Original Article

Maternal side effects of efavirenz-containing highly active antiretroviral therapy (HAART): A comparative study of HIV-positive pregnant and nonpregnant women in a tertiary hospital

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ABSTRACT

Background: Efavirenz is now a first-line non-nucleoside reverse transcriptase inhibitor used as highly active antiretroviral therapy (HAART) though its use is fraught with maternal side effects, usually of the central nervous system (CNS) and fetal complications.

Objective: The study aims to comparatively document the maternal side-effect profile of an efavirenz-containing fixed-dosage HAART and compliance with its use in HIV-positive pregnant and nonpregnant women at the Lagos University Teaching Hospital (LUTH), Idi-Araba.

Methodology: A prospective study among HIV-positive pregnant (40) and nonpregnant women (40) on efavirenz-containing fixed-dose HAART (Atripla®) who were recruited purposively at the antenatal clinic and AIDS Prevention Initiative Nigeria (APIN) clinics of LUTH. Data analysis was done with EPI Info 2014, and the results are presented in frequencies.

Results: The mean age of respondents was 31 ± 5.7 years. Atripla® was the only fixed-dose combination used. Fifty-three percent and 62.5% of pregnant and nonpregnant HIV-positive women, respectively, reported CNS side effects of Atripla® [odds ratio: 0.66, 95% confidence interval 0.27–1.62]. Adherence to the use of Atripla® was 100% among HIV-positive pregnant women. Women with baseline viral load values greater than 400 copies/mL reported more side effects to Atripla®.

Conclusion: There are similar side-effect profiles of Atripla® in HIV-positive women irrespective of pregnancy. Education and counselling can help foster adherence, resulting in improved immunological and virological outcome.

Key words: Efavirenz; HAART; maternal; side-effects.

Introduction

HIV/AIDS continues to pose a significant public health challenge globally.[1] According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 36.9 million people were living with HIV in 2017, and out of these 1.8 million were children under the age of 15 years. In 2017, there were 1.8 million new HIV infections, with a decline of new HIV infection among children by 35%, compared with 2010 figures.[2] Despite the reduction in new HIV infections, most infections in children (90%) are acquired by mother-to-child transmission.[3]

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To reduce the number of children affected or infected with HIV, the World Health Organization (WHO) and the UNAIDS have proposed a comprehensive approach consisting of four key strategies.[3] One of these is elimination of mother-to-child transmission (EMTCT) of HIV infection.[4] This is achievable through the use of highly active antiretroviral therapy (HAART), regarded as the single most important step in EMTCT.[1] Without any intervention, the risk of MTCT of HIV infection is 15%–45%.[1] Risk factors for vertical transmission include maternal progression of infection, assessed with peripheral viral load or clinical or immunological markers, prematurity, increased duration of ruptured membranes, presence of sexually transmitted infections, invasive procedures, mode of delivery, and breastfeeding.[1] The use of HAART and other components of the comprehensive approach to EMTCT could lower the risk to as low as 2%.[1] HAART also improves maternal health outcomes and reduces viral load.[1]

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI), which is now regarded by the WHO as the preferred first-line NNRTI.[4] Prior to 2013, the use of efavirenz in pregnant women was restricted due to a potential concern over teratogenicity, especially in the first trimester based on animal trials.[5,6] However, a programmatic update on HAART for pregnant women by WHO recommends efavirenz-based regimen for EMTCT.[7] This is because of the advantage of once-daily, fixed-dose combination (FDC) of tenofovir, lamivudine or emtricitabine, and efavirenz. It also allows the streamlining of antiretroviral administration in resource-constrained settings such as ours. Other advantages include antiviral potency, relative low frequency of severe adverse effects, a greater likelihood of adherence, and efficacy against hepatitis B virus.[8,9]

In addition, efavirenz is more cost-effective in direct comparison to nevirapine, and less likely to be associated with antiviral resistance.[9] Also, hepatotoxicity associated with nevirapine is unknown with efavirenz. Better viral load reduction, a lower incidence of AIDS-defining illnesses, and a 12-month increase in CD4 count are other benefits of efavirenz.[10,11] Despite the proven benefits of efavirenz use among pregnant HIV-positive women, certain adverse side effects have been associated with its use. A majority of these are central nervous system (CNS)-based and include hallucination, depression, insomnia, abnormal thinking, impaired concentration, confusion, loss of memory, euphoria, and suicidal ideation.[12-14] The side effects of efavirenz are associated with its plasma levels, hence stepwise dosing has been shown to decrease these side effects.[14] Another explanation for the occurrence of these side effects is genetic polymorphism. Efavirenz is metabolized mainly by the CYP450 enzyme system, and this enzyme is highly susceptible to genetic polymorphism, and polymorphs play a role in the variability of efavirenz plasma concentration.[1] This study is imperative because the side-effect profile of efavirenz use among HIV-positive pregnant women in our environment has not been documented. The objectives of this study were to identify the side-effect profile of Atripla® use among pregnant HIV-positive women and nonpregnant HIV-positive women at LUTH and assess the level of compliance and correlate compliance with immunologic suppression (viral load and CD4 cell count).

Methodology

Study area

The Lagos University Teaching Hospital (LUTH) is the teaching hospital of the College of Medicine of the University of Lagos. It was founded in 1962 and is situated in the heart of Lagos Mainland, which has population of over 2,150,100 inhabitants. It serves the whole of Lagos and its suburbs; and it is open to all categories of patients. The hospital operates at the tertiary level of the healthcare delivery system. Referrals are received from both private and public hospital in Lagos as well as other parts of the country.

LUTH's Obstetrics and Gynaecology Department has a total of 134 beds, out of the hospital's 720 beds. There are 74 obstetric beds in three wards (wards C2, C3, and C4) and 60 gynecological beds in two wards (wards B2 and C1). The neonatal unit/labor ward complex, which became operational in February 1987, houses the neonatal unit for babies delivered in LUTH and the labor wards unit under one roof. Also, within this complex are two standard operating theaters and four doctors' rooms shared by resident obstetricians, anesthetists, and neonatologists. It affords maximal utilization of services since obstetricians, neonatologists, and anesthetists all work together in close proximity. It has 14 delivery suites, two cardiotocography machines, 58 neonatal cots, including incubators, and two standard operating theaters. The hospital presently has an average of between 1500 and 2500 deliveries annually.

Study population

The study included booked/unbooked pregnant women and nonpregnant women who registered with the AIDS Prevention Initiative Nigeria (APIN) center of LUTH and who are on efavirenz-containing HAART – Atripla®.

Study design

The study was a prospective study among pregnant and nonpregnant women taking efavirenz, who were selected in a purposive manner.

Inclusion criteria

- Pregnant women taking efavirenz-containing antiretroviral agent (Atripla) who registered with the APIN center in LUTH
- Nonpregnant women taking efavirenz-containing antiretroviral agent (Atripla) who registered with the APIN center in LUTH.

Sample size

All HIV-positive pregnant women on efavirenz-containing regimens and a comparable number of HIV-positive nonpregnant women on efavirenz over a 6-month period were recruited for the study.

Data collection

The reason for this study with the procedure was explained to each of the respondent, and verbal consent was obtained thereafter. Data were obtained by the principal investigator through interviews using a pretested proforma. These included biodata, length of HIV diagnosis, duration of efavirenz use, drug compliance, side effects, and timing of side effects.

Data analysis

Data were inputted into an electronic database designed on Epi Info 2014, and analysis was carried out with the same statistical package. The results are presented in frequency tables and cross-tables. The association between categorical variables was tested using Chi-square, and differences in group means were assessed using *t*-test. A confidence interval of 95% was used with the level of significance set at a *P* value of <0.05.

Ethical consideration

The study was carried out after obtaining ethical approval from the Ethics Committee of the LUTH (Ref. No: ADM/DCST/HREC/APP/710). The purpose and scope of this study were explained to the respondents and verbal consent was obtained before being recruited into the study. The rights of potential respondents to participate or decline were respected and kept confidential.

Results

A total of 80 women living with HIV completed the pretested, structured questionnaire. Forty of them were pregnant, while 40 were nonpregnant. Their mean age was 31 ± 5.7 years. The demographic parameters of both groups are presented in Table 1.

Among pregnant women, 29 (72.5%) got diagnosed with HIV prior to getting pregnant, a majority of whom [(93.1%)] were diagnosed with HIV more than 2 years before the study. Many (26; 65%) pregnant women had commenced HAART for more than 2 years before pregnancy. Among all respondents, 51 (63.8%) had been on Atripla for less than a year, and this included 30 (75.0%) pregnant women.

Compliance with the use of Atripla® according to institutional criteria (client's self-reported usage and pill count) was 97.5% among all respondents. Pregnant women displayed a slightly higher level of compliance compared with nonpregnant women (97.5% vs. 95%). In assessing their level of compliance with the use of efavirenz according to institutional criteria (patient self-reporting and pill counting), 97.5% rate was obtained among all participants.

Forty-six (57.5%) women reported one or more side effects with the use of Atripla®. This occurred more in nonpregnant women [25 (62.5%)] when compared with pregnant women [21 (52.5%)] (odds ratio: 0.66, 95% confidence interval 0.27–1.62). This is shown in Table 2.

The commonly reported side effects of Atripla® were drowsiness [18 (39.1%)], nightmares [14 (30.4%)],

Table 1: Sociodemographic parameters of respondents on efavirenz

Variables	Pregnant ($n=40$)	Nonpregnant ($n=40$)
Age (years)		
20-24	1 (2.5%)	2 (5.0%)
25-29	6 (15.0%)	4 (10.0%)
30-34	19 (47.5%)	9 (22.5%)
≥35	14 (35.0%)	25 (62.5%)
Total	40 (100%)	40 (100%)
12.5%		
0	13 (32.5%)	9 (22.5%)
1	10 (25.0%)	8 (20.0%)
2	12 (30.0%)	9 (22.5%)
3	3 (7.5%)	5 (12.5%)
4	2 (5.0%)	6 (15.5%)
5	0 (0%)	3 (7.5%)
Total	40 (100%)	40 (100%)
Education		
None	1 (2.5%)	0 (0%)
Primary	5 (12.5%	0 (0%)
Secondary	10 (25.0%)	8 (20.0%)
Tertiary	23 (57.5%)	16 (40.0%)
Postgraduate	1 (2.5%)	16 (40.0%)
Total	40 (100%)	40 (100%)
Marital status		
Single	7 (17.5%)	10 (25.0%)
Married	33 (82.5%)	25 (62.5%)
Divorced	0 (0%)	1 (2.5%)
Cohabitation	0 (0%)	4 (10.0%)
Total	40 (100%)	40 (100%)

and insomnia [6 (13.0%)]. Other side effects were confusion [4 (8.7%)], loss of [memory (2.2%)], and skin rashes [(4.4%)] [Table 2]. Cross-tabulation done between age and occurrence of side effects among all respondents revealed more episodes of side effects in pregnant and nonpregnant women age ≥35 years. However, this was not statistically significant [Table 3a and b].

Only half of our pregnant participants had baseline viral load results, out of which 70% (14/20) had values greater than 400 copies/mL. However, 6 months after commencement of Atripla®, 10 (50%) had viral load values greater than 400 copies/mL [Tables 4a and 4b].

Among our nonpregnant participants, 15 (37.5%) had initial assessment of viral load, 3 (20%) of whom had viral load values ≤400 copies/mL. Six months, after commencing efavirenz therapy, 6 (40%) of these women had viral load values ≤400 copies/mL. In this study, a baseline viral load of <400 copies/mL was associated with the development of side effects among pregnant women taking Atripla.

Thirty-three (82.5%) pregnant women had both baseline and follow-up CD4 cell count results [Tables 5a and 5b].

Among nonpregnant respondents, 36 (90%) had initial CD4 count results, with 13 (36.1%) having CD4 count values greater than 500 cells/mm^3. The findings were similar following 6 months on efavirenz therapy with 13 (36.1%) women having CD4 count values greater than 500 cells/mm^3. This is depicted in Tables 6a and 6b.

Cross-tabulations between maternal side effects of efavirenz and baseline viral load with baseline CD4 count revealed pregnant respondents with CD4 cell count of <500 cells/mm^3 were more likely to develop side effects to Atripla®.

Table 2: Breakdown of side effect profile

Side effects	Pregnant	Nonpregnant
Nightmares	5 (12.5%)	9 (22.5%)
Skin rash	2 (5.0%)	0
Skin itching	0	1 (2.5%)
Insomnia	4 (10.0%)	2 (5.0%)
Drowsiness	9 (22.5%)	9 (22.5%)
Confusion	0	4 (10.0%)
Abnormal thinking	1 (2.5%)	0
Loss of memory	0	0
Total	21 (100%)	25 (100%)

Table 3a: Cross-tabulation between age and side effects of efavirenz in pregnant women

Age (years)	Nightmares	Skin rash	Insomnia	Drowsiness	Memory loss	Total
25-29	2	0	0	1	0	3
Row %	66.7	0.0	0.0	33.3	0.0	100.0
30-34	2	0	3	4	0	9
Row %	22.2	0.0	33.3	44.4	0.0	100.0
≥35	1	2	1	4	1	9
Row %	11.1	22.2	11.1	44.4	11.1	100.0
Total	5	2	4	9	1	21
Row %	100.0	9.5	16.0	36.0	4.8	100.0

Discussion

This study provides information on the side-effect profile associated with the use of Atripla® an efavirenz-containing FDC HAART in HIV-positive pregnant women for EMTCT of HIV in a low-income country, as well as comparing the side-effect profile among nonpregnant women.

The frequency of adverse drug reaction related to the use of ARVs among pregnant women ranges between 5% and 78% depending on the geographical region, social status, degree of immunodeficiency, and length of exposure to ARTs.[13] In this study, 52.5% of pregnant women on Atripla® reported side effects, with the main side effects being CNS-related ranging from insomnia to abnormal thinking. This is in keeping with several studies which show that the dominant side-effect profile associated with the use of efavirenz is CNS-related.[9,11,13-15] This is important because the development of side effects can

Table 3b: Cross-tabulation between age and side effects of efavirenz among nonpregnant respondents

Age (years)	Nightmares	Skin itching	Insomnia	Drowsiness	Confusion	Loss of memory	Total
20-24	0	0	0	1	0	0	1
Row %	0.0	0.0	0.0	100.0	0.0	0.0	100.0
25-29	3	0	0	0	1	0	4
Row %	75.0	0.0	0.0	0.0	25.0	0.0	100.0
30-34	0	0	0	3	0	1	4
Row %	0.0	0.0	0.0	75.0	0.0	25.0	100.0
≥35	6	1	2	5	1	1	16
Row %	37.5	6.3	12.5	31.3	6.3	6.3	100.0
Total	9	1	2	9	2	2	25
Row %	36.0	4.0	8.0	36.0	8.0	8.0	100.0

Table 4a: Baseline viral load values of pregnant women on Atripla

Viral load	Frequency	Percentage
≤400 copies/mL	10	50%
≥400 copies/mL	10	50%
Total	20	100%

Table 4b: Latest viral load values of pregnant women on Atripla

Viral load	Frequency	Percentage
≤400 copies/mL	6	30%
≥400 copies/mL	14	70%
Total	20	100

Table 5a: Baseline CD4 cell count of pregnant women on atripla

CD4 cell count	Frequency	Percentage
≤500 cells/mm^3	22	66.7%
≥500 cells/mm^3	11	33.3%
Total	33	100%

affect compliance.[13] Nine pregnant respondents complained of drowsiness, five complained of nightmares, while four complained of insomnia as side effects of Atripla. However, among nonpregnant respondents, higher rate of these side effects was reported (62.5%).

The level of compliance with the use of Atripla in this study was 97.5% in both pregnant and nonpregnant respondents, which is greater than the accepted value of 95%.[16,17] This study showed improved immunological and virological outcomes among pregnant women on Atripla®. This can be attributed to the high adherence levels. This is in concert with other studies that have shown that adherence with HAART results in improved immunological and virological outcome.[18] This finding was also observed among nonpregnant respondents.

Some studies have shown an increased tendency of adverse outcome with the use of HAART when the CD4 cell count is >250 cells/mm^3.[18] This study showed that pregnant respondents with CD4 counts <400 cells/mm^3 were associated with the development of side effects.

This study is among the few studies that assessed the maternal side-effect profile of efavirenz use among pregnant women in a resource-constrained setting. However, it is limited by the small sample size, the short duration of evaluation, and the self-report of adherence.

In conclusion, CNS-based side effects are the predominant side effects associated with the use of efavirenz. However, with high levels of adherence improved immunological and virological outcome has been associated with its use. It is imperative for caregivers to women with HIV infection to understand the side effects and emphasize this to the women at the point of counselling on efavirenz-containing HAART use and provide measures to reduce them to ensure compliance.

Table 5b: Latest CD4 count of pregnant women on Atripla

CD4 cell count	Frequency	Percentage
≤500 cells/mm^3	20	60.6%
>500 cells/mm^3	13	39.4%
Total	33	100%

Table 6a: Cross-tabulation between baseline viral load and maternal side effects of Atripla in Pregnant women

Baseline viral load	Side effect		
	Yes	No	Total
<400	2	4	6
Row %	33.3	66.7	100.0
Col %	22.2	36.4	30.0
<400	7	7	14
Row %	50.0	50.0	100.0
Col %	77.8	63.6	70.0
Total	9	11	20
Row %	45.0	55.0	100.0
Col %	100.0	100.0	100.0

Table 6b: Cross-tabulation between baseline CD4 count and development of side effects of Atripla in pregnant women

Baseline viral load	Side effect		
	Yes	No	Total
<500	12	10	22
Row %	54.5	45.5	100.0
Col %	66.7	66.7	66.7
≥500	6	5	11
Row %	54.5	45.5	100.0
Col %	33.3	33.3	33.3
Total	18	15	33
Row %	54.5	45.5	100.0
Col %	100.0	100.0	100.0

Ethics committee

Ethical approval was obtained from the Health Research and ethics committee of the Lagos University Teaching Hospital. Assigned Number: ADM/ DCST/HREC/APP/710. 14th April 2016.

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Conflicts of interest

There are no conflicts of interest.

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