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# Depressive Symptomatology, TNF- $\alpha$ , and Perinatal Outcomes among HIV-Seropositive Pregnant Women

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## Abstract

Many factors may be associated with depressive symptomatology among HIV seropositive pregnant women, in whom the prevalence of depression is relevant. Several studies have suggested that depression is an inflammatory condition, in terms of cytokine production. Moreover, pregnant women infected with HIV may have altered cytokine levels due to their infectious condition and pregnancy-related immunomodulation. Thus, we propose that depressive symptomatology during pregnancy could affect not only cytokine production but gestational outcomes as well. The aim of this observational, prospective, cross-sectional and non-random sampled study was to evaluate the prevalence of depressive symptomatology and its relationship to perinatal outcomes and levels of pro-inflammatory cytokines among HIV-infected pregnant women. Depressive symptomatology was related to lower newborn weight, and gestational age at delivery among HIV-infected pregnant women with CD4+ lymphocytes below 350 cells/mm$^3$. Participants who obtained higher scores in the Zung Self-rated Depression Scale had lower levels of Tumor Necrosis Factor alpha (TNF-α,) whereas Interferon-gamma (IFN-γ) levels were similar in participants with low and high depressive symptomatology. In this study, it was found that increased maternal depressive symptomatology, combined with CD4+ lymphocytes below 350 cells/mm$^3$, was related not only to lower newborn weight and height, but to lower gestational age at delivery as well.

**Keywords:** Depression; TNF-α; Pregnancy, HIV infection

## Introduction

A variable prevalence of depressive symptoms in women infected with the Human Immunodeficiency Virus (HIV) has been reported to be between 15.8% [1], 19.4% [2] and 42.2% [3], which is higher than that observed among HIV-seronegative women [2]. Perinatal depression in HIV seropositive pregnant women, measured with different psychological instruments, ranges from 15 to 53% of patients [1,4,5]. While the presence of depressive symptomatology during pregnancy is strongly predicted by the presence of depressive symptoms before pregnancy [6], social isolation, altered coping styles, and the amount of stress perceived by the pregnant women are also factors modulating the presence of depression in these patients [7]. Furthermore, depression may have potential effects on pregnancy outcomes that may be unrelated to HIV-infection or inflammatory markers, such as a decreased likelihood to look after oneself or the fetus.

The importance of screening for the depressive symptoms among HIV-infected women relies on the findings that depressive symptomatology have been related to disease progression [2], especially in women with viral loads higher than 10,000 copies/ml and CD4+ lymphocyte counts of less than 500 cells/mm$^3$ [3]. Additionally, HIV-infected pregnant women cohorts have shown an increased risk of delivering low birth weight or small for gestational-age babies, especially in mothers with inadequate prenatal care [8]. However, little is known regarding perinatal outcomes among HIV- infected pregnant women with depressive symptomatology.

It has been reported that depression among HIV-uninfected populations may be related to immune system activation and pro-inflammatory cytokines production, including Interleukin (IL)-1, IL-6 and TNF-α [9]. This is the reason why in this study, the measurement of cytokines was performed. Moreover, it has been proposed that cytokines may be involved in the etiology of other depression-associated illness [10]. Although most studies have shown significantly higher concentrations of TNF-α and IL-6 in depressed subjects [11], these findings have not been consistent with those seen in patients with different comorbidities, i.e. depression among breast cancer patients has been associated with lower levels of IL-2, IL-12 and TNF-α [12]. In pregnant women, depressive symptoms have also been associated to significantly increased levels of IL-6 [4] and marginally higher levels of TNF-α [13].

The role of depression in cytokine regulation among HIV-infected male and female patients still remains unclear. Furthermore, the role of depressive symptoms in cytokine production in HIV-infected pregnant patients, in whom the presence of fetus and pregnancy-related hormones are regulating the immune system, is also unclear. As cytokine changes have been related to adverse gestational outcomes [14], we propose that depressive symptomatology may affect pregnancy, not only because depression may be associated to a decrease in self-care but because it may be related to cytokine changes that in term could affect the required immunomodulation during pregnancy.

This study aimed to evaluate the prevalence of depressive symptomatology among HIV-infected pregnant patients at the National Institute of Perinatology, Mexico, City, the relationship of depression scores with perinatal outcomes, and the effects of depressive symptomatology in the serum levels of two inflammatory cytokines, controlling for the effect of various psychosocial factors. As alcohol

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abuse in the spouse or partner may be a predictor of the presence of abuse and psychiatric morbidity among pregnant women [15], this issue was considered as one of the covariates in this study.

Our hypothesis that depressive symptomatology can have an impact on inflammatory cytokine production and pregnancy outcomes in HIV-infected pregnant women may be considered as novel, because unlike other studies we informed less serum levels of IFN-γ and TNF-α, and perinatal results of the pregnancies were inapposite.

## Methods

### Type of study

This was an observational, prospective, cross-sectional, quantitative and non-random sampled study, in which a convenience sample was used.

### Patients

Thirty-seven HIV seropositive pregnant women, who received perinatal healthcare at the National Institute of Perinatology, Mexico, City, during the years 2010-2013, were included in this study, after providing signed informed consent. The National Institute of Perinatology is a government-funded, third level healthcare facility that attends low-income patients with high-risk pregnancies, from Mexico City and its suburban areas. The HIV status of all participants was confirmed by means of HIV-specific ELISA and Western blot antibody tests. HIV infection was monitored before and during pregnancy by measuring viral loads and CD4+ lymphocyte counts.

All patients received antiretroviral therapy throughout pregnancy. Twenty-four patients received a scheme consisting of zidovudine, lamivudine and lopinavir/ritonavir; ten patients received tenofovir, emtricitabine and lopinavir/ritonavir; two patients were treated with zidovudine, lamivudine and nevirapine; only one patient received a scheme of abacavir, lamivudine and nevirapine.

Women who participated in this study did not have HIV-related encephalopathy, AIDS-related cognitive impairment or life-threatening diseases that may have altered their ability to accurately respond the psychological instrument used in this study.

### Demographic and psychological evaluation

All participants, upon their inclusion in the study, filled a demographic questionnaire that evaluated age, marital status, socio-economic status, occupation, religion, and years of study. The 37 pregnant women were assessed using the Zung Self-rating Depression Scale (ZSRDS), which is considered as a sensitive instrument for measuring clinical severity in patients with depression [16,17], and it has adequate validity and reliability [18]. Scores of the ZSRDS were analyzed as numerical variables but where also categorized into high and low scores. The cut-off point was set at 40, out of 80 possible points, which was also the mean score of the ZSDRS test in participants. All patients who had high ZSRDS scores received psychological attention at the Institute's Psychology Department. No women received anti depressive pharmacotherapy while pregnant.

### Cytokine measurements

Peripheral whole blood specimens were taken during patient regular evaluations, between the 18$^{th}$ and 30$^{th}$ weeks of gestation. Serum samples were aliquoted and stored at -80°C until processing. Two 100 µL/well replicates of each serum were used for IFN-γ and TNF-α measurements, with separate commercial enzyme immuno assays (EIAs) (Biosource International Inc. Camarillo CA, USA). The sensitivity for the EIAs were of 4 pg/mL and 1.6 pg/mL for IFN-γ/ and TNF-α, respectively. No cross-reactivity was found with other cytokines.

### Data analysis and statistics

No transformations were required for the numerical variables evaluated in this study. Data points ≥3 standard deviations were considered as outliers. Using this cut-off, four univariate outliers in the TNF-α variable were eliminated from further analysis. No multivariate outliers, by Mahalanobis distance, were found. Descriptive statistics were calculated for the variables. ANOVAs were executed to analyze if there were significant differences between total ZSRDS scores, TNF-α and IFN-γ concentrations among women evaluated during the second and third trimesters. Three-way Factorial ANOVA analyses were also performed to evaluate if total ZSRDS scores, newborn's weight, newborn's height and gestational age by Capurro were different in patients with CD4+ lymphocyte counts higher or lower than 350 cells/mm3, among patients in CDC clinical categories A1-A2 and progressors, and between those patients with high and low depressive symptomatology. ANOVA and ANCOVA analyses were performed to evaluate if there were significant differences between depressive symptomatology scores and TNF-α, and IFN-γ concentrations in pregnant women with HIV seropositivity. Because age, years of HIV seropositivity, having an alcoholic partner and marital status may play a role in the development of depressive symptomatology, these variables were included as covariates in the analyses. Due to the sample size, these covariates were evaluated in four different analyses. Since this study included a non-randomized sample, bootstrapping was performed as resampling technique in the analyses of variance and covariance performed to evaluate cytokine differences in patients with depressive symptomatology. One thousand bootstrap samples were executed for each analysis using a Mersenne twister pseudorandom number generator.

The assumptions of homogeneity of variance and homogeneity of regression slopes were not violated in any of the analyses performed. No post hoc analyses were carried out, as all categorical variables were dichotomic. Alpha significance level was set at 0.05. Data was analyzed using IBM SPSS statistics software, version 21.

## Results

### Population and prevalence of depressive symptomatology

All participants were Mexican and lived in Mexico City and its suburban areas. The mean age of the population studied was 27.9 (SD 6.3) years old, and the mean years of HIV seropositivity were 6.02 (SD 4.8). Most women (59.5%) had a stable partner at the moment of evaluation, and 40.5% were single. Socio-economic status was low in 75.7%, medium-low in 18.9% and medium high in 5.4% of participants. The minority of participants had an alcoholic partner (18.9%). CD4+ lymphocyte counts were higher than 350 cells/mm$^3$ in 22 (59.5%) of the participants, and viral loads were lower than 50 copies/ml in 25 (67.6%). The majority (56.8%) of the women studied were in CDC clinical categories A1-A2, and the rest were in clinical categories B1 and B2.

The mean ZSRDS score among women studied was 40 (SD 9.3). High scores in the ZSRDS were present in 56.8% of participants. One-way ANOVA results did not show significant differences in ZSRDS scores among women evaluated during the second and third trimesters, $F(1,35)=3.38$, $p=0.074$.

Three-way factorial ANOVAs showed no significant differences between the participants' total ZSRDS scores and their HIV status, neither their CD4+ lymphocyte counts (F(1,33)=0.11, p=0.917 and F (1,33)=3.63, p=0.065), respectively.

Newborns' weight was significantly lower in babies from women with CD4+ lymphocyte counts below 350 cells/mm$^3$ F (1.29)=6.43, p=0.017, p Eta$^2$=0.18. No significant differences in birth weight were found among babies born from mothers with high and low ZSRDS scores; however, women with high ZSRDS scores and low CD4+ cells/mm$^3$, were the ones who delivered the babies with the lowest birth weights, F(1,29)=7.60, p=0.010, p Eta$^2$=0.20. Additionally, newborns' height was significantly lower in babies born from pregnant women who were in CDC clinical stages B1 and B2, F=5.24, p=0.029, p Eta$^2$=0.15. No significant differences were found in newborns' height among babies born from women who had high or low ZSRDS scores, but those newborns whose mothers had high depressive symptomatology and low CD4+ lymphocyte counts below 350 cells/mm$^3$ did have a significantly lower height, F (1,29)=11.36, p=0.002, p Eta$^2$=0.28.

Newborns' gestational age by Capurro, was also smaller in babies born from mothers who had CD4+ lymphocyte below 350 cells/mm$^3$ and higher ZSRDS scores, F (1,29)=8.01, p=0.008, p Eta$^2$=0.21. There were no significant differences in newborn weight and age by Capurro among participants in CDC clinical stages A1-A2 and B1-B2.

Results of the three-way factorial ANOVAs performed to evaluate differences in newborn weight, height and gestational age among women with high/low ZSRDS scores, CD4+ lymphocytes below/above 350 cells/mm$^3$, and women in CDC clinical categories A1,A2/B1,B2 can be found in Table 1.

## Relationship between depressive symptoms and production of IFN- γ

Overall serum mean IFN-γ concentration was 10.9 (SD 4.9) pg/mL, and IFN-γ means in participants with high and low ZSRDS scores were 9.1 (SD 4.8) and 13.2 (SD 4.0) pg/mL, respectively. ANOVA results showed no significant differences in IFN-γ levels between participants that were evaluated during the second and third trimester, F (1,35)=0.37, p=0.54, neither among women with CD4+ lymphocyte counts below or above 350 cells/mm$^3$, F(1,35)=0.09, p=0.76. No significant differences were found among patients with high and low ZSRDS scores, F (1,35)=2.14, p=0.15. Bias for bootstrap samples were -0.001 and -0.003 for high and low ZRDS scores, respectively. Standard error of the mean value of IFN-g across 1000 bootstrap samples was 0.078 (CI 95% 10.97, 11.28) for high ZRDS scores and 0.087 (CI 95% 10.79, 11.14) for low ZRDS scores.

After controlling the effect of age, marital status, years with HIV seropositivity, and having alcoholic partner, in separate ANCOVA analyses, no significant differences were found between the levels of IFN-γ in HIV seropositive pregnant women with low and high ZSRDS scores.

A graphic representation of the levels of TNF-α and IFN-γ in patients with high and low levels of depressive symptomatology can be found in Figure 1. Even though no significant differences were found in IFN-γ concentrations between participants with low and high ZSRDS scores, the women in this study reporting more depressive symptomatology tended to have higher IFN-γ levels.

## Relationship between depressive symptomatology and levels of TNF-α

The overall mean serum TNF-α score was 11.8 (SD 0.4) pg/mL. The mean values of TNF-α in women with high and low ZSRDS scores were 11.1 (SD 0.4) pg/mL and 10.96 (SD 0.4) pg/mL, respectively. No significant differences were found in TNF-α levels between participants that were evaluated during the second and third trimesters, F (1,35)=3.42, p=0.073, nor among women with CD4+ lymphocyte counts below or above 350 cells/mm3, F(1,35)=0.66, p=0.42. However, ANOVA results showed significant differences in TNF-α levels between participants with high and low ZSRDS scores, F(1,35)=7.92, p=0.008, p

| Newborn weight | | | | | |
|---|---|---|---|---|---|
| | **ZSRDS[a] high/low** | **CD4+ cells[b]** | **CDC clinical category[c]** | **ZSRDS[a] high/low* CD4+ cells[b]** | **ZSRDS[a] high/low* CD4+ cells[b]* CDC clinical category[c]** |
| F | 0.177 | 6.430 | 3.040 | 7.606 | 10.487 |
| *p* | 0.677 | 0.017* | 0.092 | 0.010* | 0.003* |
| p Eta$^2$ | 0.006 | 0.181 | 0.095 | 0.208 | 0.266 |
| Newborn height | | | | | |
| | **ZSRDS[a] high/low** | **CD4+ cells[b]** | **CDC clinical category[c]** | **ZSRDS[a] high/low* CD4+ cells[b]** | **ZSRDS[a] high/low* CD4+ cells[b]* CDC clinical category[c]** |
| F | 0.047 | 2.949 | 5.246 | 11.360 | 12.856 |
| *p* | 0.829 | 0.07 | 0.029 | 0.002* | 0.001* |
| p Eta$^2$ | 0.002 | 0.092 | 0.153 | 0.281 | 0.307 |
| Newborn gestational age at delivery | | | | | |
| | **ZSRDS[a] high/low** | **CD4+ cells[b]** | **CDC clinical category[c]** | **ZSRDS[a] high/low* CD4+ cells[b]** | **ZSRDS[a] high/low* CD4+ cells[b]* CDC clinical category[c]** |
| F | 2.485 | 0.001 | 1.400 | 8.015 | 11.113 |
| *p* | 0.126 | 0.974 | 0.246 | 0.008* | 0.002* |
| p Eta$^2$ | 0.079 | 0.000 | 0.046 | 0.217 | 0.277 |

Newborns' weight was significantly lower in babies from women with CD4+ lymphocyte counts below 350 cells/mm$^3$ (p=0.017).
Newborns whose mothers had high depressive symptomatology and low CD4+ lymphocyte counts below 350 cells/mm$^3$ did have a significantly lower height (p=0.002).
Newborns' gestational age by Capurro, was smaller in babies born from mothers who had CD4+ lymphocyte below 350 cells/mm$^3$ and higher ZSRDS scores. (p=0.008).
**p:* significative <0.05
a: High and Low Zung Self-rating Depression Scale scores
b: CD4+ lymphocytes below or above 350 cells/mm$^3$
c: CDC clinical categories A1,A1 vs B1,B2
p Eta$^2$: Partial Eta Squared

**Table 1:** Analysis of three-way factorial ANOVAs performed to evaluate differences in newborn weight, height and gestational age.

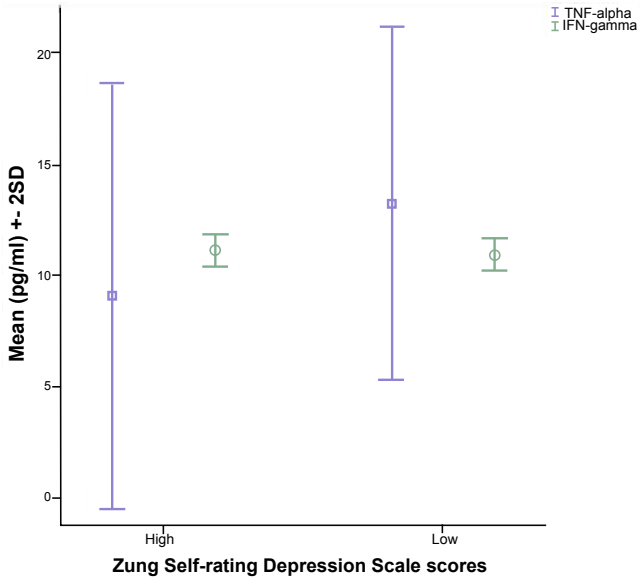


**Figure 1:** Representation of the levels of TNF-alpha and IFN-gamma in patients with high and low levels of depressive symptomatology. No significant differences were found in IFN-II concentrations between participants with low and high ZSRDS scores.

Eta$^2$=0.18. Bias for bootstrap samples were -0.033 and -0.027 for high and low ZRDS scores, respectively. Standard error of the mean value of TNF-α across 1000 bootstrap samples was 1.049 (CI 95% 7.07, 11.03) for high ZRDS scores and 0.962 (CI 95% 11.27, 14.95) for low ZRDS scores.

Subsequently, four ANCOVAs were performed in order to evaluate the differences between high and low ZSRDS scores on TNF-α levels in pregnant women infected with HIV, controlling for the effect of age, years with HIV seropositivity, marital status, and having an alcoholic partner. All analyses were significant, with a p value of 0.009, 0.009, 0.023 and 0.049, respectively for each covariate. Results of the analyses of covariance are presented in Table 2.

TNF-α levels were significantly lower in pregnant women infected with HIV and high ZSRDS scores, compared to those women with low ZSRDS scores. Partial eta squared values in the four ANCOVAs show a small size effect, in that ZSRDS scores account for 11-18% of the variance in TNF-α. The covariate with the highest influence on TNF-α levels was having an alcoholic partner because after adjusting for this variable, the effect size fell down to 0.11. A graphical representation of the differences in TNF-α between participants with low and high ZSRDS scores after adjusting for the four covariates can be found in Figure 2.

## Discussion

Comorbid depression has a significant prevalence among HIV infected men and non-pregnant women [2,19] and it ranges from 15.87% [1] to 21.3% [20]. The presence of high levels of depressive symptomatology was considerable in this study's participants, accounting for 56.8%. The prevalence of depressive symptomatology in our study population is slightly higher to that reported by other groups in HIV-infected pregnant women, ranging from 39% to 53% [5,21-23]. Chronic depressive symptomatology in HIV infected women is relevant because it has been associated to a greater risk of disease progression [3], with decreased CD4+ counts [20], and with higher viral load levels [1]. In this study, CD4+ lymphocytes below 350 cells/mm$^3$ was the most important factor affecting newborn height and weight. However, it was also found that increased maternal depressive symptomatology, combined with CD4+ lymphocytes below 350 cells/mm$^3$, was related not only to lower newborn weight and height, but to lower gestational age at delivery as well. Moreover, those women with high levels of depressive symptomatology, lower CD4+ lymphocyte counts, and in CDC clinical stages B1 and B1, were the ones who delivered the babies with the lowest weight, height and gestational age.

While several studies have reported that maternal depression may predict low birth weight [24,25] and preterm birth [26], the mechanism by which depression may contribute to unfavorable perinatal outcomes in HIV-infected pregnant women remains poorly known.

Overall, the presence of depression and, specially, major depressive disorder, have been related to the release of pro-inflammatory cytokines such as TNF-α, IL-6 [27] and IL-2 soluble receptor [28].

In HIV seronegative pregnant women with depressive symptoms, serum IL-6 has been found to be significantly higher and TNF-α marginally higher, compared to those without depressive symptoms [13]. Contrary to these findings, the results in this study show that HIV-infected pregnant patients with increased depressive symptoms have significantly lower TNF-α levels than those with low depressive symptoms.

During uncomplicated pregnancy, there is a lower production of IFN-γ and TNF-α by peripheral blood mononuclear cells [29], probably due to the presence of fetal antigens, progesterone, 17beta-estradiol and

| ANCOVA results for TNF-α levels and ZSRDS[a] scores | | F | *p* | p Eta[2b] | ZRDSD scores | Bootstrap bias | SE (95% CI) |
|---|---|---|---|---|---|---|---|
| TNF-α and high/low ZSRDS scores | Controlling for age | 7.73 | 0.009* | 0.18 | High | -0.041 | 1.06 (7.1, 11.1) |
| | | | | | Low | -0.022 | 0.971 (11.3, 14.9) |
| | Controlling for years of HIV-seropositivity | 7.63 | 0.009* | 0.18 | High | -0.43 | 1.057 (7.1, 10.98) |
| | | | | | Low | -0.17 | 0.99 (11.7, 15.1) |
| | Controlling for marital status | 5.70 | 0.023* | 0.14 | High | -0.36 | 1.085 (7.1, 11.31) |
| | | | | | Low | -0.40 | 1.094 (10.7, 14.9) |
| | Controlling for effect of alcoholic partner | 4.18 | 0.049* | 0.11 | High | -0.063 | 1.155 (7.1, 11.6) |
| | | | | | Low | -0.006 | 1.046 (10.5, 14.8) |

ANCOVAs were performed in order to evaluate the differences between high and low ZSRDS scores on TNF- α levels in pregnant women infected with HIV, controlling for the effect of age, years with HIV seropositivity, marital status, and having an alcoholic partner, all analyses were significant ($p < 0.05$ per each covariate).
*$p$ significative: < 0.05
a: Zung Self-rating Depression Scale; b: Partial Eta Squared; SE: Standard error of the mean value of TNF- α across 1000 bootstrap samples; CI: Confidence interval for Standard error

**Table 2:** ANCOVA results for TNF-α levels and ZSRDS[a] scores.

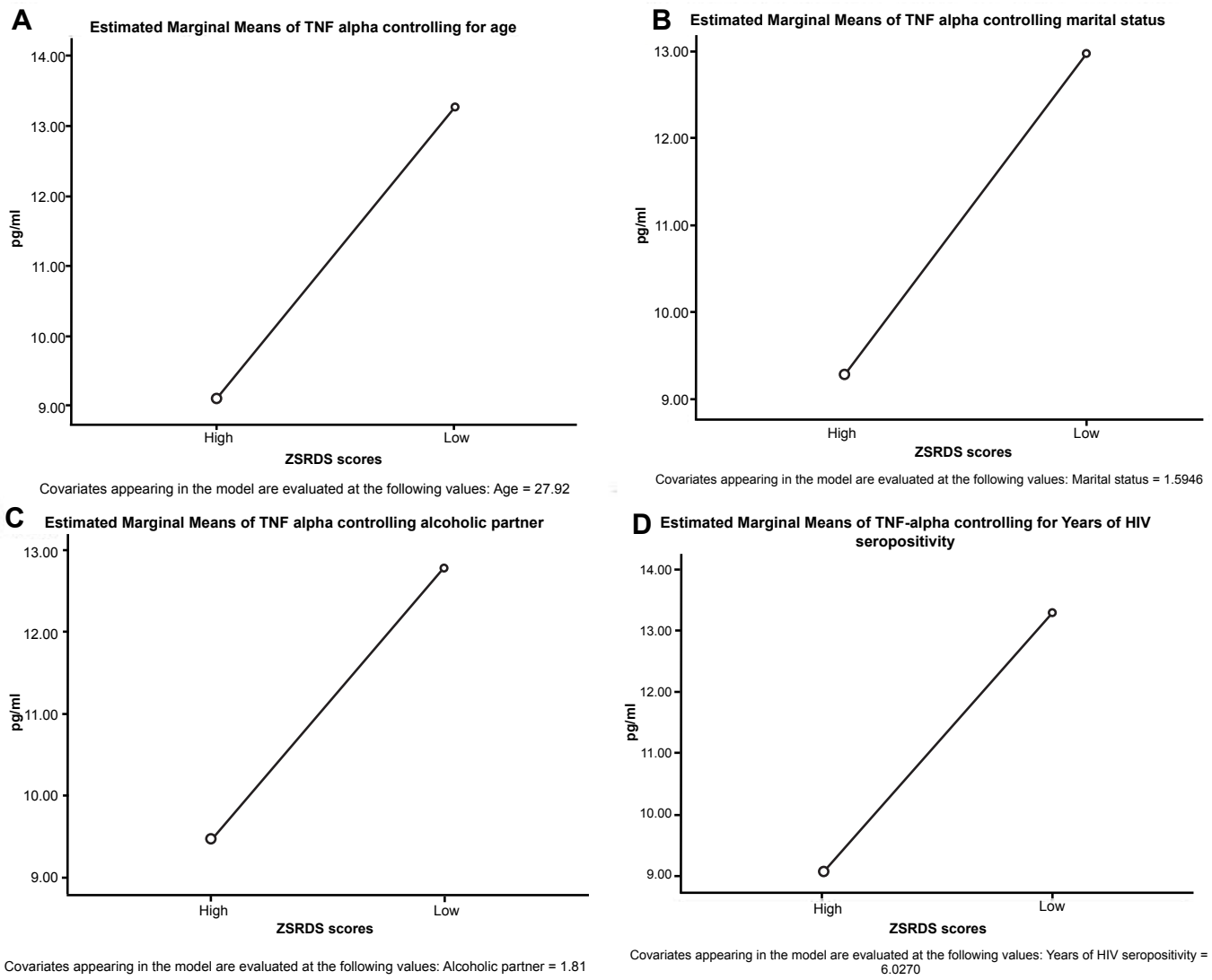


**Figure 2:** Graphical representation of the differences in TNF-alpha between participants with low and high ZSRDS scores after adjusting for the covariates age, years with HIV seropositivity, marital status, and having an alcoholic partner.

by regulatory T cells (Tregs) [30], and contributes to the $T_{H2}$ bias of the $T_{H1}/T_{H2}/T_{H17}$/Treg paradigm used to explain immune regulation during pregnancy [31].

It has been reported that the levels of TNF-α in advanced HIV-infected individuals may range from 59-130 pg/mL, while TNF-α levels in patients with not pregressive HIV infection are similar to those in non-infected controls, ranging from 42-76 pg/mL [32]. Among HIV-infected pregnant women, Richardson and Weinberg found that concentrations of TNF-α and IFN-γ (12.6 pg/mL and 1.6 pg/mL, respectively) are significantly higher than those present in non-infected pregnant women. In this study, HIV infected pregnant women had TNF-α concentrations that ranged from 1.89 to 19.06 pg/mL and IFN-γ concentrations ranging from 10.32 to 11.82 pg/mL, which are higher concentrations than those reported previously in HIV-infected pregnant women, especially for IFN-γ [33]. Nevertheless, the overall concentrations of cytokines found in this study were lower than those levels reported in non-pregnant patients infected with HIV. This may be due to the fine regulation of the immune system during the gestational period, in which Tregs may potently suppress IL-2, TNF-α and IFN-γ secretion in pregnant patients [30].

It is widely known the interference of depressive symptoms on therapeutic adherence of HIV seropositive patients. Diverse studies have showed that adherence to antiretroviral therapy is worse among those with depression [34]. Nevetherless, we think that the HAART therapy had no effect on the develop of depression in our patients, because the relationship of antiretroviral drugs with depressive symptoms or psychiatric disorders, has only been described for efavirenz and raltegravir, both of them have been associated with the adverse effects of suicidal ideation and depression [35]; but is important note that none of our patients were receiving these kind of drugs during the evaluation period.

With regard to the possible effects of the HAART therapy on the level of cytokines, it has been showed that upon starting antiretroviral treatment, a gradual recovery of immune function occurs [36]; the immune reconstitution has been associated with increased circulating pro-inflammatory cytokines TNFα, IL-6, and IFN-γ; almost all the

cytokines demonstrated significantly higher concentrations at week 2 and week 4 of starting HAART therapy, returning to baseline levels by week 12 [37]. In contrast to this information, in our study we observed low serum levels of IFN-γ and TNF-α, so we do not discard the possibility that the gestational condition may influence the behavior of those cytokines.

Multiple factors such as the HIV infection itself, co-morbidity, pregnancy-related hormones, and antiretroviral therapy could be participating in decreasing TNF-α concentrations in these women with high depression scores, which certainly complicate the explanation of this feature. It may be possible that cytokines other than those measured in this study may be modulating depressive symptomatology and counteracting with TNF-α in these patients, such as IL-10, which has been found to be a significant predictor for depressive mood in non-pregnant HIV seronegative patients [38]. The role of Indoleamine 2-dioxigenase (IDO) and Tryptophan 2-dioxigenase (TDO) should also be discussed and perhaps studied in future studies because these enzymes degrade tryptophan, affecting serotonin serum concentrations. While TDO is activated by cortisol, IDO is activated by pro-inflammatory cytokines such as IFN-γ and TNF-α [39]. As women with depressive symptomatology in this study had lower levels of TNF-α, it is likely to argue that depression among these patients may not be related to increased IDO activity, but to increased TDO activity. However, neither cortisol levels nor TDO activity were evaluated in this study.

Out work reports the presence of lower levels of TNF-α in HIV pregnant patients with high prevalence of depressive symptomatology, which is a finding not previously reported for Mexican populations. Additionally, the results of this study show that increased depressive symptomatology in HIV-infected pregnant women may be related to adverse newborn outcomes, especially in those women with CD4+ lymphocytes below 350 cells/mm$^3$. However, this study also has its limitations. One important limitation is that no neuroendocrine biomarkers that may modulate cytokine response in these patients were measured, such as cortisol and epinephrine. Another limitation is that only two cytokines were evaluated.

We propose that future work on this topic should include measuring the concentrations of serum IL-10, cortisol, progesterone and IDO/TDO activity in these patients, thus helping to clarify the actual picture. Additionally, a bigger sample size could have let us perform more complex analyses to evaluate this population.

## Conclusions

In this study depressive symptomatology was related to lower newborn height, weight and gestational age among HIV-infected pregnant women lymphocyte counts below 350 cells/mm$^3$. On the other hand, inflammatory cytokine microenvironments may not always be present in patients with depressive symptoms, especially in patients who have co-morbidities or conditions promoting immune system regulation, such as those present in HIV seropositive pregnant women.

Further studies are needed to clarify the interplay of depression and cytokine expression on the development of depression in these patients, in which immunorregulation is being affected by the presence of HIV infection and pregnancy-related hormones.

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