MENSTRUAL CHANGES AMONG HIV POSITIVE WOMEN ON ANTI-RETROVIRAL TREATMENT IN SOUTHWESTERN NIGERIA

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ABSTRACT

There are conflicting reports regarding menstrual irregularities and HIV infection in women. Varying degrees of menstrual abnormalities have been reported with prolonged ARV use, and these have implications for drug adherence. The objective of this study was to assess the effect of ARV drugs on menstrual pattern among HIV positive women in South-western Nigeria. It was a descriptive cross-sectional survey among 238 HIV positive women on anti-retroviral therapy randomly selected after excluding for co-morbidities. Research instrument was semi structured interviewer administered questionnaires, and data was analyzed using the SPSS software. Level of significance for statistic test was $p \leq 0.05$

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Mean age of respondents was 38.6±2.3 years and 205(86.1%) had commenced ART for a period of 1-5 years mostly 1st line ART, 45(18.9%) have missed their ARVs at one time or the other in the last 1year. Self reported adherence was good among 227(95.4%), calculated adherence was above 95% among 185(77.7%) with a mean calculated adherence of 93.0±3.6% and a median of 95.0%. About 167(70.2%) of respondents reported a change in their menstrual pattern.

Different patterns of menstrual changes reported were changes in number of days, interval between menstruations and flow of menstrual blood, 52(73.2%) believed that use of ART caused these menstrual changes, only 36(50.7%) reported these changes to the doctor. Predictors of having menstrual disturbances include missing pills, poor adherence and use of ARVs for period longer than 5years. ARVs were found to be common causes of menstrual irregularities. Thus, clients' concerns should always be addressed most especially issues that may compromise ARV adherence

KEYWORDS

Anti-retroviral therapy, Menstrual irregularities, Adherence, ARV

INTRODUCTION

Many women with human immunodeficiency virus (HIV) infection complain of abnormalities or changes in their menstrual cycle. (Chirgwin et al. 1996; Hoytt 1998; Maclean 2000) These changes vary from one woman to another and they include: heavier bleeding that lasts longer than usual, bleeding or spotting between periods, more frequent periods, lighter periods with longer time in between, missed periods and no periods at all.(Maclean 2000)

Clinicians experienced in the care of women with HIV infection also often feel that a higher than expected percentage of women in their care complain of menstrual problems. The absence of menstrual period (amenorrhea), lighter than normal menstrual bleeding (oligomenorrhea) and other menstrual changes from HIV-related cause is however still speculative.(Hoytt 1998) Factors such as severe weight loss, chronic diseases, drug abuse, use of contraception, uterine fibroids, genital tract infections or peri-menopausal symptoms can also cause such changes.(The Well Project 2011)

The objective of this study was to study the effect of HIV infection and treatment on self-reported menstrual changes among HIV positive women

REVIEW OF LITERATURE

Some menstrual changes are directly related to HIV disease and associated immune suppression. Others are associated epidemiologically with HIV because of common risk factors, such as sexual behavior or substance abuse.(Abularach and Anderson 2005) Severe weight loss or wasting syndrome may present with amenorrhoea; chronic illnesses, low levels of platelets may contribute to heavier bleeding, long-term constant stress can affect any woman's menstrual cycle, significant use of illegal drugs especially heroin and marijuana may also alter menstrual flow and cycle, herbal preparations may contain herbs that affect menstruation such as black cohosh, raspberry root, and some anti-retroviral drugs may also affect menstruation.(Abularach and Anderson 2005; Nielsen 1999; Treat Yourself Right 2009)Protease inhibitors have been linked to increased bleeding in some individuals, but this association has only been well established for hemophiliacs.(New York State Department of Health AIDS Institute 2011)

There are conflicting reports regarding menstrual irregularities and HIV infection in women. Studies have shown that women receiving anti-retroviral therapies (ART) have fewer menstrual abnormalities than immune-compromised HIV-infected women who are not receiving ART; higher viral loads and lower CD4+ counts have been associated with increased cycle variability

and polymenorrhea.(Harlow SD, Schuman P, Cohen et al. 2000; New York State Department of Health AIDS Institute 2011) However, menstrual irregularities have been reported despite the use of ART among some subjects.(Ogundahunsi et al. 2011)Another study among HIV-positive women found that, overall, being HIV-positive only slightly increased a woman's chances of having either a very short menstrual cycle (less than 18 days) or a very long cycle (more than 90 days).(Chirgwin et al. 1996)

Often, menstrual problems are caused by hormonal changes that occur naturally in most women over time. They may also be due to conditions not related to HIV. However, HIV and anti-retroviral drugs have been said to have some effects on menstrual cycle.(Treat Yourself Right 2009) There have been a few anecdotal reports but no clinical studies suggesting that the protease inhibitor ritonavir may cause heavier and longer periods.(New York State Department of Health AIDS Institute 2011; Nielsen 1999; Treat Yourself Right 2009) A study done on the characteristics of menstruation in women infected with HIV observed no association between HIV status and menstrual changes.(Ellerbrock et al. 1996).

Whether these menstrual changes are related to HIV, clinical staging, CD4 count and most especially pattern of adherence to ART are important factors not yet given prominence among available studies. This is coming at a time when the HIV epidemic is gradually becoming a feminine issue, when second line drugs are gradually taking over from first line and adherence strategy discussed and managed holistically with clients.

In HIV-infected women, little is known about menstruation and abnormal vaginal bleeding,(Hoytt 1998) despite the importance of the menstrual history in evaluating ovarian function and detecting gynaecologic disorders among these group of women Clinicians prescribing anti-retroviral drug for HIV positive women may also benefit from the outcome of this study. The objective of this study was to study the effect of HIV infection and treatment on self-reported menstrual changes among HIV positive women.

Methodology

The study was a descriptive cross sectional survey carried out in Osogbo, the capital of Osun State in South-western Nigeria. HIV treatment, care and support in the capital city takes place in the secondary (State government hospital) and tertiary (State government University teaching hospital) health care levels. Primary health care centres were mainly for HIV counselling and testing services and were excluded from this study. HIV prevalence in the city was 2.5%, a bit lower than the national average put at 4.1%. Target population constitutes HIV positive women of reproductive age group.

Eligible women would have been on ART for at least one year. In addition, women on treatments or medications or drugs that could influence menstruation (such as contraceptives) were totally excluded from this study. Women with history of genital tract infections and fibroids were also excluded from the study through clinical history taking and abdominal palpation or examination as well as other relevant investigations (where necessary). Using Leslie Fischer's formula for calculation of sample size for population less than 10,000, a sample size of 218 was estimated,

and this was increased to 240 to account for attrition and non-response. A total of 250 questionnaires were taken to the field.

There were 2 eligible facilities in Osogbo, Asubiaro general Hospital which is secondary, and LAUTECH teaching hospitals which is tertiary in nature, and both have about 2000 registered clients of ART. Questionnaires were equally shared among the 2 facilities. On a bi-weekly clinic day per facility, a list or sampling frame of all eligible women of reproductive age group was obtained from the triage nurse. A systematic sampling of one in three eligible women on the list was done, and this continued until the questionnaires allocated for that day got exhausted. Data collection took place between January 2013 and June 2013.

Data were collected by trained research assistants using pre tested interviewer administered semi structured questionnaires. Interviews were conducted under strict confidentiality and privacy in the post test counseling rooms of the clinics. Details of the study and its objectives were explained to all respondents and participation voluntary, informed consent was obtained from each participant. Ethical clearance was obtained from Osun State University, Osogbo ethical review committee. Permission was also obtained from the Project Coordinators of the respective HIV/ART program as well as the Medical Director of the health facilities used. A limitations: of this study was our inability to screen for other organic causes such as fibroids, though clinical history were taken in order to exclude them.

Questionnaires were manually sorted out and data obtained were entered into the computer. Statistical Package for social Sciences (SPSS) version 17 was used to analyse the double entered data that was also checked for outlier values to ensure its validity. Frequency tables were generated and relevant summary measures calculated. The chi square test was used to demonstrate association between categorical variables while level of significance for the statistical tests was considered at $p < 0.05$.

RESULTS

Mean age of respondents was 38.6+ 2.3 years with about 46.2% of them being in the 30-39 years age group. 205(86.1%) had commenced ART for a period of 1-5 years mostly 1st line ART, 184(77.3%) are married, 158(66.4%) had more than primary level education, while about half 129(54.2%) of them were traders by occupation (Table 1). Table 2 showed that 45(18.9%) have missed their ARVs at one time or the other in the last one year. Self-reported adherence was good among 227(95.4%), calculated adherence was above 95% among 185(77.7%) with a mean calculated adherence of 93.0+3.6% (How is it calculated) and a median of 95.0%.

Figure I showed that 167(70.2%) of respondents reported a change in their menstrual pattern. Different patterns of menstrual change were reported including changes in number of days, interval between menstruations and flow of menstrual blood, 52(73.2%) beloved that use of ART caused these menstrual changes, and 22(31.0%) of them said they can identify their drugs

combination associated with menstrual changes, 36(50.7%) reported these changes to the doctor while 27(38.0%) did nothing.

Table 5 showed association between menstrual changes and some selected variables.Women who have missed pills in the last one year are two and a half time more likely to have experienced menstrual disturbances than those adhering well to ARVs. Women who scored a calculated adherence rate of >95% are about 7 times more likely to have experienced menstrual disturbances than those adhering well to ARVs. Women who had been on ART for prolonged period of >5 years are twice more likely to have experienced menstrual disturbances than those using ARVs for <5 years. Thus menstrual changes were more of adherence with ARVs in this study, especially when taken for more than 5 years.

DISCUSSION

About two-third of the respondents in this study were in the age range 20 – 39 years, age range considered to be very sexually active and those usually involved in high risk sexual practices;(Okochi, Oladepo, and Ajuwon 2000; Olugbenga-Bello, Adeoye, and Osagbemi 2013) it is thus not surprising that HIV infection is more among this age group.

A recent national estimate of HIV prevalence show that HIV prevalence rate for youths (age 20-24 years) peaked at 4.6%.(Omoyeni, Akinyemi, and Fatusi 2012) Over seventy percent were however found to be married; an observation which differs from a previous study where sero-prevalence of HIV was higher among the singles than the married.(Okonko, Okerentuga, and Akinpelu A O 2012) In another study that assesses the determinants of antiretroviral treatment adherence among HIV/AIDS patients, majority of the respondents were found to be married and this characteristic was found to positively influence adherence.(Bach et al. 2013)

Only about 2 out of every 10 respondents reported missing their anti-retroviral drug between the last one week and one year prior to the study, this is in congruent with the calculated adherence where about 7 out of respondents had adherence to be optimal (greater than ninety five percent). This level of adherence is also reflected in the ART regimen found among respondents as more than ninety percent of them were using the first line ART regimen.

Complete adherence to ART drugs are associated with low probabilities of resistance,(Sethi et al. 2003) while poor adherence can lead to the virological failure of cheap first-line treatment regimens and the spread of multi-drug resistant forms of the virus, resulting in a public health calamity.(Paterson et al. 2000; S. P. Wasti et al. 2012) Majority of the respondents in this study were on the first-line treatment regimen probably due to their optimal adherence to ART.

Almost a third of the respondents in this study reported change in their pattern of menstruation since commencement of ART. The change in pattern varies and they include irregular menstruation, ceased menses (amenorrhoea), lighter than normal menstrual bleeding (oligomenorrhea) and menorrhagia. Previous studies have reported similar findings of varying

menstrual problems among females infected with HIV.(Harlow SD, Schuman P, Cohen et al. 2000; Hoytt 1998; New York State Department of Health AIDS Institute 2011; Treat Yourself Right 2009) Causes of menstrual problems among HIV-seropositive women include higher viral loads and lower CD4+ counts usually associated with increased cycle variability and polymenorrhea,(Harlow SD, Schuman P, Cohen et al. 2000) heavy bleeding (menorrhagia) or painful periods (dysmenorrhea) could be due to low platelets (thrombocytopenia) associated with HIV infection, or a complication of severe pelvic inflammatory disease,(Hoytt 1998) weight loss, chronic diseases, drug abuse, use of birth control medications, ART drugs, uterine fibroids, itching, genital tract infections, or peri-menopause have all been implicated in menstrual problems.(The Well Project 2011)

Among respondents that reported change in their menstruation pattern in this study, about two-thirds of them thought it was due to their ART drugs. The protease inhibitor Ritonavir has been implicated in a previous study and there have also been reports of the ARV drugs such as Zidovudine (AZT), Stavudine (d4T) and Didanosine (ddI) changing menstrual patterns(Treat Yourself Right 2009).Actions taken by the women who thought ART drugs were responsible for their change in menstruation pattern ranged from stopping all their medications to stopping only suspected drugs.

About half of women with reported menstrual changes reported this observation to their doctor. This finding is very important as such actions of stopping ARV medications without the care givers knowledge could lead to drug resistance. Previous studies have also revealed that patients who had side-effects were more likely to be non-adherent.(S. P. Wasti et al. 2012; S. Wasti et al. 2011) The significant association between respondents that have been on ART drugs for more than one year and change in menstruation pattern may be supporting previous findings that have implicated ARV drugs, especially the protease inhibitors.(Treat Yourself Right 2009)

It is important to however note that HIV-infected women with abnormal or dramatically changed menstrual bleeding should have the full investigation accorded HIV-negative women to determine the cause of the abnormality. Heavy bleeding can cause anaemia, a problem already prominent among women with advanced HIV infection, and can be a symptom of an underlying problem such as a fibroid tumor, blood clotting problems, or infection. Amenorrhea can be a symptom of pregnancy, ovarian cyst, ovarian failure, or menopause.(Hoytt 1998)

When evaluating amenorrhea and other menstrual irregularities in HIV-infected women, clinicians should review the patient's disease status, including the presence of opportunistic infections, and inquire about substance use and use of medications, such as psychotropics, that contribute to abnormal menses.

Clinicians should obtain a pregnancy test for all HIV-infected women of childbearing potential who give a current history of amenorrhea or irregular vaginal bleeding, regardless of history of sexual activity or contraception use. Patients who are pregnant should be referred to an obstetrical HIV-experienced clinician for evaluation and management as soon as possible.(New York State Department of Health AIDS Institute 2011)In the course of identifying the cause of

menstrual irregularities, women should report to their providers any side effects observed and all related symptoms.

CONCLUSION

ARVs are common causes of menstrual irregularities among women. Women may be tempted to miss drugs or seek alternative care elsewhere when these menstrual abnormalities get unbearable. Stakeholders in ART care should always strive to address concerns of clients, most especially issues that may compromise ARV adherence.

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TABLE 1: SOCIO-DEMOGRAPHIC CHARACTERISTICS OF RESPONDENTS

Variable	Frequency (n = 238)	Percentage (%)
Age group (years)		
20-29	60	25.2
30-39	110	46.2
40-49	68	28.6
Marital status		
Single	29	12.2
Married	184	77.3
Separated/Divorced	25	10.5
Educational status		
None	29	12.2
Primary	51	21.4
Secondary	78	32.8
Tertiary	80	33.6
Occupation		
Student	15	6.3
Petty Trader	129	54.2
Farmer	13	5.5
Artisan	13	5.5
Civil servants	48	20.2
Unemployed	20	8.3
Religion		
Christian	150	63.0
Islam	78	32.8
Traditional;	3	1.2
Others	7	3.0

TABLE 2: ART USE AND ADHERENCE

Variable	Frequency (n=238)	Percentage (%)
Missed medications		
Never	193	81.1
In the last one week	6	2.5
In the last one month	5	2.1
In the last six months	8	3.4
In the last one year	26	10.9
Self reported adherence		
Good	227	95.4
Bad	5	2.1
Can't say	6	2.5
Calculated adherence		
<90	11	4.6
90-94	42	17.7
>95	185	77.7
ART commencement		
1-5 years	205	86.1
>5 year	33	13.9
ART regimen		
1st line	230	96.6
2nd line	8	3.4

FIGURE 1: RESPONDENTS EXPERIENCING A CHANGE IN MENSTRUAL PATTERN

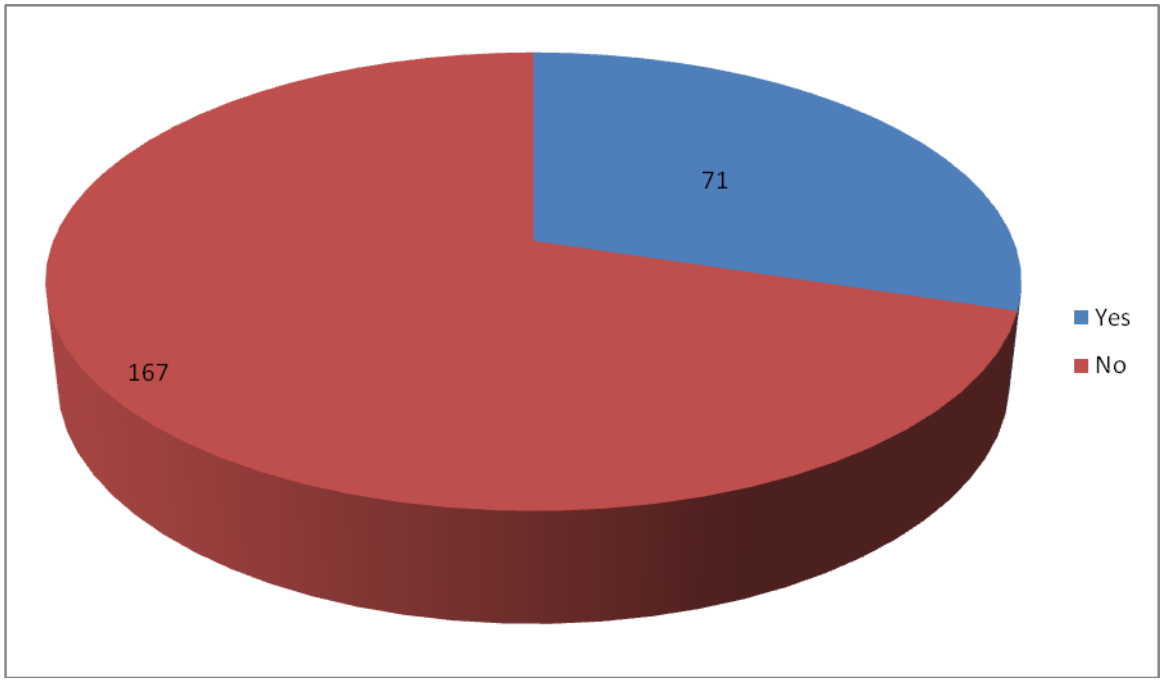

TABLE 3: TYPES OF CHANGE IN MENSTRUAL PATTERN OF RESPONDENTS SINCE COMMENCEMENT OF ART

Types of change in menstrual pattern (n=71 with multiple responses)	Frequency (n=71)	Percentage (%)
Menstruation has been irregular	39	54.9
Menstruation disappeared for some months, then comes again	15	21.1
Menstruation has disappeared since then and never come back	16	22.5
Menstrual flow has reduced in number of days	20	28.2
Menstrual flow has increased in number of days	12	16.9
Menstrual flow heavier than before	6	8.5
Interval between 2 consecutive months menstruation is now prolonged	9	12.7
Interval between 2 months menstruation is now reduced	23	32.4

TABLE 4- ASSOCIATED GYNAECOLOGICAL PROBLEMS EXPERIENCED AND RESPONDENTS' REACTIONS CONCERNING THE CHANGES IN MENSTRUAL PATTERNS

Variables (n-71 with multiple responses)	Frequency (n)	Percentage (%)
Associated painful sexual intercourse	16	22.5
Associated reduced enjoyment during sexual intercourse	10	14.1
I strongly belief that ARVs caused these menstrual changes	52	73.2
I can even identify which ARV may be responsible	22	31.0
Actions respondents have taken		
Reported to the doctor	36	50.7
Had once stopped ARVs	8	11.3
Did nothing	27	38.0

TABLE 5: ASSOCIATION BETWEEN MENSTRUAL CHANGES AND SOME SELECTED VARIABLES

Variables	**My menstrual pattern has changed**		**Statistics**
(a) Bi-variate analysis	Yes (n/%)	No (n/%)	
Age			
<24	21(15.7)	22(16.5)	X^2=99.8,
25-40	26(19.1)	53(39.4)	p=0.151
>40 years	20(15.0)	19(14.0)	
Missed pills in the last one year			
Yes	13(6.2)	59(27.2)	X^2=15.7,
No	52(24.8)	88(41.8)	p=0.001
Calculated adherence			
<95%	64(30.5)	23(11.0)	X^2=18.7,
>95%	35(16.7)	88 (41.8)	p=0.001
Duration of ART			
1-5 years	58(28.0)	27 (12.8)	X^2=2.01,
>5 years	102(49.2)	21(10.0)	p=0.361
(b) Bi-variate analysis	OR	p value	95%CI
Missed pills in the last one year (constant=No)	0.4	0.002	0.18-0.74
Calculated adherence (constant = <95%)	7.0	0.001	3.8-13.0
Duration of ART(constant=>5 years)	0.4	0.007	0.2-0.9