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ORIGINAL PAPER

The Use of Efavirenz During Pregnancy is Associated with Suicidal Ideation in Postpartum Women in Rural South Africa

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Abstract

Efavirenz is used for the management of HIV infection during pregnancy in South Africa (SA), but it is contraindicated in patients with history of depression due to possible suicidal ideation. This study compared suicidal ideation 12-months postpartum among women receiving and not receiving efavirenz in rural SA, where high rates of depression have been identified. Antenatal psychological intimate partner violence (IPV; AOR = 1.04), depression (AOR = 1.06) and detection of efavirenz in dried blood spot at 32 weeks predicted suicidal ideation 12-months postnatally (AOR = 2.29), controlling for antenatal stigma and physical IPV. Findings support using alternative agents for the management of HIV during pregnancy.

Keywords Pregnancy · WOMEN · Efavirenz · Suicidal ideation · Postpartum · South Africa

Resumen

Efavirenz es comúnmente utilizado para el tratamiento de la infección por el VIH durante el embarazo en Sudáfrica, pero está contraindicado en pacientes con antecedentes de depresión debido a la posible asociación de su uso con la ideación suicida. Este estudio comparó la ideación suicida a los 12 meses después del parto en mujeres que tomaron o no tomaron Efavirenz durante el embarazo en zonas rurales de Sudáfrica, donde se han identificado altas tasas de depresión. La violencia psicológica prenatal en la pareja (IPV, AOR = 1.04), la depresión (AOR = 1.06) y la detección de Efavirenz en la sangre (medida en muestras de sangre seca) a las 32 semanas predijeron ideación suicida a los 12 meses postparto (AOR = 2.29) en un analysis controlando el estigma prenatal y la IPV física. Los hallazgos respaldan el uso de agentes alternativos para el tratamiento del VIH durante el embarazo.

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Introduction

Efavirenz, one of the most widely used antiretrovirals (ARV) worldwide, is a highly effective medication recommended by the World Health Organization (WHO) as a component of first-line antiretroviral therapy (ART), including during pregnancy and postpartum, unless contraindicated or unavailable [1]. However, due to its adverse neuropsychiatric effects (i.e., difficulties concentrating or sleeping, behavioral changes, strange thoughts and dreams, hallucinations, and depressive symptoms), the lower potency when compared with other new ARVs, the potential risk of teratogenicity, and the high prevalence of transmitted drug-resistant mutations [2, 3], its use has significantly decreased in high income countries where it is no longer recommended as first-line therapy for HIV [4, 5]. Recommendations from the European AIDS Clinical Society support the provision of alternatives to efavirenz

for those with a history of depressive, anxious, or psychiatric symptoms, and assessment of suicide risk, depression, and mental health consequences of HIV diagnosis prior to initiation of efavirenz [1, 5].

Efavirenz suicide-related complications include suicidal thoughts or behaviors, and suicide attempts or completions. Previous analyses of randomized controlled trials with ARV naïve patients found that the adjusted risk of attempted or completed suicide was higher in participants receiving efavirenz, although results were not confirmed [6–9]. In contrast, investigators recently found "no strong evidence" that initiation of efavirenz-containing ARV regimens increased the risk of suicidal thoughts among US patients in routine care with detectable viral load [10]. However, in switch studies in which efavirenz has been changed for newer agents, discontinuation has been associated with improved neuropsychological status, and recent reports confirm the relationship between the use of efavirenz and suicidal behaviors [11], supporting the association of adverse neuropsychiatric effects with efavirenz [12].

High rates of perinatal depression and suicidal ideation have been reported among HIV-infected African women [13] and among women in low and medium income countries (LMIC), where screening for depression is not routinely performed [14]. In rural South Africa (SA), where ~ 50% of HIV diagnoses in women occur during pregnancy, high levels of depressive symptoms and suicidal ideation have been identified [15, 16]. There is ongoing discussion regarding the use of efavirenz during pregnancy [17], and though efavirenz has been approved in SA for use in pregnant women, in a population already experiencing high levels of depression and suicidal ideation, such as perinatal HIV-infected women in SA, the addition of efavirenz may exacerbate existing depressive symptoms and suicidal ideation, and could have a direct impact on neonatal health or an indirect influence on maternal mental health [18]. Additionally, although WHO recommendations indicate that depression usually resolves over time with discontinuation of efavirenz, time to resolution is variable and may extend to the postpartum period, when the susceptibility to depression is higher in women [1, 19]. Perinatal depression may also have irreversible effects on infant neurodevelopmental outcomes [20].

Previous research in SA with pregnant and non-pregnant women has relied on clinic medical records, which may fail to identify patient depression or suicidality [21]. This longitudinal study of HIV-infected perinatal women in rural SA compared rates of suicidal ideation at 12-months postpartum in women with detectable versus undetectable efavirenz at 32 weeks of pregnancy. Results have implications for the optimal management of HIV infection among pregnant women in LMIC.

Methods

Participants and Procedures

Participants (n = 599) were recruited and enrolled during pregnancy (M = 18.07 weeks, SD = 5.54) into the baseline phase of a randomized clinical trial from April 2014 to July 2016, Protect Your Family, focused on the prevention of mother-to-child transmission (PMTCT) of HIV, as previously described [22]. Participants were HIV infected women less than 25 weeks pregnant and at least 18 years old. Women completed study measures in their preferred language (English, Zulu, Sotho) using an Audio Computer-Assisted Self-Interview (ACASI) and were assessed at baseline (prior to 24 weeks of pregnancy), 32 weeks of pregnancy, and 12-months postpartum. All women provided written informed consent. Ethical approval was obtained from the Mpumalanga Department of Health, the Human Sciences Research Council, and the University of Miami Institutional Review Board prior to study onset. ART was prescribed as per the SA HIV ARV Medication Protocol, tenofovir disoproxil fumarate + (either lamivudine or emtricitabine) + efavirenz [23, 24].

Measures

Baseline Covariates

At baseline, participants completed a *Demographic and Medical History Questionnaire* which included age, educational attainment, employment status, monthly income, relationship status, disclosure of HIV status to partner, and alcohol use. *HIV issues* included whether the participant was diagnosed during the current pregnancy and time of ART initiation by self-report. The *Conflict Tactics Scale* 18 (CTS-18) [25] was used to assess physical ($\alpha = 0.92$) and psychological ($\alpha = 0.76$) intimate partner violence (IPV) in the past month, and subscales were included as covariates [26]. The *AIDS-Related Stigma Scale* (ARSS), a nine-item scale, was used to assess HIV stigma ($\alpha = 0.74$), and was included as a covariate [27].

Efavirenz Detection in Dried Blood Spot at 32-weeks of Pregnancy

Levels of efavirenz, lamivudine, and tenofovir disoproxil fumarate were assessed among all women using dried blood spot (DBS) collection. Women were asked to provide five blood drops drawn with a sterile lancet using a Guthrie card. ARVs were considered undetectable if below

0.02 µg/ml and detectable if above 0.02 µg/ml using liquid chromatography/tandem mass spectrometry [28].

Baseline and Postpartum Variables

The *Edinburgh Postnatal Depression Scale 10* (EPDS-10) was used to assess depression and suicidal ideation. [29]. The suicidal ideation item, which refers to self-harm, has been found to have good sensitivity (77%) and excellent specificity (92%) for suicidal ideation in SA and other low and middle-income countries [30–32]. Responses of "*Yes, quite often*", "*Sometimes*", and "*Hardly ever*" were coded as suicidal and "*Never*" as non-suicidal. The suicidal ideation item was excluded from the total depression score at baseline to prevent overestimating the effect of depression on suicidal ideation.

Data Analyses

Univariate and bivariate analyses were used to describe the sample and compare non-suicidal and suicidal women at 12-months postpartum. A logistic regression model was used to predict suicidal ideation at 12-months postpartum by levels of efavirenz (not detected versus detected), after controlling for baseline psychological and physical IPV, depression, and stigma. Logistic regression was used because the objective of this study was to test the relationship between a dichotomous outcome (suicidal ideation) and independent variables associated with suicidal ideation in previous research, including efavirenz and the covariates previously specified [11, 12, 15, 16].

Results

Detection of Efavirenz in Dried Blood Spot

Eighty-four percent of women had efavirenz detected. Two or three drugs were detected in DBS in 58% of women; 57% of these had tenofovir disoproxil fumarate and efavirenz detected, and 1% had all three ARVs detected. Among women not having two or three drugs detected (42%), 12% had no ARVs detected, 26% had 1 ARV detected, and 3% had two ARVs (not tenofovir disoproxil fumarate and efavirenz) detected. Adherence by self-report was over 80% and had a low agreement with DBS levels, as well as low sensitivity and specificity to detect nonadherence [33].

Baseline Socioeconomic, HIV, Partner and Mental Health Characteristics Associated with Suicidal Ideation 12-months Postnatally

At baseline, participants were 28.66 ± 5.83 years of age. Two-thirds (68%) of women had completed ≤ 10 years of education, 82% were unemployed, 48% had a monthly household income of < 600 ZAR (~ USD$50), and 80% were unmarried. Half (48%) were diagnosed during the current pregnancy; women had initiated ART ~ 16.89 ± 27.02 months prior to the baseline assessment. Two-thirds (62%) had disclosed their HIV status to partners. Women reporting suicidal ideation at 12-months had greater levels of psychological and physical IPV, and depression at baseline. A greater proportion of women reporting suicidal ideation at 12-months also had efavirenz detected at 32 weeks (see Table 1).

Baseline and 32 Weeks Predictors of Suicidal Ideation 12-months Postnatally

In multivariable logistic regression, baseline psychological IPV (AOR = 1.04 [1.00, 1.09]), depression (AOR = 1.06 [1.02, 1.10]), and detection of efavirenz in DBS at 32 weeks predicted suicidal ideation 12-months postnatally (AOR = 2.29 [1.13, 4.65]), controlling for baseline stigma and physical IPV (see Supplemental Table 2).

Discussion

This study of pregnant women in rural SA examined suicidal ideation in the postpartum period, comparing women with detectable and undetectable efavirenz at 32 weeks of pregnancy, and found that women who had detectable efavirenz at 32 weeks had greater odds of suicidal ideation at 12-months postpartum, after controlling for baseline depression, stigma, and physical and psychological IPV. The use of efavirenz during pregnancy is recommended by WHO [1] and by South African guidelines [23], although due to potential toxicity of efavirenz, other ARVs (integrase inhibitors and protease inhibitors) have recently been added as first-line therapy. While efavirenz has been removed from the HIV guidelines during pregnancy in high income countries, its continued use in LMIC may reflect cost and toxicity concerns related to the association of neural tube defect and the use of dolutegravir in the periconception period [34].

A recent study [10] has suggested that the impact of efavirenz on suicidal ideation is neither clinically relevant nor time limited, finding "no strong evidence" that self-reported initiation of efavirenz-containing ARV regimens increased suicidal thoughts. However, using DBS drug levels, the current study found that detectable efavirenz at 32-weeks predicted suicidal ideation at 12-months postpartum [35]. Biological and hormonal changes in pregnancy influence drug metabolism, suggesting that efavirenz metabolism is lower and levels could be increased in blood over time, resulting in a differential effect on the response to medication and increased incidence of adverse side effects.

Table 1 Baseline socioeconomic, HIV, partner and mental health characteristics associated with suicidal ideation 12 months postnatally (N = 599)

Characteristic	All (N = 599) Mean(SD) n (%)	Not suicidal (n = 483) Mean(SD) n (%)	Suicidal (n = 116) Mean(SD) n (%)	t/X^2, p
Socioeconomic status				
Age	28.66 (5.83)	28.62 (5.65)	29.35 (6.36)	1.13, 0.258
Educational attainment				
Grade 0-9	124 (20.7%)	98 (20.3%)	26 (22.4%)	2.41, 0.300
Grade 10-11	284 (47.4%)	224 (46.4%)	60 (51.7%)	
Grade 12 or more	191 (31.9%)	161 (33.3%)	30 (25.9%)	
Employed				
No	510 (82.4%)	411 (82.5%)	99 (81.8%)	
Yes	109 (17.6%)	87 (17.5%)	22 (18.2%)	0.03, 0.854
Monthly household income (South African Rand)				
< 600 (~ $50)	288 (48.1%)	236 (48.9%)	52 (44.8%)	
≥ 600	311 (51.9%)	247 (51.1%)	64 (55.2%)	0.61, 0.435
Relationship status				
Unmarried, living separate	325 (54.3%)	258 (53.4%)	67 (57.8%)	
Unmarried, living together	154 (25.7%)	125 (25.9%)	29 (25.0%)	
Married	120 (20.0%)	100 (20.7%)	20 (17.2%)	0.91, 0.633
HIV issues				
Diagnosed during this pregnancy				
No	289 (48.2%)	232 (48.0%)	57 (49.1%)	
Yes	310 (51.8%)	251 (52.0%)	59 (50.9%)	0.05, 0.831
Months since ART initiation	16.89 (27.02)	16.71 (27.11)	17.60 (26.72)	1.23, 0.220[a]
Efavirenz at 32 weeks				
Not detectable	95 (15.3%)	85 (17.1%)	10 (8.3%)	
Detectable	524 (84.7%)	413 (82.9%)	111 (91.7%)	**5.81, 0.016**
Partner issues				
Disclosure of HIV status (to partner)				
No	230 (38.4%)	189 (39.1%)	41 (35.3%)	
Yes	369 (61.9%)	294 (60.9%)	75 (64.7%)	0.57, 0.452
Psychological Intimate partner violence	3.50 (5.87)	3.18 (5.48)	5.04 (7.12)	**3.62, < 0.001**[a]
Physical intimate partner violence	1.18 (3.80)	1.03 (3.67)	1.84 (4.25)	**3.34, 0.001**[a]
Alcohol use, stigma, and depression				
Alcohol (> 2 drinks last month)				
No	521 (87.0%)	419 (86.7%)	102 (87.9%)	
Yes	78 (13.0%)	64 (13.3%)	14 (12.1%)	0.12, 0.734
Stigma	1.26 (1.22)	1.21 (1.18)	1.35 (1.46)	**2.13, 0.033**[a]
Depression	11.06 (5.46)	10.54 (5.47)	12.55 (5.11)	**3.61, < 0.001**

Bold values indicate significance at $p < 0.05$

SD Standard Deviation

[a]Mann-Whitney tests were used for median comparison of groups

These biological effects, in combination with interpersonal and cultural factors (e.g., IPV, depression and stigma), may result in increased suicidal ideation. Regardless of the etiology, results highlight the risk for postpartum suicidal ideation associated with efavirenz during pregnancy, and support the need to discontinue efavirenz use during pregnancy and postpartum [13]. Results also support careful screening for suicidal ideation during perinatal care. Clinical programs for perinatal anxiety and depression have been established and interventions for mental illness including depression exist in some regions of SA [36, 37]. As the perinatal period is associated with high rates of depression among HIV-infected women [13],

implementation of existing mental health protocols for pregnancy is needed for this vulnerable population.

Limitations of this study include the assessment of efavirenz at a single point during pregnancy. Additionally, suicidal ideation was only assessed using one question, and structured psychiatric assessments of suicidal ideation and behavior are merited in future studies. Longitudinal assessment of suicidality and efavirenz levels were not available in this study and would have provided stronger data to support the association of efavirenz and suicidal ideation. In addition, clinical factors (immune status and virological failure) were not measured and could have contributed to the development of suicidal ideation. Finally, this study reports associations that do not imply causality. Despite these limitations, a strength of the present study compared to previous studies was the assessment of efavirenz by DBS [38].

Conclusions

This study highlights the high risk associated with efavirenz use for women during pregnancy and postpartum, a period of high risk for the development of depression, and screening for depression during pregnancy. In addition, results highlight the importance of providing alternative medication for HIV treatment among women in settings where screening for suicidality may not be available.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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