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REVIEW

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The burden of menstrual irregularities among women living with HIV in Nigeria: a comprehensive review

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Abstract

Background Menstrual irregularities significantly distress women living with HIV (WLHIV), impacting their reproductive health and quality of life. Although the underlying mechanism remains inconclusive, studies have outlined possible contributory factors. This narrative review explores the burden of menstrual irregularities and associated hormonal dysregulation among women living with HIV in Nigeria. It synthesises data from studies to present an overview of the prevalence, patterns, potential etiology, and impacts of menstrual irregularities among WLHIV.

Main body A literature search across electronic databases such as PubMed, Google Scholar, and Web of Science was conducted, and information was extracted and synthesized to delineate the burden of menstrual irregularities in WLHIV. Eligibility criteria included original studies assessing the prevalence, aetiology, and impact of menstrual abnormalities among WLHIV in Nigeria. A narrative data synthesis approach utilized common themes and key concept extraction, including identifying patterns in the literature to present specific trends such as prevalence, patterns, etiology, and determinants. Menstrual irregularities were found to be prevalent among Nigerian WLHIV, varying from 29 to 76% across different regions, exceeding reports of similar studies in developed nations. Similarly, menstrual disorders including amenorrhea, oligomenorrhea, and polymenorrhea, were attributed to factors like HIV acquisition, antiretroviral therapy, low body mass index, and hormonal imbalances. Low CD4 count and high viral load with associated complications have been identified as major contributing factors. Distortion of the hypogonadal-pituitary-ovarian axis by viral-induced pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) may disrupt the hormonal balance necessary for regular menstrual cycles. Fluctuating levels of follicle-stimulating hormone (FSH), luteinising hormone (LH), estradiol, and prolactin have been reported among WLHIV. Although adherence to antiretroviral therapy has offered immense relief, its direct therapeutic effects on menstrual irregularities are inconclusive..

Conclusions This study highlights the burden of menstrual disorders among WLHIV. It underscores the interplay between clinical, therapeutic, and client-associated factors as determinants of these abnormalities. Exploring associated complications like secondary infertility, reduced bone mineral density, and resultant osteoporosis, mirrors the significant impact of menstrual and hormonal irregularities on the reproductive health and quality of life of WLHIV.

Keywords HIV, Menstrual irregularities, Women living with HIV, Nigeria

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Introduction

HIV remains a global health concern, posing a substantial threat and health burden on those living with it. It has disproportionately impacted persons residing in low and middle-income countries (LMIC), particularly in Africa [1]. The region is most affected by HIV epidemics, with approximately 26 million people living with the virus as of 2023 [2]. While antiretroviral therapy (ART) has undoubtedly improved the life expectancy of people living with HIV/AIDS (PLHIV), it has also led to an increased prevalence of comorbidities among this population. As a result of this increased life expectancy, health issues previously unaddressed during the early years of the epidemic have emerged, presenting novel challenges for healthcare providers [3]. According to UNAIDS (2023), approximately 1.2 million of the 1.9 million adults aged 15 and above living with HIV are women [4]. This underscores the need to investigate the health concerns of women living with HIV (WLHIV). Chronic HIV infection, associated with a plethora of health complications, poses a dual challenge for WLHIV as they confront an incurable virus alongside increased reproductive health risks. The International Conference on Population and Development in Cairo, Egypt, (1994) highlighted the necessity of holistic reproductive health and rights for women [5, 6]. Considering the central role reproduction plays in women's lives, acknowledging the significant impact of HIV on the reproductive health of WLHIV is crucial.

Menstrual irregularities are variations in menstrual cycle length, frequency, or duration, such as irregular cycle length, anovulatory cycles, and luteal phase defects. Menstrual disorders on the other hand are conditions affecting the menstrual cycle, such as abnormal uterine bleeding (AUB), dysmenorrhea, menorrhagia, metrorrhagia, oligomenorrhea, amenorrhea, and polymenorrhea [7, 8]. These deviations could also manifest as non-menopausal amenorrhea. While a definitive causal relationship between HIV and menstrual disorders has not been established, existing studies have demonstrated a heightened prevalence of menstrual abnormalities among WLHIV [7, 8]. Menstrual irregularities are permissible concerns among WLHIV, as a cessation of menstruation, particularly in the absence of pregnancy, is a significant source of anxiety for women [9]. The underlying mechanisms responsible for these aberrations are not fully understood but are considered multifactorial, involving a complex interplay between HIV infection, the immune system, and hormonal imbalances [9–11]. HIV infection can directly or indirectly affect the hypothalamus, pituitary gland, and ovaries—which are vital organs regulating the menstrual cycle [12]. Whether menstrual irregularities among WLHIV are a direct consequence of the viral infection or are secondary to comorbid complications remains contentious [8, 13, 14]. Some studies have implicated weight loss, low body mass index (BMI), and nutritional deficiencies, as central etiologic mechanisms for menstrual irregularities and disorders [11, 13, 15, 16]. Others have reported hormonal imbalances from the chronic disease process or direct viral impact on reproductive and endocrine organs as possible causative factors [15].

ART has significantly improved the overall quality of life of WLHIV, including a reduction in associated morbidity. However, other findings have suggested a possible association between HIV treatment with ART, menstrual irregularities, and subsequent infertility [6, 17]. According to Leeansyah et al., lamivudine, abacavir, zidovudine, emtricitabine, and tenofovir have been found to inhibit telomerase activity, which plays a crucial role in the aging of tissues and stem cells [18]. This finding implicates these ARTs for early aging and may invariably lead to the early onset of age-related conditions such as menstrual irregularities and infertility. Furthermore, while some studies suggest a median age of menopause in Nigeria at approximately 50 years, there is evidence that HIV infection and associated immunosuppression may contribute to the early onset of menopause [19–21]. Menstrual disorders in WLHIV, regardless of disease stage, increase uncertainty about whether the virus directly impacts normal menstrual function. There is a need to highlight the issues impacting WLHIV and to explore further research on their reproductive potential. This review summarizes the current evidence on the prevalence and burden of HIV and menstrual irregularities among WLHIV in Nigeria, the mechanisms behind this co-existence, and its effects on their reproductive health.

Methodology

A comprehensive literature search was conducted across electronic databases to identify studies reporting on menstrual irregularities and disorders among WLHIV in Nigeria (Table 1). The search on PubMed utilized Medical Subject Headings (MeSH) terms "Disturbances, Menstruation", "Disorders, Menstruation", "Menstrual Irregularity", "Amenorrhea", "Hormonal dysregulation", "Hypomenorrhea", "Human Immunodeficiency Virus", "HIV" and "Nigeria". Keywords such as "menstrual cycle", 'HIV-1' and 'Human Immunodeficiency Virus infection' were added to maximize article results. Additional search was conducted on Google Scholar using pertinent keywords to find relevant studies. Also, a bibliographic search was carried out among relevant studies related to the theme. The search was not limited to publication dates and was carried out in May 2024. All studies addressing various menstrual disorders among

Table 1 Methodology

Methodology component	Description
Literature search sources	PubMed, Google Scholar, Web of Science
Search starategy and keywords	The search was conducted using Medical Subject Headings (MeSH) terms. It was not limited to publication dates and was carried out in May 2024
Keywords	"Menstrual disturbances", " Menstrual disorders", "Menstrual irregularities", " Amenorrhea", " Hormonal dysregulation", " Hypomenorrhea", " Human Immunodeficiency Virus", " HIV", " Nigeria", and other related terms
Inclusion criteria	All original studies addressing various menstrual abnormalities among premenopausal WLHIV were included
Exclusion criteria Ethical approval	Studies not directly related to the scope of this study, those on amenorrhea due to menopause orhysterectomy, and those not published in English were excluded from the review Ethical approval was not required for this study
Screening process	Titles and abstracts were checked against the eligibility criteria. Articles that met the citeria were examined further and screened, and 7 articles were finally included in this review
Data extraction	All studies that passed the final screening were used for relevant data extraction. Essential information was presented in a table
Narrative synthesis	Significant findings from the selected studies were meticulously synthesised to comprehensively understand the burden of menstrual and hormonal abnormalities among WLHIV

WLHIV in Nigeria were included. Contrarily, studies not directly related to the scope of HIV infection, menstrual disorders, studies reporting amenorrhea due to menopause or hysterectomy, and those not published in English were excluded from the review. Ethical approval was not required for this study as no human subjects or animal models were used. An in-depth assessment was performed to assess study suitability. Study titles and abstracts were first reviewed and compared with the eligibility criteria. Studies that passed this initial evaluation were scrutinized further by full-text screening. Additional studies relating to the study theme found through a manual bibliographic search, were included in the review. All seven studies that met the inclusion criteria were reviewed and subjected to data extraction. Information such as study author, publication year, study design, sample size, and key findings, including disease prevalence, outcomes, and treatment modalities were extracted and summarized in a table (Table 2). The review also discussed the etiology and patterns of menstrual disorders, their determinants, and current interventions for treatment among WLHIV. After carefully identifying trends, disparities, and notable gaps, significant findings from the selected studies were meticulously synthesized to understand the burden of menstrual irregularities among WLHIV.

Result and discussion

Prevalence of HIV-associated menstrual abnormalities in Nigeria

The prevalence of HIV-associated menstrual irregularities and disorders has been examined among HIV-positive women of reproductive age (15–45 years), and findings varied between 29 and 76%, substantially exceeding those reported in studies conducted in developed nations [9, 15, 22, 23]. The observed menstrual disorders included intermenstrual bleeding, menorrhagia, hypermenorrhea, amenorrhea, oligomenorrhea, and secondary dysmenorrhea [6, 9, 15, 22, 23]. According to Ezechi et al. [15] the most common menstrual irregularities and disorders reported among HIV seropositive women were irregular periods (7.9%), oligomenorrhea (6.4%), amenorrhea (3.8%), and secondary dysmenorrhea (2.6%), with an overall 29.1% prevalence for menstrual irregularities among WLHIV. In contrast, the seronegative group exhibited lower rates of 4.4%, 3.9%, 1.8%, and 1.9% for the named disorders. This study found no significant difference in the prevalence of heavy or intermenstrual bleeding but noted higher rates of amenorrhea and irregular menstrual cycles among WLHIV compared to HIV seronegative individuals [15]. In 2013 and 2017, Ukibe et al. presented two different studies with a prevalence of 76% (163 of 214) and 40% (18 of 35) in Nnewi Anambra State of South-Eastern Nigeria, respectively [9, 23]. The decrease in the latter may be attributed to its small sample size. Notably, Osun State in the Southwest had a significantly higher prevalence of 70.2% (167 of 238), as highlighted by Adebimpe et al. in 2014 [22].

Patterns and contributing etiologies of menstrual abnormalities

Patterns of menstrual abnormalities among WLHIV in Nigeria

A study assessing menstrual cycle patterns among Nigerian WLHIV who were symptomatic but not on ART, symptomatic on ART, and non-infected control subjects reported secondary amenorrhea as the commonest observed menstrual disorder (40.5%), followed by hypomenorrhea (20.3%), dysmenorrhea (16.5%),

Table 2 Characteristics of included studies

Author/Year	Study objective	Study type/ Location	Sample population and size	Median/Mean age of respondents (years)	Prevalence	Pattern of menstrual abnormalities	Management modalities	Main findings
Agaba et al. [5]	To assess the frequency of reproductive organ diseases in a cohort of HIV Positive women with a view to determine the effect of HAART on the frequency of occurence	Prospective cohort study (Plateau State)	369 HIV positive women	HAART group = 34.8 ± 7.3 HAART naïve group = 33.4 ± 7.3	N/A	The two groups (non HAART vs HAART) had: Amenorrhea – 80.7% vs 22.0%, irregularmenses – 81.7% vs 18.3%, post-coital bleeding-86.7% vs 13.3%	Antiretroviral therapy	The study revealed a higher frequency of reproductive organ disease in HIV positive women who are HAART naive compared to those on HAART
Rose et al. [8]	To evaluate some hormonal impact on the menstrual cycle pattern of HIV infected women of child bearing age and to assess whether the changes observed are directly related to HIV Infections	Prospective cohort study (Anambra State)	214 females, 79 seropositives not on ART, 80 seropositive on ART, 55 seronegative	N/A	76%	Secondary amenorrhea was observed in 32 (40.5%) ART-naïve HIV positive subjects, 20 (25%) of HIV patients on ART Hypomenorrhea was observed in 16 (20.3%) of HIV subjects on ART and 1(1.8%) in control subjects Hypermenorrhea was observed in 18(22.5%) of HIV subjects on ART when compared with 1(1.8%) in control subjects	Antiretroviral therapy	The study suggests a marked hormonal impact on menstrual cycle pattern observed in study subjects which was attributed to HIV infection and ART

Table 2 (continued)

Author/Year	Study objective	Study type/ Location	Sample population and size	Median/Mean age of respondents (years)	Prevalence	Pattern of menstrual abnormalities	Management modalities	Main findings
Ezechi et al. [14]	To determine the prevalence, pattern and determinants of menstrual abnormalities in HIV-Positive Nigerian Women	Cross sectional study (Lagos and Benue States)	3473 women (2549 HIV- sero-positive and 924 seronegative)	HIV positive = 32.7 ± 4.9 HIV negative = 33.2 ± 5.7	29.1% in sero-positive women and 18.9% in seronegative women	The proportion of women in the two groups with intermenstrual bleeding, menorrhagia, hypermenorrhea and postcoital bleeding were similar. While amenorrhea with (3.8%) to (1.8%), oligomenorrhea (6.4%) to (3.9%), irregular periods (7.9%) to (4.4%), and secondary dysmenorrhea (2.6%) to (1.9%) were more common in HIV sero-positive women	Antiretroviral therapy	-The HIV negative women had statistically significant higher BMI compared to HIV positive women ($p < 0.005$) - Menstrual abnormalities are more common in WLHIV (29.1%) - The proportion of women with intermenstrual bleeding, menorrhagia, hypermenorrhea and postcoital bleeding is similar in both group of WLHIV and HIV negative women ($p > 0.005$) - Amenorrhea, oligomenorrhea, irregular periods and secondary dysmenorrhea were more common in WLHIV ($p < 0.02$) - Among the HIV positive women those with CD4 count < 200, BMI < 20 and who do not take ARDs are at greater risk of Menstrual Irregularities

Table 2 (continued)

Author/Year	Study objective	Study type/ Location	Sample population and size	Median/Mean age of respondents (years)	Prevalence	Pattern of menstrual abnormalities	Management modalities	Main findings
Adebimpe et al. [21]	To assess the effect of ART on menstrual pattern of HIV positive women	Cross sectional descriptive study (Osun State)	238 HIV positive Nigerian women	38.6 ± 2.3	70.2% prevalence	Patterns include changes in number of days, interval between menstruation and flow of menstrual blood, 52(73.2%) believed the use of ART caused these changes and only 36(50.7%) reported to the doctor		ARVs are common causes of menstrual irregularities among women. Those who had 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 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

Table 2 (continued)

Author/Year	Study objective	Study type/ Location	Sample population and size	Median/Mean age of respondents (years)	Prevalence	Pattern of menstrual abnormalities	Management modalities	Main findings
Ukibe et al. [22]	To assess the impact of thyroid abnormality on the reproductive life of HIV infected females within reproductive age	Prospective cohort study (Anambra State)	70 HIV positive women, 35 symptomatic HIV infected women and 35 HIV infected women on HAART	Symptomatic HIV females on HAART = 38.63 ± 10.65 Symptomatic HIV infected females on HAART = 37.11 ± 13.24 Control group = 39.95 ± 10.57	65.7%	Menstrual irregularities higher in symptomatic HIV females not on ART (40%) as compared to symptomatic HIV females ART	Antiretroviral therapy	- Percentage of menstrual irregularities was higher in symptomatic HIV infected females compared to symptomatic patients on ART - Mean serum levels FSH, LH, progesterone and estradiol in symptomatic HIV women were not significantly different between follicular and luteal phase of menstrual cycle - The study demonstrated hypothyroidism and a significant degree of hypogonadism in symptomatic HIV women both at follicular and luteal phase of menstrual cycle which tends to normalise on treatment

Table 2 (continued)

Author/Year	Study objective	Study type/ Location	Sample population and size	Median/Mean age of respondents (years)	Prevalence	Pattern of menstrual abnormalities	Management modalities	Main findings
Ukibe et al. [28]	To evaluate sex hormonal changes in HIV infected premenopausal women	Prospective cohort Study (Anambra State)	90 women (30 HIV seropositive on ART, 30 HIV seropositive who were not on ART, 30 control)	N/A	N/A	Secondary amenorrhea was observed in 32 (40.5%) of HIV subjects, 20 (25%) of HIV subjects on ART when compared with 1(1.8%) in control subjects. Hypomenorrhea was observed in 16 (20.3%) of HIV subjects, when compared with 1(1.8%) observed in control subjects. Hypermenorrhea was observed in 18 (22.5%) of HIV subjects on ART when compared with the 1(1.8%) in control subjects	Antiretroviral therapy	The study showed that the sex hormones (progesterone, estradiol and testosterone) were significantly lower at both phases of the menstrual cycle in HIV infected women - The study revealed some degree of hypogonadism in HIV infected women which may have some implication in their reproductive life
Ohihoin et al. [34]	To determine the effect of antiretroviral agents on menstrual functions of HIV positive women	Cross sectional comperative study (Nigeria)	54 HIV infected women, 18 each of reproductive age, outside reproductive age, HIV Negative women	Group A = 37.58 Group B = 33.4 Group C = 32	N/A	Menstrual irregularities found more among HIV patients on ART ($p = 0.007$). The commonest menstrual abnormality was dysmenorrhea seen in 83% of all respondents. There was no significant difference in the mean duration of menstrual flow ($p = 0.210$) and mean cycle interval ($p = 0.378$)		Long term use of some first line HAART may be associated with increased menstrual abnormalities

NA Not available, *HAART* Highly active anti retroviral therapy, *ART* Antiretroviral therapy, *WLHIV* Women living with HIV, *FSH* Follicular stimulating hormone, *LH* Leuteinizing hormone

polymenorrhea (3.7%) [9], and hypermenorrhea (3.7%). These findings were in keeping with those of previous studies where amenorrhea was the most prevalent menstrual disorder among WLHIV [8, 10, 24]. A similar study conducted among WLHIV in Benue and Lagos States [22] revealed that about one-third of the respondents reported a change in their menstrual pattern since commencing ART, and pattern changes included irregular menstruation, amenorrhea, lighter than normal menstruation (oligomenorrhea) and menorrhagia. These findings were also in keeping with a previous study that suggested a strong association between ART adherence and menstrual disturbances among WLHIV [8]. It surmised that WLHIV classified as non-adherent, with calculated adherence levels below 95%, were seven times more likely to experience menstrual irregularities than their adherent counterparts. Furthermore, the prevalence and patterns of menstrual disorders varied significantly among WLHIV based on the duration of ART. Women who had been on ART for over 5 years exhibited a higher prevalence and diversity of menstrual irregularities and disorders compared to those who had been on ART for a shorter duration; although the authors did not state whether this was a consequence of longer duration of disease or if adherence rates over this period were considered [22]. Ezechi et al. reported that over 700 of approximately 2500 participants experienced a form of menstrual disorders [15]. Among these, irregular periods, oligomenorrhea, and amenorrhea were ranked the top three symptoms, respectively, whereas menorrhagia and dysmenorrhea were the least reported menstrual disorders [15]. The median age of study respondents was 32.7 for the seropositive cohort and 33.2 for the control negatives. The ART regimen respondents received was not stated across reviewed studies. In addition, a closer look at the trends and patterns reveals that many WLHIV in Nigeria and globally of reproductive age often suffer from other systemic complications such as weight loss, depressive conditions, and substance abuse [8, 14, 15].

Contributing etiology to reported menstrual irregularities

The etiology of menstrual irregularities among WLHIV remains unclear. However, several contributing factors have been outlined (Fig. 1). The literature suggests the presence of menstrual irregularities in patients with background immunosuppression. This is often a result of increased viral load and decreased CD4 count levels. The level of immunosuppression, mirrored by the degree of viremia and CD4 count, is relative to patient adherence to ART. CD4 cells are crucial immune system cells targeted by HIV. Low CD4 count, which implies a weakened immune system, can disrupt hormonal regulation in the

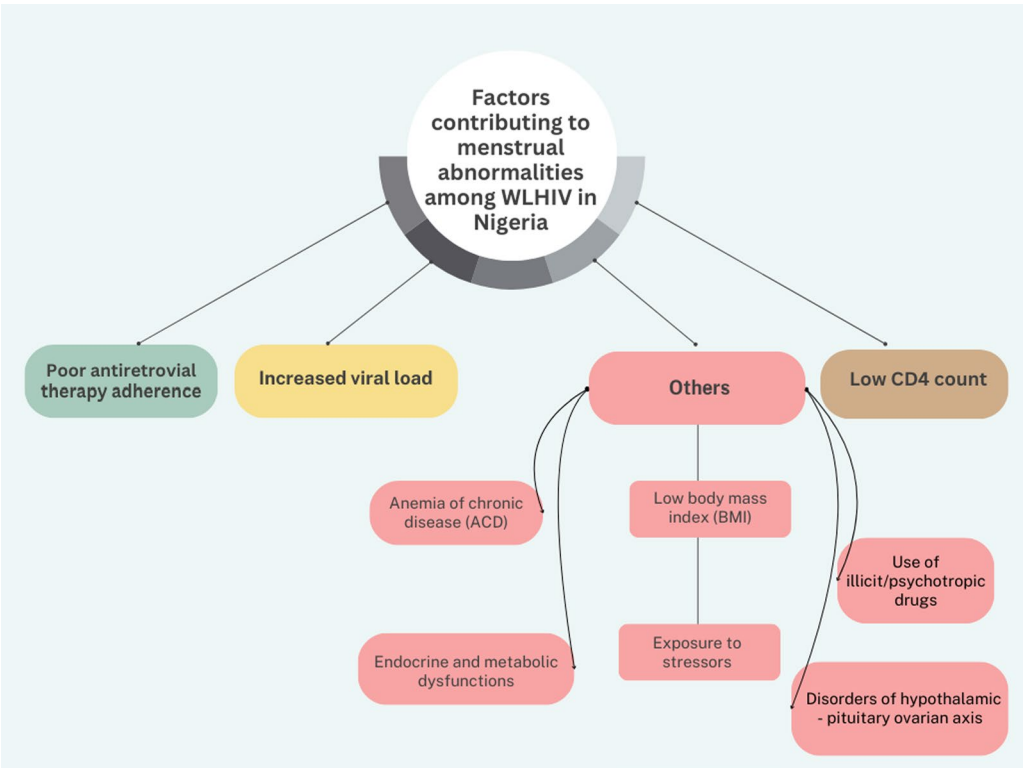

Fig. 1 Factors contributing to menstrual abnormalities among Nigeria WLHIV. WLHIV women living with HIV

body, leading to menstrual irregularities. A study among Nigerian WLHIV found that amenorrhea and irregular menstruation were as high as 80.7% and 81.7%, respectively, among the ART naïve group when compared with a control ART adherent group that recorded just about 22% and 18% prevalence, respectively [6]. Similarly, another study found that WLHIV who were adherent to ART with consequent high CD4 counts had a very low percentage (< 20%) of menstrual irregularities [25]. In contrast, those who were ART-naive or reported suboptimal ART adherence with increased viral load counts and low CD4 counts had reported one or more menstrual irregularities or disorders [3]. The direct pharmacological effects of ART on the menstrual cycle remain unclear. While few studies have investigated potential associations between ART use and menstrual cycle characteristics, others have consistently reported no direct effect of ARTs on menstrual cycle length, regularity, or bleeding patterns [8].

Additionally, ovarian dysfunctions linked to HIV infection and related comorbidities have contributed significantly to menstrual irregularities among WLHIV. This is usually a consequence of the dysregulation of hormones produced by the ovaries. Studies have demonstrated that WLHIV who experience abnormal menstruation exhibit fluctuating levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and prolactin [9, 15, 26]. Two studies have produced conflicting results as regards levels of these hormones among HIV-infected patients. Oghundahunsi et al. suggested low levels of FSH, LH, and increased prolactin levels [27]; Rose NU et al. found significantly higher than normal levels of FSH, LH, and prolactin in HIV clients across both phases of the menstrual cycle when compared with the controls [9]. Research findings have associated HIV infection and ART use with a spectrum of endocrine and metabolic dysfunctions. Hypogonadism, characterized by reduced testosterone levels, has been associated with weight loss and a decline in CD4 cell counts [28, 29]. Testosterone deficiency observed in HIV seropositive males and females can manifest in a range of symptoms including wasting syndrome, fatigue, anemia, depression, and decreased libido, all of which are common complications of HIV infection. These hormonal imbalances often result in menstrual disorders, including amenorrhea, oligomenorrhea, and irregular menstrual cycles. Hyperprolactinemia, particularly, is a known disruptor of the menstrual and reproductive cycles, with research indicating its profound impact on hormonal balance and menstrual function. The exact mechanisms underlying these hormonal changes are still being investigated, but several factors may contribute. HIV infection can directly disrupt the hypothalamic-pituitary-ovarian (HPO) axis, the intricate signaling pathway that regulates reproductive hormones. In addition, HIV infection makes women more susceptible to various opportunistic infections [23], such as tuberculosis. These infections can cause widespread inflammation, with increased production of pro-inflammatory cytokines that may disrupt the delicate hormonal balance necessary for regular menstrual cycles [23]. In addition, treatment for some opportunistic infections can have side effects that contribute to menstrual irregularities. HIV-associated inflammation and immune dysregulation may further impair hormonal production and release.

Furthermore, in evaluating the possible etiology of menstrual disorders among WLHIV, it is imperative to consider confounding variables like body mass index (BMI). More WLHIV have lower BMI when compared to their seronegative counterparts [15]. These low BMI and poor nutritional status can contribute to menstrual irregularities, particularly amenorrhea. A longitudinal study revealed that severe weight loss was a common occurrence, affecting one-third of the WLHIV population, and was linked to amenorrhea [30]. A study investigating the link between low BMI and the occurrence of amenorrhea revealed that up to 38% of WLHIV with a BMI below 90% of their ideal weight reported experiencing the absence of menstruation or those with irregular frequencies [13]. Other potential contributing factors may include the use of illicit drugs among patients with a psychiatric disorder as well as anxiety about health conditions [31, 32]. Additionally, anemia of chronic disease (ACD) associated with chronic HIV infection may contribute to the prevalence of amenorrhea [33]. Exposure to a variety of stressors can lead to an increase in the release of stress hormones, which negatively affects the gonadotrophin-releasing hormones. This can result in menstrual irregularities or even the complete cessation of menstruation [34]. Diagnostic modalities should consider eliminating other possible causes of amenorrhea and menstrual irregularities, like the use of hormonal or intrauterine contraceptive methods, coexisting uterine fibroids, and women who may be pregnant or lactating when managing these conditions.

Determinants and impact of menstrual disorders among WLHIV

Clinical and patient-related factors

The pathogenesis of menstrual disorders in WLHIV is a multifaceted phenomenon influenced by a complex interplay of clinical, therapeutic, and patient-related factors. Many studies have demonstrated an association between CD4 cell count and menstrual disorders among WLHIV. In particular, low CD4 cell counts have been shown to significantly elevate the risk of menstrual irregularities,

underscoring the profound influence of the immune system on women's reproductive health. Research has demonstrated that both overweight and underweight conditions can lead to menstrual irregularities. However, underweight individuals living with HIV are at a higher risk of experiencing amenorrhea and irregular menstrual cycles. Although ART has reduced the incidence of menstrual disorders among WLHIV, there have been reported changes in menstruation patterns upon commencement of ART [8, 35]. High viral load and low CD4 + cell counts have been implicated as major contributors to menstrual irregularities in WLHIV by causing cytopenias [36]. Thrombocytopenia due to bone marrow suppression associated with HIV has also been reported as a contributing factor [37]. Zidovudine has been shown to raise platelet counts, without necessarily demonstrating a corresponding antiviral effect in about 40–60% of the patients, and reported as a choice treatment for HIV-associated thrombocytopenia [38]. Lamivudine, zidovudine, and nevirapine have been reported as post-treatment predictors of anemia [35].

Impact of menstrual irregularities on PLHIV

Abnormal menstruation can lead to anemia, reduced fertility, and an overall reduction of quality of life. Iron deficiency anemia commonly results from prolonged and heavy menstrual bleeding [39]. Anemia in WLHIV not only contributes to an increased rate of infertility but has been linked to the early onset of menopause and ovarian insufficiency [10, 25]. While most ART can effectively resolve anemia, ART-naivety or poor adherence can exacerbate the condition due to the immunosuppressive state caused by untreated HIV, which further compounds anemia-associated complications. Physical health and mental well-being are affected as a result of abnormal menstruation, especially prolonged amenorrhea, lasting over 12 months [40]. Other factors such as oral contraceptive pills (OCPs), use of medications and recreational drugs, mental illness, and profound stress also contribute to the prolonged amenorrhea observed in WLHIV [41]. A compelling association exists between amenorrhea and lower educational attainment in women, a finding that mirrors the link between menopause and lower socioeconomic status and education level [42]. While the underlying biological mechanisms remain elusive, this association highlights the intricate interplay between social and biological factors in the menstrual health of WLHIV.

Interventions for menstrual abnormalities among WLHIV and therapeutic effectiveness

Women's experiences with HIV infection and associated complications necessitate tailored and targeted healthcare services that address their specific needs. Pharmacological and nonpharmacological strategies have been utilized in the management of menstrual disorders among WLHIV, and both approaches have proven to be effective in their holistic care. Pharmacological interventions such as hormone replacement therapy (HRT) and ART adjustment to minimize side effects have been proven effective. The use of integrase strand transfer inhibitors (INSTIs) led to notable improvements in the overall well-being of WLHIV, with observed weight gain, and and the resolution of previously experienced menstrual irregularities [15, 43]. Various etiologic factors attributed to menstrual abnormalities were found to be significantly mitigated with high adherence to ART. A study revealed that WLHIV with menstrual disorders exhibited significantly lower adherence rates to ART compared to women without these disorders [3]. Similarly, pharmacotherapy has been deployed to manage coexisting comorbidities like osteopenia and osteoporosis, which may be caused by low estrogen levels among WLHIV. Bisphosphonates, such as alendronate sodium, risedronate, and ibandronate, have demonstrated remarkable efficacy and safety in increasing BMD when administered alongside calcium and vitamin D supplementation [44, 45]. These medications effectively inhibit osteoclast activity, reducing bone resorption and promoting bone formation. Selective estrogen receptor modulators (SERMs), including raloxifene and tamoxifen, have also emerged as valuable therapeutic options for managing osteoporosis among WLHIV [45]. Nonpharmacological methods involve lifestyle adjustments, nutritional support, and stress reduction techniques [46]. It is pertinent that clinicians conduct pregnancy investigations for all HIV-infected women of childbearing potential presenting with current amenorrhea, irrespective of their history of sexual activity or contraceptive use, to exclude amenorrhea due to pregnancy. Serum FSH may be useful in diagnosing early menopause if suspected in the setting of prolonged amenorrhea [44].

The use of HRT and ART adjustments has shown positive outcomes in restoring menstruation among PLHIV with menstrual irregularities, particularly amenorrhea [47]. A study model incorporating only HIV-seropositive women found that higher CD4 cell counts were associated with a lesser occurrence of menstrual irregularities compared to women with lower CD4 cell counts (less than 200/mm^3). Separate analysis revealed that the longer the duration of ART, the lower the risk of amenorrhea. In addition, women with lower CD4 cell counts (200–500/mm^3) who were ART-naive or non-compliant were more likely to experience oligomenorrhea [47]. However, Fumaz et al. reported that ART use for 2–4 years and above was protective against oligomenorrhea and

intermenstrual bleeding [3]. Lifestyle changes and nutritional support have also yielded promising results, promoting overall health and potentially alleviating amenorrhea. The level of therapeutic effectiveness may vary among individuals, making it essential to personalize treatment strategies.

Research gaps and prospects

Previous studies faced certain limitations, including a lack of information on other potential causes of menstrual disorders, particularly amenorrhea and irregular cycles, and specific ART regimens used by respondents. Much of the research on menstrual disorders in WLHIV was conducted during the early epidemic, a time marked by a higher prevalence of advanced disease and wasting syndrome in WLHIV. There is a need for extended research to further explore the intricate interplay between major systems such as the renal, pituitary, thyroid and parathyroid, hypothalamic, and hepatobiliary systems in the setting of HIV infections and ART use to better understand the underlying factors contributing to menstrual irregularities. Existing studies have highlighted several gaps, including the need for more robust, diverse, and representative sample populations for a more comprehensive understanding of the subject. Moreover, the heightened prevalence of menstrual irregularities and subsequent infertility among WLHIV who are adherent to ART with undetectable viral loads remains unclear and needs further investigation.

Future research should explore preventive therapies to reduce the incidence of menstrual irregularities among WLHIV. Developing guidelines for gynecological care tailored to WLHIV in Nigeria is a promising direction. Recent longitudinal studies assessing the current effects and trends of HIV infection, and treatment with combined ART on the menstrual cycle are crucial. Clinicians should take a holistic approach when evaluating amenorrhea and other menstrual irregularities in HIV-positive women, considering the patient's overall health and potential contributing factors, such as substance use, medications, and opportunistic infections. A complete diagnostic workup is necessary to determine the cause of the menstrual disorder, as symptoms may mimic those of co-existing pregnancy, ovarian cyst, ovarian failure, or menopause. Lastly, exploring stress levels and markers of chronic anovulation, such as the presence of multiple follicles on ultrasound, and ruling out thyroid disease and disorders of prolactin secretion in this group is necessary.

Limitations and strengths of the study

Our review was constrained by limitations that may have influenced our findings. The majority of studies identified were conducted during the early stages of the HIV/AIDS epidemic. This lack of recent research restricted our ability to conduct a time-based analysis, necessitating the inclusion of older studies. Consequently, the findings may not fully reflect the current landscape of menstrual irregularities among WLHIV. There is a dearth of research investigating the prevalence, patterns, and correlates of menstrual irregularities among WLHIV across Nigerian states, this may have further influenced our review's conclusions. Additionally, studies included in this review captured a few states in the country, which may not reflect regional peculiarities. Several studies were found to have limited sample sizes, and many failed to specify the ART regimen utilized, which hindered our analysis and gave an impression of generalization when ART was referred to. Despite these limitations, by synthesizing both local and international studies spanning a broad range of years and employing a rigorous systematic methodology, we have shed light on the profound impact of this often-overlooked burden on WLHIV. Restricting our review to studies involving premenopausal women, eliminated ambiguity regarding studies of participants' menstrual status.

Conclusion

The advent of combined ART has markedly improved HIV treatment outcomes and extended the lifespans of PLHIV. Consequently, a greater number of PLHIVs now experience and live with comorbid conditions, including menstrual irregularities. Other complications, such as reduced BMD, cytopenias, and secondary infertility, have been found to coexist with menstrual irregularities among WLHIV. The interplay of factors such as viral load, CD4 cell count, BMI, illicit and psychotropic drug use, and disturbances of the hypothalamic-pituitary-ovarian axis and consequent fluctuating patterns of the female sex hormones, particularly FSH, LH, and prolactin have been identified as possible etiologic factors. These disorders have been attributed to consequences negatively impacting reproductive potential and overall quality of life for WLHIV. Improved ART adherence is a crucial treatment and preventive strategy for this condition. Other pharmacological and nonpharmacological interventions treating menstrual irregularities and other comorbidity have also been reported as effective measures. Although the literature is limited and inconclusive, understanding the underlying mechanisms and associated factors is invaluable in providing clinical guidance for HIV-positive women experiencing menstrual irregularities. To overcome the limitations of previous research, large-scale, multi-center studies are needed to accurately represent the prevalence of menstrual irregularities among WLHIV. Additionally, establishing guidelines for gynecological care tailored to the unique challenges of

WLHIV in Nigeria is essential. Integrating gynecological care into the HIV care cascade, with a holistic multidisciplinary approach to care delivery can significantly reduce this burden and better the quality of life of WLHIV.

Abbreviations

LMIC	Low and middle-income countries
ART	Antiretroviral therapy
PLHIV	People living with HIV/AIDS
WLHIV	Women living with HIV/AIDS
BMI	Body mass index
ACD	Anemia of chronic disease
FSH	Follicular stimulating hormone
LH	Luteinizing hormone
SERMs	Selective estrogen receptor modulators
OCP	Oral contraceptive pills
HRT	Hormonal replacement therapy
INSTIs	Integrase strand transfer inhibitors

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BMU, AHA, and MAG conceptualized and designed this study. They also conducted a literature search to put together relevant studies. BMU and TWA conducted the data extraction table, which two external reviewers reviewed. BMU, AHA, FMD, MAG, IJO, OJO, and KUA wrote the initial draft, which BMU and FMD edited. BMU is the corresponding author and is responsible for the work's credibility.

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