HIV/pregnancy histories were comparable across the 2 groups.

To address missing data, we performed 2 sets of analyses: (1) our primary analytical models included only complete cases [22] with fully observed data on the 3 main study variables, substance use, and confounders, and (2) in secondary analyses, we performed multiple imputation (MI) of missing data followed by similar analytical models that incorporate MI data and account for uncertainty due to imputation [23].

To impute missing data, we performed 2-fold MI using chained equations (MICE), which leverages available time-varying and non–time-varying data, providing effective imputation in longitudinal settings [24, 25], outperforming standard MICE [26, 27]. We used linear and logistic 2-fold MICE models to impute missing data, respectively, for the continuous depressive symptoms score and for binary VS, ART adherence, smoking, and alcohol consumption. Our imputation models included all study variables, including those predictive of missingness (age, race, prenatal care entry, and enrollment year dummies). We created 100 MI datasets [28, 29] to ensure stability and reproducibility of the estimates [23, 28].

Mediation Analysis

We performed mediation analysis to estimate the overall association (ie, total effect) of depressive symptoms on VS throughout the perinatal period and to estimate the extent to which this association is mediated by ART adherence—that is, the indirect effect of depressive symptoms on VS that is through changes in adherence. To accomplish this, we built a longitudinal mediation model composed of 2 linear mixed models: (1) an "outcome model" of VS, regressed on depressive symptoms, adherence, and confounders, and (2) a "mediator model" of adherence, regressed on depressive symptoms and confounders. Both models also included person-specific random intercepts, which account for unobserved, between-person heterogeneity, a key confounder in longitudinal data. We implemented our longitudinal mediation approach, illustrated in Figure 1, in Stata's generalized structural equation modeling (GSEM) suite "gsem" [30, 31]. Our approach follows recent work deriving causal mediation formulas in longitudinal mixed-effects models [32–34] and produces similar results to standard causal mediation routines [35–37] (see
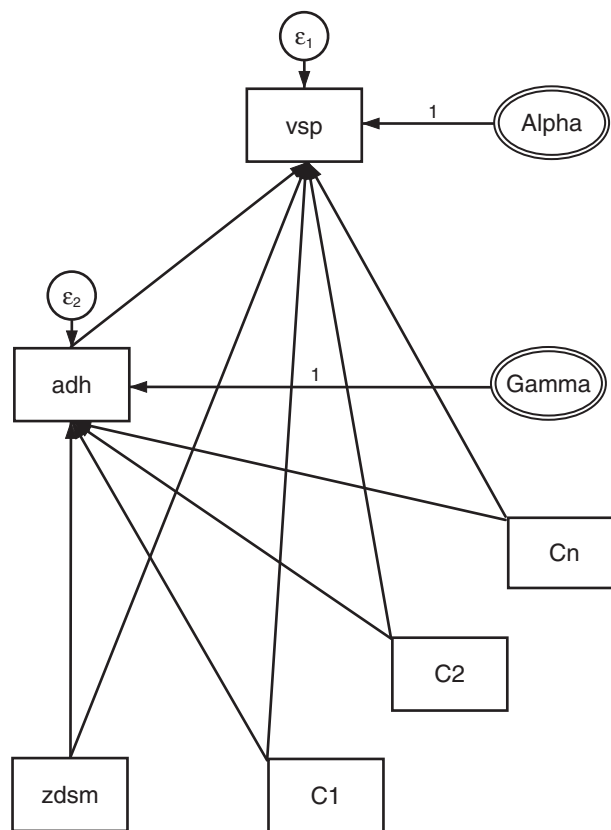
Figure 1. General longitudinal (random-effects) SEM approach for assessing mediation of the effects of depressive symptoms on viral suppression through ART adherence. C1, C2, and Cn are measured confounders; Alpha and Gamma (multilevel latent variables, with coefficients constrained to equal 1) are random intercepts for participants; arrows denote associations; ε in circles represent error terms for each of the outcome (vsp) and mediator (adh) regressions. Model constructed in Stata "gsem" builder for generalized structural equation models. Abbreviations: adh, adherence; ART, antiretroviral therapy; SEM, structural equation modeling; vsp, viral suppression; zdsm, depressive symptoms z score.

Supplementary Table 5). We calculated the standard errors for all estimates using nonparametric bootstrapping (500 replications). For analyses of MI data, we estimated the models with bootstrapped standard errors in each MI dataset and then combined the estimates using Rubin's rules [29], a method shown to provide valid bootstrap inference with MI [38].

We addressed major confounding through a tiered strategy over 4 sets of adjusted mediation models. Model 1 includes the random intercepts, visit period fixed effects (indicators), and timing of study entry. Model 2 and model 3 adjust known confounders: first, demographics including age, race, and education; then, HIV and pregnancy variables such as prenatal care entry, duration of HIV infection, and year of delivery. Model 4, our preferred specification, further adjusts time-varying smoking and alcohol use, which not only may especially confound the adherence–VS association but their perinatal shifts (Supplementary Figure 1) may drive depressive symptoms as well. We did not further adjust for marijuana or illicit substance use; in preliminary analyses, this adjustment did not change the findings and caused convergence problems. Finally, we also performed these 4 mediation models in the MI data to assess how findings change upon accounting for uncertainty due to missing data.

RESULTS

Characteristics of the Study Sample
Among 1869 participants included in the current study (Table 1), 47.62% were 21–29 years old, 57.57% were non-Hispanic Black, and 38.10% had not graduated high school. Most women (67.10%) initiated prenatal care in the first trimester and had an average of 3 pregnancies prior to their index P1025 pregnancy; 76.94% were known to have HIV before pregnancy and for an average of 5.8 years. Approximately 42.75% delivered/enrolled between 2006 and 2009. Based on complete data, 15.71% reported smoking during pregnancy, 6.27% consumed alcohol, 7.19% smoked marijuana, and 3.05% used illicit substances. As seen in Supplementary Figure 1, levels of smoking and drinking declined towards delivery, but substantially spiked postpartum.

Depressive Symptoms, ART Adherence, and Viral Suppression Over Time
In the third trimester, the mean depressive symptoms score was 14.0 (±5.24); 68.12% of women adhered to their ART consistently and 77.31% of women in the sample achieved VS (Table 1). At delivery, average depressive symptoms scores slightly declined while levels of adherence and VS steadily increased. However, while depressive symptoms continued to decline postpartum, adherence and VS fell precipitously, from 69.5% and 74.4% at delivery to 59.8% and 53.0% at 6 months postpartum, respectively (Figure 2). This pattern holds throughout study years (2002–2013), notwithstanding changes in ART guidelines (Supplementary Figure 2).

Table 1. Baseline Characteristics of the Study Sample: IMPAACT P1025 Cohort (N = 1869)

Characteristics, as of Baseline (Third Trimester)	Statistic
Y: Viral suppression,[a] %	
Suppressed: viral load <400 copies/mL	77.31
Not suppressed: viral load ≥400 copies/mL	22.69
X: Depressive symptoms[a]: past month, 6-item scale,[b] mean (SD)	14.00 (5.24)
M: ART adherence[a]: last missed dose, %	
Consistent: never or > 4 weeks ago	68.12
Inconsistent: last 1–4 weeks	31.88
Demographics	
Age, %	
13–20 years	11.40
21–29 years	47.62
30–34 years	23.22
≥35 years	17.76
Race/ethnicity, %	
White/other Non-Hispanic	11.72
Black non-Hispanic	57.57
Hispanic	30.71
Education, %	
Less than high school	38.10
High school graduate	42.22
Some college or more	19.69
Total no. of pregnancies, mean (SD)	3.38 (2.20)
Duration of HIV infection	
Diagnosed before pregnancy, %	76.94
Diagnosed during pregnancy, %	23.06
Years since diagnosis, mean (SD)	5.80 (5.52)
Trimester first received prenatal care, %	
First trimester	67.10
Second trimester	29.13
Third trimester	3.77
Delivery year, %	
2002–2005	23.65
2006–2009	42.75
2010–2013	33.60
Substance use since pregnancy started,[a] %	
Drink alcohol at least once a month, %	6.27
Currently smoke cigarettes, %	15.71
Marijuana at least once a month, %	7.19
Any controlled/illicit substance use,[c] %	3.05

Abbreviations: ART, antiretroviral therapy; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trial Network; SD, standard deviation.

[a]Reported statistics for the following variables are based on available data, excluding missing observations: viral suppression (n with available data = 1525; 18% missing), depressive symptoms (n = 1235; 34% missing), adherence (n = 1311; 30% missing), drinking alcohol (n = 1276; 32% missing), cigarette smoking (n = 1190; 36% missing), marijuana (n = 1266; 32% missing), controlled/illicit substances (n = 1214; 35% missing). Additional details on missing data are available in Supplementary Table 3.

[b]Items: felt down, felt unhappy, trouble keeping attention, trouble problem-solving, lacking energy, fatigue (Cronbach's α = 0.78).

[c]Substances: cocaine, heroin, speed, MDMA, barbiturates, ecstasy, prescription opioids.

Mediation Models of Depressive Symptoms, ART Adherence, and Viral Suppression
Adjusted associations and mediation estimates from the complete-case sample are shown in Table 2. The first 2 panels show coefficients directly from the outcome and mediator
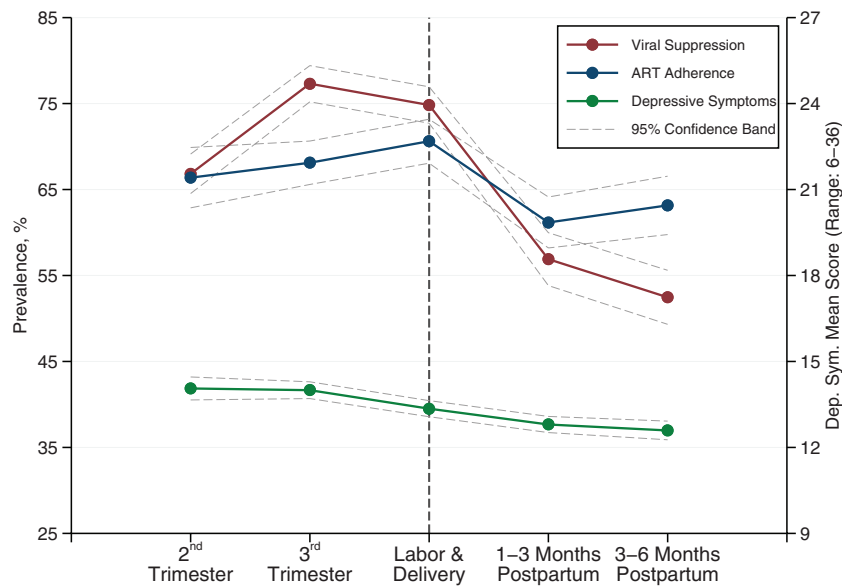
Figure 2. Observed changes in viral suppression, ART adherence, and depressive symptoms across the perinatal period in the study sample: IMPAACT P1025 cohort. (Respective numbers of participants with data for each variable by period are listed in Supplementary Table 3.) Abbreviations: ART, antiretroviral therapy; Dep., depressive; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trial Network; Sym., symptoms.

regressions followed by mediation estimates. Overall, based on the fully adjusted specification in model 4, a 1-SD increase in the depressive symptoms score is associated with a total of 3.8-percentage-point (%pts; 95% confidence interval [CI]: −5.7, −1.9) reduction in VS (total effect). This effect is the sum of the indirect effect of depressive symptoms on suppression via ART adherence (−.4%pts; 95% CI: −.7, −.2) and the direct effect through other pathways (−3.4%pts; 95% CI: −5.2, −1.5) (Table 2, column 4). The indirect effect reflects 2 components: (1) a positive effect of ART adherence on suppression, where having consistent adherence is associated with an increase in suppression by 6.6%pts (95% CI: 2.6, 10.5), and (2) a negative effect of depressive symptoms on adherence: a 1-SD increase in depressive symptoms is associated with a reduction in the probability of consistent adherence by 6.6%pts (95% CI: −8.7, −4.4). Together, the indirect effect mediated through adherence accounts for 11.3% of the total effect of depressive symptoms on suppression (Table 2, column 4). Sequential control for confounding in models 1 through 4 results in progressive, albeit small, attenuation of the estimates, with control for HIV/pregnancy variables (model 2→model 3) and alcohol/smoking (model 3→model 4) driving most attenuation in outcome and mediator regressions, respectively (Table 2).

Secondary Analyses

In Table 3, we present the results of a secondary analysis comparing the main model 4 estimates from the complete-case sample with their counterparts estimated in the MI data. As in columns 1 and 2, the total effect of depressive symptoms was smaller (−2.7%pts with MI vs −3.8%pts in the complete-case

sample), the direct effect was smaller (−2.1%pts vs −3.4%pts), and the indirect effect was larger (−0.6%pts vs −0.4%pts), now accounting for a much larger proportion of its total effect (22.4% vs 11.3%). While the effect of depressive symptoms on adherence is identical across MI and complete-case samples (−6.6%pts), the effect of adherence on suppression is much larger (9.3%pts vs 6.6%pts). Attenuation of estimates upon confounding control in MI data followed similar patterns to those in the main analysis with complete-case data (Supplementary Table 6).

Finally, considering the inclusion of second-trimester data (Table 3), we found that both in the complete-case sample (columns 1 and 3) and MI data (columns 2 and 4), the addition of second-trimester data generally led to slightly smaller estimates than in the main analysis, with the indirect effects accounting for a slightly larger proportion of the total effect (eg, 12.5% vs 11.3% in the complete-case sample).

DISCUSSION

This study examines the overall impact of depressive symptoms on VS throughout the perinatal period and the extent to which this association is mediated by ART adherence among pregnant women with HIV. Prior studies examining these associations were often exploratory analyses of small cross-sectional samples, usually lacking the longitudinal perspective of how these important variables change over the perinatal period [9, 10, 39]. Gaining such understanding is important as effective interventions to improve ART adherence and VS for women with HIV in the perinatal period continue to be needed. Our longitudinal

Table 2. Adjusted Associations and Mediation Estimates Over the Perinatal Period (Third Trimester–6 Months Postpartum) in the IMPAACT P1025 Cohort

	(1)	(2)	(3)	(4)
	Model 1	Model 2	Model 3	Model 4 (Main Model)
Outcome model (viral suppression)				
M: Adherence (a)	.086	.079	.065	.066
	[.047, .125]	[.039, .119]	[.028, .103]	[.026, .105]
X: Depressive symptoms z score (b)	−.041	−.041	−.035	−.034
	[−.059, −.023]	[−.059, −.022]	[−.051, −.018]	[−.052, −.015]
Mediator model (adherence)				
X: Depressive symptoms z score (c)	−.082	−.079	−.074	−.066
	[−.104, −.06]	[−.099, −.058]	[−.095, −.053]	[−.087, −.044]
Mediation estimates				
Natural indirect effect (NIE = a × c)	−.007	−.006	−.005	−.004
	[−.01, −.004]	[−.009, −.003]	[−.007, −.002]	[−.007, −.002]
Controlled direct effect (CDE = b)	−.041	−.041	−.035	−.034
	[−.059, −.023]	[−.059, −.022]	[−.051, −.018]	[−.052, −.015]
Total effect (TE = CDE + NIE)	−.048	−.047	−.039	−.038
	[−.066, −.031]	[−.065, −.028]	[−.056, −.023]	[−.057, −.019]
Percent mediated (NIE/TE)	14.6%	13.3%	12.3%	11.3%
Controls				
Sample	CC	CC	CC	CC
Person-specific random intercept	Yes	Yes	Yes	Yes
Visit period fixed effects	Yes	Yes	Yes	Yes
On/off-study status	Yes	Yes	Yes	Yes
Demographics		Yes	Yes	Yes
HIV and pregnancy variables			Yes	Yes
Alcohol and smoking				Yes
Sample				
No. of observations	2702	2702	2702	2702
No. of persons	1375	1375	1375	1375
ICC, outcome model	46%	44%	39%	39%
ICC, mediator model	30%	28%	26%	26%

All estimates are in percentage-point units. Bootstrapped 95% confidence intervals (500 replications) in brackets. All *P* values < .01.

Abbreviations: CC, complete case; HIV, human immunodeficiency virus; ICC, intraclass correlation coefficient (residual); IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trial Network.

analysis revealed 2 key findings. First, a relatively moderate increase in depressive symptoms was associated with a potentially clinically important decline in VS as well as ART adherence. Second, the decline in adherence driven by depressive symptoms accounted for at least a sizable 11% of the total negative effect of depressive symptoms on the probability of VS. These observations are consistent with existing literature. For example, Psaros et al [40] and Peltzer et al [6] found that elevated depressive symptoms were associated with significantly lower ART adherence in pregnant women with HIV living in South Africa. A review of the literature also shows a moderate effect of depressive symptoms on ART adherence and suppression among the larger population of people living with HIV [41].

Our results highlight the need for universal screening for perinatal depressive symptoms, as recommended by national guidelines [42]. However, diagnosis and treatment are often left unaddressed, with up to 85% of women being untreated for perinatal depression [43]. Pharmacological treatment is thought to be generally safe despite the lack of robust data, since pregnant women are usually excluded from clinical trials [44]. In addition, psychotherapies such as interpersonal psychotherapy and cognitive behavioral therapy have been shown to be effective in treating perinatal depression [45]. Structural barriers often limit access to these effective treatments, with lack of health insurance coverage and limited workforce capacity in mental health being significant contributors [46, 47]. Addressing barriers, in addition to creating multidisciplinary care models to deliver family-centered care for pregnant or postpartum women with HIV, shows promise in improving maternal outcomes [48].

In addition to depressive symptoms, factors at multiple levels contribute to the low rates of ART adherence and VS observed, particularly in the postpartum period when the stresses and demands of caring for a new baby are acute [49]. It is also important to note that, early in the study period, some women stopped taking their ART postpartum in accordance with treatment guidelines at the time; however, this alone does not explain the drop in VS postpartum as VS continued to decline regardless of study period. Unmeasured psychosocial and structural factors

Table 3. Secondary Analyses of the Main Adjusted Associations and Mediation Estimates (Model 4) Over the Perinatal Period in the IMPAACT P1025 Cohort

	Third Trimester–6 Months PP		Second Trimester–6 Months PP	
	(1) Complete Case (Main Model)	(2) Multiple Imputation	(3) Complete Case	(4) Multiple Imputation
Outcome model (viral suppression)				
M: Adherence (a)	.066	.093	.059	.083
	[.026, .105]	[.056, .13]	[.023, .095]	[.05, .116]
X: Depressive symptoms z score (b)	−.034	−.021	−.029	−.014
	[−.052, −.015]	[−.037, −.006]	[−.046, −.012]	[−.028, 0]
Mediator model (adherence)				
X: Depressive symptoms z score (c)	−.066	−.066	−.069	−.065
	[−.087, −.044]	[−.082, −.05]	[−.089, −.049]	[−.08, −.051]
Mediation estimates				
Natural indirect effect (NIE = a × c)	−.004	−.006	−.004	−.005
	[−.007, −.002]	[−.009, −.003]	[−.006, −.002]	[−.008, −.003]
Controlled direct effect (CDE = b)	−.034	−.021	−.029	−0.014
	[−.052, −.015]	[−.037, −.006]	[−.046, −.012]	[−.028, 0]
Total effect (TE = CDE + NIE)	−.038	−.027	−.033	−.019
	[−.057, −.019]	[−.042, −.012]	[−.049, −.016]	[−.034, −.005]
Percent mediated (NIE/TE)	11.3%	22.4%	12.5%	27.8%
Sample				
No. of observations	2702	7476	3140	9345
No. of persons	1375	1869	1437	1869

All estimates are in percentage-point units. Bootstrapped 95% confidence intervals (500 replications) in brackets. All *P* values < .01.
Abbreviations: IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trial Network; PP, postpartum.

associated with depression (such as stigma, intimate partner violence, housing, or food insecurity) likely play a role. Some studies have found that depressive symptoms can be higher prenatally than in the postpartum period for women with HIV [6, 50]. This can be explained by the elevated prevalence of unplanned pregnancy in that population [51] and stress of obtaining an HIV diagnosis during pregnancy (this occurred for about one-quarter of our sample).

Our study has several notable strengths, including its prospective design, use of a large multiethnic sample from a high-resource setting (addressing a key gap in the available literature), and the corroboration of our findings across modeling approaches. Although breastfeeding is not recommended for women living with HIV in the United States, our findings highlight the need for continued assessment of ART adherence and VS in the postpartum period for women who desire to breastfeed.

A few limitations deserve mention. First, P1025 lacked a validated depressive symptoms scale. While the items in our scale are consistent with DSM-V criteria and with clinically validated depressive symptom measures, its comparability is not formally established. Additionally, the dataset did not capture information on depression treatment, psychosocial and structural factors, or social support measures inside or outside of the clinic that might influence adherence and suppression prospects. Second, the cohort had large portions of missing data for key study variables. We addressed this using MI [23] and our

models accounted for uncertainty due to imputation. Further, although our analyses adjusted for major confounding, residual confounding might be present. Our quantitative estimates should thus be cautiously interpreted. Third, study participants were limited to women in care in the United States; therefore, findings may not necessarily generalize to all pregnant women with HIV.

In conclusion, perinatal depressive symptoms were associated with significantly lower adherence to ART, and with lower VS. These results highlight the need to screen, diagnose, and treat perinatal depression to prevent mental and HIV-related complications that may adversely affect both mother and child.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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