

# The Effect of First Line Anti-Retroviral Drugs on the Menstrual Cycle of HIV Positive Patients

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## Abstract

**Background:** The quality of life and life expectancy of individuals living with HIV has improved significantly. This improvement is largely due to the use of Highly Active Anti-Retroviral Therapy (HAART). The effect of prolonged usage of this therapy on the menstrual function of the females within the reproductive age range is poorly understood. **Methodology:** A cross-sectional comparative study that involved women within the reproductive age range of 15-45 years. The women were grouped into A, B and C categories. Group A had HIV positive women already on Anti-Retroviral (ARV) therapy. Group B were HIV positive women naïve to anti-retroviral drugs at the time of recruitment. Group C comprised of HIV negative women within the reproductive age range not being managed for infertility. **Results:** The mean age of the participants across the study groups were respectively 32 years, 33.4 years and 37.58 years. The average weight among participants in the study was 66.38 kg, with a range of 53-94 kg. The average duration of use of ARVs was 81.12 months (6.7 years). The mean CD4 values across the study population who were HIV positive were 725 and the average viral load was 20 copies per ml. The commonest menstrual abnormality was oligomenorrhea, occurring in close to 25% of respondent who were HIV positive and on ARVs. Menstrual abnormality was more in the HIV positive women receiving anti-retroviral drugs than in the other two cohorts. (p=0.007). **Conclusion:** Long term usage of some first line highly active anti-retroviral therapy is associated with increased menstrual abnormality.

**Keywords:** First line Anti-retroviral drugs, Women, HIV Positive, Menstrual cycle, Nigeria

## Introduction

The quality of life and life expectancy of individuals living with HIV has improved significantly over the past decade. <sup>[1]</sup> This improvement is largely due to the advent of HAART. <sup>[2]</sup> The prolonged usage of this therapy has been postulated to be associated with side effects that disrupt other systemic functions. <sup>[3]</sup> Adverse effects related to the central nervous system have been implicated in non-nucleoside reverse transcriptase inhibitors (NNRTI). <sup>[4]</sup>

There is some evidence to suggest that some of the side effects can affect the reproductive efficiency of the patients as evidence abound that some anti-retroviral drugs can affect sperm motility in some males. <sup>[5]</sup> There is also suggestion that ARVs can lead to testicular atrophy. <sup>[6]</sup> This evidence has not been clearly established especially for the female reproductive functions, particularly the menstrual cycle, hence the need for this study.

The objective of the study is to determine the effect of anti-retroviral agents on the menstrual functions of HIV positive women.

## Materials and Methods

### Study design

A cross-sectional comparative study, involving women within the reproductive age range of 15-45 years. The women were grouped into A, B and C. Group A was made up of HIV positive women already on ARVs. Group B comprised of HIV positive women who were naïve to ARVs at the time of recruitment (newly diagnosed who had not yet been commenced on ARVs and were being worked up to commence drugs) and Group C consisted of HIV negative women within the reproductive age range not being managed for infertility.

### Inclusion criteria for group A

1. HIV positive females within the reproductive age range of

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15-45 years.

- HIV positive females within the reproductive age range of 15-45 years who were on HAART combination of Lamivudine, Tenofovir and Efavirenz
- Women who satisfied criteria one and two above and had been on the medication for at least one month.

**Exclusion criteria**

- HIV positive women who were outside the reproductive age range.
- HIV positive women who had not commenced HAART.
- HIV positive women who were pregnant.
- Women within the reproductive age range who were being evaluated for infertility.

**Inclusion criteria for group B**

- HIV positive women within the reproductive age range.
- HIV positive women with a new diagnosis of HIV who had not been commenced on ARVs.

**Exclusion criteria**

- HIV positive women outside the reproductive age range.
- HIV positive women on ARVs.
- Pregnant HIV positive women.
- Women within the reproductive age range who were being evaluated for infertility.

**Inclusion criteria for group C**

- HIV negative women within the reproductive age range
- HIV negative women who satisfied the criteria 1 and 2 above and were not evaluated for infertility.

**Exclusion criteria for group C**

- Non-sexually active HIV negative women within the reproductive age range.
- HIV negative women within the reproductive age range who were evaluated for infertility.

**Sample size calculation**

The sample size was determined using the following formula:

$$N = \frac{Z_2 Pq}{D_2}$$

N: Sample size

Z: Z value at 95% (0.95) confidence limit read from standardized normal distribution table

P: Estimated prevalence on the basis of previous studies

Q=1-P

D: Precision

For this study,

P: (Prevalence of premature ovarian failure in the general

**Table 1: Average duration of menstrual flow among the three different groups.**

Group	N	Mean	Std deviation	Statistical test	Confidence interval	P value
A	18	3.58	0.515		3.26-3.91	
B	18	4.33	0.816	ANOVA	3.48-5.19	0.21
C	18	4.06	1.11		3.50-4.61	

**Table 2: Menstrual abnormality across the 3 groups.**

Group	N	Mean	Std deviation	Statistical Test	Confidence interval	P value
A	18	3.67	1.557		2.64-4.66	
B	18	5.20	0.919	ANOVA	4.54-5.86	0.007
C	18	4.67	0.767		4.29-5.05	

population)=1.0% [vii]

D=50% (0.05)

Q=0.98

$$N = \frac{1.926 \times 0.01 \times 0.99}{(0.05)^2} = 15$$

15 per group was calculated which is equivalent to 45 for the three groups, but 18 per group which is equivalent to 54 were recruited for the study in order to correct for attrition.

**Study group A**

Eighteen HIV positive women who were on Lamivudine, Efavirenz, and Tenofovir for up to six months and were not evaluated for infertility.

**Study group B**

Eighteen newly diagnosed treatment naïve participants who were being evaluated towards commencement of HAART.

**Study group C**

Eighteen HIV negative women within the reproductive age range who were not evaluated for infertility.

**Results**

The age of menarche across all three groups was between 13-15 years. While the average age of the women in group C was 32 years, those of groups B and A were 33.4 years and 37.58 years respectively. The average weight among the women in the study was 66.38 kg, with a range of 53-94 kg. The average weight of group A was 82.42 kg, while that of group B was 71.38 kg. The average weight of group C was 58.8 kg.

The mean CD4 values across the study population who were HIV positive was 725 and the average viral load was 20 copies per ml. The average duration of use of ARVs was 81.12 months (6.7 years). The commonest menstrual abnormality was dysmenorrhea seen in 83% of all the respondents (n=45). There was no statistically significant difference in the mean duration of menstrual flow (p=0.210) [Table 1] and mean cycle interval (p=0.378). However, there was significant increase in menstrual abnormality among the women in group A when compared to groups B and C. (p=0.007) [Table 2]. [8]

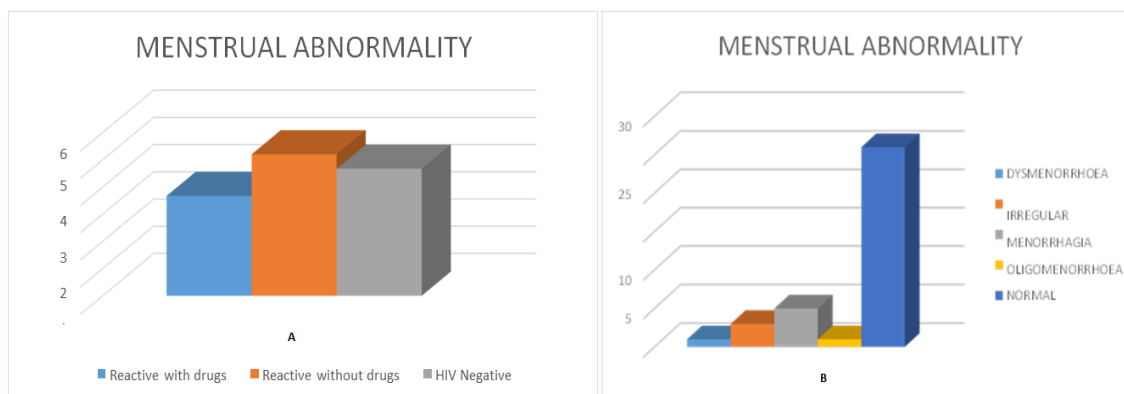


Figure 1: Comparison of diagnostic measures.

## Discussion

The age of menarche across all three groups was between 13-15 years. Menarche is largely influenced by the percentage of body fat as there is a critical mass of body fat that should be attained before menarche will occur.<sup>[7]</sup> Hence, it is not surprising that there was no significant difference in the age of menarche across the different study groups.

This study revealed that there was no statistically significant difference in the average duration of menstrual flow ( $p=0.21$ ) and the average cycle interval ( $p=0.378$ ). This was not, however, the case in the analysis of menstrual abnormalities; as there was a significant increase in menstrual abnormality noted among women taking anti-retroviral medications when compared with those who were not using the medication and HIV negative women ( $p=0.007$ ) [Figures 1A and 1B].<sup>[9]</sup>

Menstrual abnormalities have been noted to be higher among HIV positive women.<sup>[9,13]</sup> The rationale for this menstrual abnormality was thought to be weight loss related menstrual abnormality. However, this is no longer the case as HIV infected individuals are not affected by weight loss as in the past.<sup>[10]</sup> The weights of HIV positive women on drugs, HIV positive women not on drug and HIV negative women in this study was found to be 82.28 kg, 76.12 kg and 74.28 kg respectively. These findings did not show any marked weight discrepancy. As a matter of fact, the average weight of the women in the HIV positive group on drugs was higher than the women in the other two groups.<sup>[10]</sup>

The women in the study group who are HIV positive and on drugs tended to have more menstrual abnormality than the other two groups. Studies on the effect of anti-retroviral medications on menstrual functions are scanty and most of the studies done tend towards studying the effect of the disease on menstrual dysfunction rather than the effect of the drug. It was noted that menstrual dysfunction was found more among patients with CD4 count below 200 than in patients with CD4 count greater than 200.<sup>[11]</sup> The average CD4 value across the study population who were HIV positive was 725 and the average viral load was 20 copies per ml. This finding shows that the women who participated in the study, were immunologically and virologically stable, hence, the influence of the pathology of the disease condition cannot be used as a cofounder influencing the findings above. Patients with viral load of 20 copies per ml

are classified as having undetectable viraemia. These patients are, therefore, in a good state of health. Hormonal dysfunctions have been noted in HIV positive women, irrespective of usage of anti-retroviral medications. It is not; however, clear if hormonal abnormalities are linked to menstrual dysfunction.<sup>[12]</sup> While the cross-sectional nature of this study and a total sample size of 54 may not tell the full story of the menstrual abnormality noted among HIV positive women on anti-retroviral drugs, it however stimulates the need to consider large longitudinal study to validate or refute this finding.<sup>[13]</sup>

## Conclusion

In conclusion, Long term usage of some first line highly active anti-retroviral therapy may be associated with increased menstrual abnormality. A larger longitudinal study is needed to evaluate the effect of anti-retroviral therapy on the menstrual pattern and reproductive functions of women within the reproductive age range.

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