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Correlates of Perinatal Depression in HIV-Infected Women

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Abstract

Maternal perinatal depression (PND) may interfere with effective perinatal HIV care. In order to begin examining the prevalence and characteristics of PND in HIV-infected women, we analyzed data from the medical records of all HIV-infected women who had received perinatal care in the Maternal-Child and Adolescent Center for Infectious Diseases and Virology at LAC/USC Medical Center from 1997 through 2006. Data from 273 individual women (328 live births) were analyzed. Demographic, medical history, psychosocial, pregnancy-related, and HIV-related factors measured during the perinatal period were examined for an association with PND using multivariate logistic regression with generalized estimating equations to account for the within-subject correlation due to multiple births per mother. The overall prevalence of PND was 30.8%. Multivariate analysis showed that PND was significantly associated with substance abuse during pregnancy (odds ratio [OR] = 2.81, 95% confidence interval [CI]: 1.35–5.82) and past history of psychiatric illness (OR = 3.72, 95% CI: 2.06–6.71). Compared to mothers with CD4 nadir greater than 500 cells/mm^3, mothers with a CD4 nadir during pregnancy ≤200 cells/mm^3 were 3.1 times more likely to experience PND (OR = 3.01, 95% CI: 1.32–6.88). Women who had antiretroviral (ARV) medications adherence problems during pregnancy were more likely to experience PND than women who were adherent (OR = 2.14, 95% CI: 1.08–4.23). These preliminary results suggest that rates of PND among HIV-infected women are substantial. We conclude that pregnant HIV-infected women should be routinely screened for PND. Prospective studies examining the bio-psycho-social markers of PND in HIV-infected women are indicated.

Introduction

Women of childbearing age are increasingly infected with HIV worldwide.[1–4] For example, in the United States, they constitute nearly 20% of persons living with HIV. In sub-Saharan Africa, 76% of infected persons are women.[1] Such trends result in increased numbers of pregnant women who are HIV-infected.[2–6] In developed countries, a combination of perinatal highly active antiretroviral therapy (HAART), elective cesarean section, and substitution of breastfeeding with formula has resulted in dramatic reduction of vertical HIV transmission rates.[6] This progress has made it possible for the clinicians caring for HIV-infected pregnant women to focus on psychosocial issues that might create barriers to effective perinatal HIV care. One such barrier is depression, which is highly prevalent among HIV-infected women and has been associated with HAART non-adherence, especially in women with high parity.[7–9] This association raises an additional clinical concern: that maternal nonadherence during pregnancy and/or postpartum period might jeopardize the health of the developing fetus or a newborn.

Pregnancy and the postpartum period are often complicated by maternal depression. In a rigorous systematic review and meta-analysis of prevalence studies published between 1980 and 2004, Gaynes et al.[10] found that point prevalence of major depression at different time points during pregnancy ("antenatal depression") ranged from 3.1% to 4.9%, incidence of a new major depressive episode (MDE) during pregnancy was 7.5%, and incidence of a new MDE during the first 3 months postpartum was 6.5%.

Since antenatal and postpartum depression frequently overlap, the more inclusive term perinatal depression (PND) has been increasingly used in the literature as more clinically relevant.[11–13] PND has been linked with multiple adverse developmental outcomes, including increased risk of childhood behavioral problems, poor cognitive outcomes, failure to thrive, learning disorders and, rarely, infanticide.[14–17]

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Furthermore, growing evidence suggests that perinatally depressed mothers are at risk to miss their infants' routine medical visits and immunizations, and to delay seeking help for potentially serious childhood illnesses.[18]

Limited data on the rates of antenatal depression in HIV-infected women are alarming. For example, Smith Fawzi et al.[19] reported a 42% prevalence of depression in a cohort of 1078 HIV-infected pregnant women in Tanzania between April 1995 and July 1997. Blaney et al.[20] found certain psychosocial factors, such as perceived stress, social isolation, and disengaged coping to be associated with more depressive symptoms among U.S. HIV-infected pregnant women, while positive partner support was associated with lower depression. However, to our knowledge, no studies have been published concerning prevalence of depression during the entire perinatal period in HIV-infected women. Furthermore, little is known about the relationship between a broader range of factors that are salient to this population (such as virologic, immunologic, pharmacologic, and obstetric factors) and the risk of PND. At this point in time, when HAART is promising to transform HIV into a chronic illness, it is becoming increasingly important to improve our knowledge about the relationship between such factors and the mental health of all people living with HIV, including HIV-infected pregnant women.

The primary objective of this study is to examine the prevalence and identify the psychosocial, obstetric, perinatal, and HIV-related (i.e., virologic, immunologic and pharmacologic) correlates of PND in a 10-year cohort of HIV-infected women.

Methods

Study site and sample

The study was carried out at the Maternal-Child and Adolescent Center for Infectious Diseases and Virology (MCA) at LAC-USC Medical Center in Los Angeles. MCA is the only designated HIV Perinatal Center for the vast network of hospitals and clinics in the County of Los Angeles and is the principal referral site for low-income and indigent uninsured or underinsured HIV-infected youth, pregnant women, and their families throughout the County of Los Angeles. MCA receives approximately 2–5 referrals of pregnant women each month with approximately 50 deliveries at LAC + USC Medical Center each year. In this study, we included all HIV-infected women who received care at MCA and delivered at LAC + USC Medical Center from January 1997 through December 2006.

Medical record review

Medical records of these patients were reviewed by one medical student (F.L.), trained and directly supervised by the principal investigator of the study (S.K.). These records consisted of electronic medical records (covering all laboratory values, all medications, demographics, mode of HIV transmission, clinic visit dates, and obstetric data) and multidisciplinary clinical charts that included initial assessments as well as the progress notes entered by the following clinicians: obstetrician-specialist in HIV perinatal care (A.S.), who met with the women at least every 4 weeks during the first 28 weeks of pregnancy, every 2 weeks between gestational weeks 28 and 32, and then weekly until birth; infectious disease/HIV specialists (F.K. and L.S.), who followed the women before and after pregnancy; and assigned social workers and case managers. The study protocol was reviewed and approved by the USC Institutional Review Board.

Assessment of depression

It is a routine protocol at MCA for the social workers and case managers to meet with the patients during every clinic visit and conduct depression screening using the "SIG E CAPS + Mood" (Sleep, Interest, Guilt, Energy, Concentration, Psychomotor, Suicide + Mood) mnemonic.[21] The screening results are then documented in the chart and communicated to the attending physician who follows up by verifying the diagnosis and addressing it in the treatment plan. Both clinical interventions (i.e., screening and the verification) are then documented in the multidisciplinary chart notes. The patient care is regularly discussed and coordinated in a multidisciplinary patient management meeting, where the depression assessment and treatment plan is finalized.

Depression diagnoses were abstracted from the multidisciplinary chart notes. All women whose chart notes indicated onset of depression during pregnancy and/or within the first 4 weeks of delivering their child were classified as "perinatally depressed." The 4-week window was used in accordance with the *DSM-IV TR* definition of postpartum depression (i.e., onset within 4 weeks following childbirth).[22] In order to capture the depression data as accurately as possible, the charts were reviewed in their entirety; i.e., not only notes covering the perinatal period. For example, if depression was mentioned in a chart note 3 months postpartum, but the note stated that the onset of the depressive symptoms dated back to the first 4 weeks postpartum or the pregnancy, this was still counted as PND. On the other hand, if a subjective complaint of "depression" was mentioned in the charts, but the chart indicated the depression was primarily attributed to the so-called "baby blues," and further review revealed a short duration and low intensity of the "depression," this was not coded as PND by the reviewer.

Assessment of risk factors

Demographic, psychosocial (social stress, diagnosis of HIV during pregnancy, substance use in pregnancy, history of psychiatric illness), history of thyroid abnormalities, pregnancy-related information (parity, pregnancy and birth-related complications), and HIV-related information (maternal HIV transmission mode, HIV diagnosis during pregnancy, HIV-1 viral load and CD4 count, antiretroviral [ARV] and other medications, ARV adherence problems) were collected from the records. The clinical assesment of ARV adherence problems has been standardized by the obstetrician who asked the women, "In the past 2 weeks, how many doses have you missed" at each perinatal visit, and provided adherence counseling if the answer was "one" or more. Having missed one or more ARV doses at any point was documented in the charts and coded as "adherence problem" by our chart reviewer. "Social stress during pregnancy" included: domestic violence, housing issues, lack of transportation, lost custody of child(ren), recent death of a loved one, marital problems, financial problems, incarceration and sick family member. "Past history of psychiatric

illness" included a past history of any DSM-IV psychiatric diagnosis documented in the initial comprehensive medical history and physical exam conducted by a physician or in the initial comprehensive psychosocial assessment conducted by a social worker. "Pregnancy complications" included: preeclampsia, gestational diabetes mellitus, oligohydramnios, placenta praevia, sexually transmitted disease (STD), vaginitis, rubella, HELLP syndrome, intrauterine growth retardation (IUGR), amnionitis, placental abruption, polyhydramnios, pregnancy-induced hypertension and cholestasis of pregnancy. "Birth-related complications" included prematurity, group B streptococcus neonatal infection, fetal distress, macrosomia, breech, meconium aspiration, hemorrhage, fetal tachycardia, arrest of dilation and atony. HIV treatment was grouped by clinical regimen: "none," "monotherapy or combined therapy," other HAART, and HAART. HAART was defined as a therapy regimen containing: (1) two or more nucleoside reverse transcriptase inhibitors (NRTIs) with at least one protease inhibitor (PI) or one non-nucleoside transcriptase inhibitor (NNRTI), (2) one NRTI with at least 1 PI and at least one NNRTI, or (3) ritonavir and saquinavir in combination with one NRTI and no NNRTIs. Other HAART therapy was defined as: an abacavir-containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs. Among HAART users, we further grouped regimens by: (1) mechanism of action: NNRTI-based, PI-based, or containing both NNRTI and PI and (2) whether the regimen included any cerebrospinal fluid (CSF)-penetrating ARVs. We used the criteria for "CSF-penetrating" ARVs described by Letendre et al.[23] (i.e., those with CSF concentrations higher than needed to inhibit HIV replication). Accordingly, the following ARVs were classified as CSF-penetrating: stavudine (D4T), zidovudine (ZDV), abacavir (ABV), efavirenz (EFV), nevirapine (NVP), and indinavir (IDV).

All of these data, except for race and maternal HIV transmission mode, were specific to the time of each pregnancy for women with multiple childbirths at MCA.

Data analysis

For women who received perinatal care at MCA and gave birth at the LAC+USC Medical Center between January 1997 and December 2006, logistic regression models with generalized estimating equations (GEE) were used to evaluate the risk factors associated with PND. The GEE method accounts for the nonindependent nature of the data due to some women having multiple births and adjusts the standard errors of regression parameter estimates according to clustering of data within women. We examined the association between the demographic, medical history, psychosocial, pregnancy-related and HIV-related factors and PND using bivariate analyses that included the factor and a clustering on the mother. A multivariate model was developed that retained independent variables that had associations with a p value of <0.20. To further understand the association of $CD4^+$ cell count with PND, multivariate models were evaluated on the subset of women who were adherent to their ARV medications during pregnancy. The results of the multivariate models are presented as odds ratios (OR) with 95% confidence intervals (CI) and two-sided p values. Data were analyzed using Stata Version 9.0 software (StataCorp LP, College Station, TX).

Results

Medical charts were identified from 310 HIV-infected women. Of these, 37 women with limited contact with MCA (e.g., prenatal care only, HIV-testing only, postpartum care only etc.) were excluded from the analysis. Medical charts were reviewed for the remaining 273 HIV-infected women. Of the 273 women, 47 (17%) had multiple deliveries during this time period. Demographic and depression correlates of the women are shown in Table 1. Mean (standard deviation) age of the women at the time of first delivery at LAC+USC Medical Center was 28.4 (6.3) years. The majority of women were Hispanic (68.9%), followed by African American (25.6%), Caucasian (4.4%), Asian (0.7%), and Native American (0.4%). The majority of women (78%) reported sexual contact as the primary mode of HIV transmission.

Among the 273 HIV-infected women, 61 (22%) experienced antenatal depression during one or more of their pregnancies. Fifty women (18%) had a diagnosis of depression within 4 weeks postpartum (either as a continuation of their antenatal depression or as a new episode). The overall prevalence of PND (i.e., either antenatal OR postpartum depression) was

Table 1. Demographic and Depression Characteristics of 273 HIV+ Female Patients of MCA who gave Birth between January 1997 and December 2006

	n	%
Race/ethnicity		
Caucasian	12	4.4
African American	70	25.6
Hispanic	188	68.9
Other	3	1.1
Age at first delivery, mean (SD)	273	28.4 (6.3)
Primary risk factor for HIV transmission		
Sexual contact	213	78.0
Transfusion	6	2.2
Perinatal	1	0.4
IDU drug use	17	6.2
Undetermined/unknown	36	13.2
Number of births		
1 birth	226	82.8
2 births	40	14.7
3 births	6	2.2
4 births	1	0.4
Ever had a diagnosis of depression during pregnancy during the study period	61	22.3
Ever had a diagnosis of depression within 4 weeks postpartum during the study period	50	18.3
Ever had a diagnosis of depression either during pregnancy or within 4 weeks postpartum (=perinatal depression) during the study period.	84	30.8

IDU, injection drug use.

31% ($n = 84$). Of 328 individual pregnancies, 87 (26.5%) were characterized with PND.

Bivariate analysis showed that history of psychiatric illness, substance use during pregnancy, social stress during pregnancy, and adherence problems during pregnancy were statistically significantly associated with a higher likelihood of PND (Table 2). None of the subcategories of HAART examined were associated with PND (Table 2). There was no significant association between PND and adverse birth outcomes, or with parity (Table 2). History of psychiatric illness, substance use during pregnancy, and social stress during pregnancy remained significant independent correlates of PND after controlling for age, plasma HIV RNA concentration (per $\log_{10}$ increase in copies per milliliter), CD4 cell count, and ARV adherence problems (Table 3). ARV adherence problems were marginally associated with PND in the multivariate analysis. Multivariate analysis also showed that CD4 nadir during pregnancy 200 cells/mm^3 or less was a significant independent correlate of PND. When compared to mothers with CD4 pregnancy nadir greater than 500 cells/mm^3, mothers with a CD4 nadir during pregnancy 200 cells/mm^3 or less were 2.9 times more likely to develop PND (95% CI: 1.26–6.68). There was a significant increasing trend in the risk of PND with decreasing nadir CD4 count during pregnancy (p for trend $= 0.02$). The associations between younger age at delivery, history of psychiatric illness, and substance use during pregnancy with PND were significant within the subset of women who were adherent to the ARV medications during pregnancy. The association between CD4 nadir during pregnancy 200 cells/mm^3 or less and PND was slightly stronger in the subset of adherent women. Social stress during pregnancy was not statistically significantly associated with PND in the subset of adherent women.

Discussion

In this study, we evaluated the prevalence and correlates of PND in HIV-infected women who received perinatal care at MCA between 1997 and 2006. We found that the rates of depression during the overall perinatal period were substantial, even though we used the narrow, *DSM-IV TR*-based definition of the postpartum period (i.e., 4 weeks following childbirth). Since most studies in the general population have used broader definitions (i.e., extending the postpartum period to 3, 6, or even 12 months following childbirth) we are concerned that the rates of a more broadly defined PND among HIV-infected women might be even higher.[10] This finding is consistent with high rates of *antenatal* depression in HIV-infected women reported previously by other groups.[19,20] One possible explanation for such high rates of PND in this population is that HIV-infected individuals in general have been noted to be at higher risk of depression.[8,24–26] Additionally, specific psychosocial issues surrounding pregnancy in HIV-infected women (e.g., maternal guilt, fear of infecting the newborn, stigma, insufficient social support, poverty, interpersonal issues emerging around diagnostic disclosure) might further deepen their vulnerability to develop depression.

We did not demonstrate an association between parity and PND, suggesting that parity might be associated with nonadherence via mechanism independent of depression.[9] This remains to be investigated in the future, as the relationship between parity and nonadherence was not among the objectives of this study. The association between adherence problems and depression has already been demonstrated in HIV-infected individuals, and the present study shows that it exists in pregnant HIV-infected women as well.[8] Yet, in the case of pregnant HIV-infected women, the potential impact of this association is even higher, given the risk of vertical HIV transmission. Since there has not been a single case of vertical HIV transmission at MCA during the study period, we obviously could not evaluate this particular outcome. However, this is still a significant concern in resource-limited parts of the world, where HIV-infected pregnant women do not receive intensive education and adherence support to the same degree they do in the developed countries, and perinatal transmission rates are still high.[27]

Our data also suggest that past history of a psychiatric illness, substance use during pregnancy, social stress during pregnancy and lower CD4$^+$ pregnancy nadir are independently associated with PND risk in this population. While the former three associations are quite intuitive, the latter deserves additional comments. The association between CD4$^+$ pregnancy nadir 200 cells/mm^3 or less and PND, which was even stronger among the subset of adherent women, suggests that a treatment-independent immunologic process may play a significant role in the biology of PND in HIV-infected women. Indeed, several mechanisms have been proposed in related literature that might ultimately help us understand the link between immunologic processes and neuropsychiatric symptoms, such as depression. For example, inflammation has been proposed as an underlying mechanism that interacts with phenomena commonly occurring in pregnancy, such as stress, sleep deprivation, and pain to increase the risk of PND.[28] Next, proinflammatory endogenous cytokines have been associated with symptoms of depression in the context of viral infection.[29]

Finally, it has been demonstrated that immune activation inside the CNS (specifically macrophage activation and intrathecal immunoglobulin production) continues to be present in HIV-infected individuals even after plasma HIV-1 RNA levels have been successfully reduced to less than 50 copies per milliliter (i.e., to "undetectable" levels) and maintained at that level for 4 years or longer.[30] Such persistence of immune activation in the CNS despite long-lasting undetectable plasma HIV-1 RNA levels may help explain why neither plasma HIV-1 RNA trends nor different HAART regimens were significantly associated with depression outcomes in the present study.

The lack of association between PND and race/ethnicity suggests that the PND in HIV-infected women might indeed be primarily caused by a biological mechanism that significantly outweighs the cultural factors.

The lack of association between PND and adverse birth outcomes in the present study is consistent with the findings reported in non-HIV–infected women, suggesting that PND does not interact with maternal HIV to increase the risk of adverse birth outcomes.[31]

The present study has a few limitations. The study relied on the accuracy of written records, which may have been influenced by the clinicians' subjective judgment as well as the patients' selective reporting of depressive symptoms. As a result, we were unable to ascertain more specific diagnostic subcategories of depressive disorders (e.g., major depressive

Table 2. Association of Demographic, Pregnancy Related, Psychosocial, and HIV-Related Characteristics with Perinatal Depression (PND) for 328 Births to HIV+ Female Patients at MCA between January 1997 and December 2006

	Diagnosed with perinatal depression						
	No (n = *241*)		*Yes* (n = *87*)				
	n	%	n	%	*Odds ratio*	*95% CI*	p *value*
Race							
Caucasian	8	66.7	4	33.3	1.00		
African American	54	66.7	27	33.3	1.00	0.28–3.63	>0.99
Hispanic	176	75.9	56	24.1	0.64	0.18–2.20	0.48
Other	3	100.0	0	0.0	n/a	n/a	n/a
Age at delivery categories (years)							
<18	6	85.7	1	14.3	1.00		
18 to 24	63	72.4	24	27.6	2.29	0.26–19.97	0.46
25 to 29	67	69.8	29	30.2	2.60	0.30–22.60	0.39
30 to 34	56	76.7	17	23.3	1.82	0.20–16.35	0.59
35+	49	75.4	16	24.6	1.96	0.22–17.60	0.55
							p-trend = 0.65
Age at delivery (years)	241	29 (16, 44)[a]	87	28 (16, 43)[a]	0.97[b]	0.79–1.18	0.76
Parity (# previous births)							
0	62	76.5	19	23.5	1.00		
1	81	74.3	28	25.7	1.13	0.57–2.21	0.73
2	45	75.0	15	25.0	1.09	0.50–2.38	0.83
3 or more	53	69.7	23	30.3	1.42	0.69–2.89	0.34
							p-trend = 0.38
Number of prenatal visits	238	5 (1, 11)[a]	84	5 (1, 11)[a]	1.00[b]	0.88–1.12	0.95
History of psychiatric illness							
No	192	80.7	46	19.3	1.00		
Yes	49	54.4	41	45.6	3.49	2.02–6.04	<0.001
History of thyroid abnormalities							
No	233	73.5	84	26.5	1.00		
Yes	8	72.7	3	27.3	1.04	0.33–3.27	0.95
Pregnancy complications[c]							
No	147	71.4	59	28.6	1.00		
Yes	94	77.0	28	23.0	0.74	0.44–1.26	0.27
Substance use during pregnancy[d]							
No	224	75.9	71	24.1	1.00		
Yes	17	51.5	16	48.5	2.97	1.48–5.95	0.002
Social stress during pregnancy[e]							
No	225	75.2	74	24.8	1.00		
Yes	16	55.2	13	44.8	2.47	1.13–5.40	0.02
HIV diagnosis during pregnancy							
No	177	72.2	68	27.8	1.00		
Yes	64	77.1	19	22.9	0.77	0.43–1.40	0.39
HIV RNA viral load[f] categories							
<400 copies/mL	78	72.2	30	27.8	1.00		
≥400 to <10,000 copies/mL	75	72.8	28	27.2	0.97	0.53–1.78	0.92
≥10,000 copies/mL	82	75.9	26	24.1	0.82	0.44–1.54	0.54
							p-trend = 0.55
HIV RNA viral load[f] (log_{10} copies/mL)	235	8.2 (≤6.0, 13.8)[a]	84	8.0 (≤6.0, 11.9)[a]	0.95[b]	0.84–1.07	0.40
CD4 cell count[g] categories							
>500 cells/mm^3	60	75.9	19	24.1	1.00		
>350 to ≤500 cells/mm^3	54	78.3	15	21.7	0.88	0.40–1.95	0.75
>200 to ≤350 cells/mm^3	74	71.8	29	28.2	1.24	0.62–2.48	0.55
≤200 cells/mm^3	46	67.6	22	32.4	1.51	0.74–3.07	0.26
							p-trend = 0.19
CD4 cell count[g] (log_{10} cells/mm^3)	234	5.8 (1.4, 7.1)[a]	84	5.7 (0.7, 9.2)[a]	0.92[b]	0.67–1.27	0.60
Adherent to antiretroviral medications during pregnancy							
Yes	203	77.5	59	22.5	1.00		
No	31	53.4	27	46.6	2.91	1.58–5.35	0.001

(*continued*)

Table 2. (Continued)

	Diagnosed with perinatal depression						
	No (n = *241*)		*Yes* (n = *87*)				
	n	%	n	%	*Odds ratio*	*95% CI*	p *value*
HIV treatment[h]							
None	4	80.0	1	20.0	1.00		
Mono or combo therapy	15	71.4	6	28.6	1.60	0.14–17.99	0.70
HAART	196	73.4	71	27.0	1.45	0.16–13.24	0.74
Other HAART	19	76.0	6	24.0	1.26	0.12–13.71	0.85
HAART regimen[i]							
NNRTI based	82	71.9	32	28.1	1.00		
PI based	104	73.8	37	26.2	0.91	0.52–1.60	0.75
Both PI & NNRTI	10	83.3	2	16.7	0.51	0.10–2.61	0.42
HAART includes CSF penetrating ARV(s)[i]							
No	9	90.0	1	10.0	1.00		
Yes	187	72.8	70	27.2	3.37	0.42–27.23	0.26

[a]Median (range).
[b]ORs for continuous variables interpreted as the proportional change in the odds of perinatal depression per unit increase. Age: per 5-year increase; number of prenatal visits: per visit increase; HIV RNA viral load: per $\log_{10}$ copies/mL increase, CD4 cell count: per $\log_{10}$ cells/mm^3 increase.
[c]Pregnancy complications include: pre-eclampsia, gestational diabetes mellitus, oligohydramnios, placenta previa, sexually transmitted disease, vaginitis, rubella, HELLP syndrome, intrauterine growth restriction, amnionitis, abruption, polyhydramnios, pregnancy induced hypertension, and cholestasis of pregnancy.
[d]Substance use during pregnancy includes: amphetamines, cocaine, heroine, opiates, alcohol, tobacco, and cannabis.
[e]Social stress during pregnancy includes: domestic violence, housing issues, lack of transportation, lost custody of child(ren), recent death of a loved one, marital problems, financial problems, incarceration, and sick family member.
[f]Patient's highest HIV viral load during pregnancy.
[g]Patient's lowest CD4 cell count during pregnancy.
[h]HIV treatment medications are for last visit in third trimester. HAART therapy defined as: (1) 2 or more NRTIs with at least 1 PI or 1 NNRTI; (2) 1 NRTI with at least 1 PI and at least 1 NNRTI; (3) ritonavir and saquinavir in combination with 1 NRTI and no NNRTIs. Other HAART defined as: an abacavir-containing regimen of 3 or more NRTIs in the absence of both PIs and NNRTIs.
[i]Restricted to HAART users only. CSF penetrating drugs include: stavudine (D4T), zidovudine (ZDV), abacavir (ABV), efavirenz (EFV), nevirapine (NVP) and indinavir (IDV).
HAART, highly active antiretroviral therapy; NNRT, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; CSF, cerebrospinal fluid; ARV, antiretroviral drugs. Odds ratios, 95% CI, and *p* values estimated from logistic regression with generalized estimating equations to account for within subject correlation.

disorder [MDD], or depression secondary to a medical condition). To minimize this limitation, we reviewed charts in their entirety and included only those depressive episodes documented in the charts that had been considered clinically significant by the clinicians and were not considered merely a "baby blues." Thus, while our method of ascertaining depression diagnoses was less rigorous in following *DSM-IV TR* nomenclature, it was specific enough to ascertain that the depression was clinically relevant.

The present study did not include a demographically matched comparison group of HIV-negative pregnant women, so we could not directly compare the rates of PND. It remains unclear to what extent does the interaction between their HIV-infected status and sociodemographic factors such as minority status or poverty is contributing to the high rates of PND. However, the focus of the study was to evaluate the correlates of PND within the population of HIV-infected women. Thus, we cannot claim that the rates of PND among HIV-infected women are higher than in non-HIV–infected women with similar sociodemographic background. Still, our data suggest that these rates are substantial, and therefore worth further investigation.

One of the strengths of this study was that, due to the highly specialized and truly multidisciplinary nature of the MCA, we were able to evaluate a highly concentrated population of pregnant women suffering from comorbid HIV infection and PND that have access to perinatal ARV therapy. This enabled us to systematically examine the rates and correlates of PND in a large number of women from a single site. The present findings allow for generating hypotheses for future research. The high representation of minority women in the present study is strength because the rates of HIV in minority women are increasing.[32] It also adds more diversity to the overall body of literature on rates of PND in the United States, since most studies on this subject have dealt with predominantly Caucasian women.[10]

The main clinical lesson from this study is that HIV-infected pregnant women are at high risk for depression, both during pregnancy and postpartum. The risk is present even when the women have access to state-of-the-art perinatal HIV care, and its association with adherence problems might create a significant obstacle to the perinatal HIV care. Clinicians caring for HIV-infected women should be aware of this risk, and consider screening the women routinely for depression, both antenatally and postpartum, preferably with one of the standard validated screening tools (e.g., Edinburgh Postnatal Depression Scale).[33]

For HIV-infected women with a past history of mental illness, substance use during pregnancy, significant social stressors and $CD4^+$ counts 200 cells/mm^3 or less at any

Table 3. Multivariate Associations of Perinatal Depression (PND) for HIV-Positive Female Patients of MCA between Jan 1997 and Dec 2006, All Births and for Births to Women Who Were Adherent to ARV Medications During the Pregnancy

	All births (n = *312*)			*Births to women who were adherent to ARV medications during pregnancy* (n = *256*)		
	Odds ratio	*95% CI*	p *value*	*Odds ratio*	*95% CI*	p *value*
Age at delivery, per year increase	0.96	0.92–1.00	0.07	0.95	0.90–1.00	0.04
History of psychiatric illness	4.09	2.23–7.50	<0.001	4.37	2.19–8.72	<0.001
Substance use during pregnancy	2.60	1.26–5.38	0.01	2.59	0.98–6.87	0.06
Social stress during pregnancy	2.48	1.10–5.59	0.03	1.40	0.45–4.38	0.56
HIV RNA viral load (highest in pregnancy), per $\log_{10}$ copies/mL increase	0.89	0.76–1.04	0.14	0.85	0.71–1.03	0.09
CD4 cell count (lowest in pregnancy)						
>500 cells/mm^3	1.00			1.00		
>350 to ≤500 cells/mm^3	1.13	0.47–2.69	0.79	0.91	0.35–2.36	0.85
>200 to ≤350 cells/mm^3	1.49	0.68–3.25	0.31	1.71	0.73–4.01	0.22
≤200 cells/mm^3	2.90	1.26–6.68	0.01	3.49	1.36–8.98	0.009
			p-trend[a] = *0.02*			*p-trend*[a] = *0.01*
ARV medication adherence problems during pregnancy	1.92	0.95–3.86	0.07			

[a]CD4 group trend test estimated from Wald's χ^2 test from multivariate model.

Odds ratios, 95% CI, and *p* values estimated from multivariate logistic regression including all variables listed in table with generalized estimating equations to account for within subject correlation. Separate multivariate models were run by adherence to ARV medications during pregnancy.

point during pregnancy, we believe that such screening is strongly indicated. It also seems reasonable to suggest that $CD4^+$ count 200 cells/mm^3 or less should be considered as a clinical marker of the PND risk in HIV-infected pregnant women.

Future research should test these hypotheses prospectively, in larger cohorts that are representative of the population of HIV-infected pregnant women. Future research will also need to evaluate the independent impact of sociodemographic factors, parity, pain sleep deprivation, and examine the role of immune dysregulation in the etiology of PND in HIV-infected women. The impact of PND on pregnancy outcomes and maternal postpartum HIV disease outcomes should be investigated as well. This should include the examination of the relationship between PND and vertical transmission rates in an area where such rates are unfortunately still quite high.[27]

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