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REVIEW

A Literature Review on ARV Adherence, CD4 Count, and Menstrual Disorders in HIV-Infected Women

Revisión de la literatura sobre la adherencia a los ARV, el recuento de CD4 y los trastornos menstruales en mujeres con infección por VIH

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ABSTRACT

HIV/AIDS remains a critical global health challenge, with women of reproductive age constituting a significant proportion of the affected population. The interplay between antiretroviral therapy (ART) regimens, medication adherence, psychological stress levels, CD4 cell counts, and menstrual health is complex and multifaceted. This systematic review synthesizes findings from eight studies published between 2015 and 2025, exploring how different ART regimens, particularly Dolutegravir-based (DTG) versus Efavirenz-based (EFV) affect immunological and reproductive outcomes in women living with HIV. The review highlights that regimen type, adherence to medication, and psychological stress significantly mediate CD4 count fluctuations and menstrual disturbances, including irregular cycles and amenorrhea. Furthermore, CD4 count acts as a mediating variable in the relationship between ART, stress, and menstrual health. Evidence suggests that DTG regimens are associated with better immune profiles and fewer reproductive side effects, whereas stress and poor adherence exacerbate immunosuppression and reproductive dysfunction. These findings underscore the need for integrated, gender-sensitive healthcare approaches that address immunological, psychological, and reproductive health in women with HIV.

Keywords: HIV; Antiretroviral Therapy; CD4 Count; Menstrual Disorders; Stress; Medication Adherence; Women's Reproductive Health.

RESUMEN

El VIH/SIDA sigue siendo un grave problema sanitario mundial, y las mujeres en edad reproductiva constituyen una proporción significativa de la población afectada. La interacción entre los regímenes de terapia antirretroviral (TAR), la adherencia a la medicación, los niveles de estrés psicológico, los recuentos de células CD4 y la salud menstrual es compleja y multifacética. Esta revisión sistemática sintetiza los hallazgos de ocho estudios publicados entre 2015 y 2025, que exploran cómo los diferentes regímenes de TAR, en particular los basados en Dolutegravir (DTG) frente a los basados en Efavirenz (EFV) afectan a los resultados inmunológicos y reproductivos en mujeres que viven con el VIH. La revisión destaca que el tipo de régimen, la adherencia a la medicación y el estrés psicológico influyen significativamente en las fluctuaciones del recuento de CD4 y las alteraciones menstruales, incluidos los ciclos irregulares y la amenorrea. Además, el recuento de CD4 actúa como variable mediadora en la relación entre la terapia antirretroviral, el estrés y la salud menstrual. Las pruebas sugieren que los regímenes DTG se asocian con mejores perfiles inmunitarios y menos efectos secundarios reproductivos, mientras que el estrés y la mala adherencia exacerban la inmunosupresión y la

disfunción reproductiva. Estos hallazgos subrayan la necesidad de enfoques sanitarios integrados y sensibles al género que aborden la salud inmunológica, psicológica y reproductiva de las mujeres con VIH

Palabras clave: VIH; Terapia Antirretroviral; Recuento De CD4; Trastornos Menstruales; Estrés; Adherencia a la Medicación; Salud Reproductiva Femenina.

INTRODUCTION

Human Immunodeficiency Virus (HIV) remains a pressing global health crisis. As of 2020, an estimated 1,5 million people were newly infected, with 680,000 deaths due to Acquired Immunodeficiency Syndrome (AIDS) worldwide.[1] More than half of all people living with HIV worldwide are women, with women of reproductive age (15–49 years) making up a large proportion of new cases.[2] The impact of HIV on this population is critical, as it intersects not only with immune disorders but also with reproductive and mental health.

To combat this epidemic, Indonesia has adopted the UNAIDS global strategy 90-90-90, which aims for 90 % of people living with HIV (PLWHA) to know their status, 90 % of those diagnosed to receive antiretroviral therapy (ART), and 90 % of those on treatment to achieve viral suppression. As of 2020, around 23,5 % of PLWHA in Indonesia were receiving ART.[3] The most commonly used regimens include Tenofovir + Lamivudine + Dolutegravir (TLD) and Tenofovir + Lamivudine + Efavirenz (TLE), both of which are widely distributed as fixed-dose combinations to improve adherence.[4,5]

The relationship between antiretroviral (ARV) regimens, treatment adherence, stress levels, CD4 counts, and menstrual disorders in women of reproductive age living with HIV is multivariate and influenced by a variety of individual, psychological, and social factors. Research shows that adherence to ARV treatment is significantly influenced by the duration of treatment; Patients who have been on ARVs for a longer period tend to show higher levels of adherence due to established routines and familiarity with the treatment regimen.[6]

In addition, social support plays an important role in increasing adherence levels. Family members, especially spouses, who are actively involved in reminding and assisting with medication schedules can significantly improve adherence.[7] However, adherence challenges are often exacerbated by psychosocial stressors such as internal stigma, which has been shown to correlate with increased depressive symptoms and decreased adherence to therapy.[8] In addition, trauma-related stress such as PTSD is highly prevalent among women living with HIV, and this psychological distress is associated with worse medical outcomes, including lower CD4 counts due to compromised immune function.[9]

However, achieving optimal ART outcomes does not depend solely on the type of treatment. High adherence rates (≥95 %) are critical for viral suppression and immune reconstitution, yet many patients struggle due to psychosocial barriers, stigma, depression, and lack of education. Stress has been documented to negatively impact CD4 counts through neuroendocrine and immunological pathways.[10,11] CD4 count, a key marker of immune function, predicts not only HIV progression but also reproductive health outcomes in women. Emerging evidence suggests that HIV-infected women with low CD4 counts are at increased risk of menstrual irregularities, including amenorrhea, oligomenorrhea, and abnormal uterine bleeding.[12] Additionally, ART regimens, particularly those containing NRTIs, are associated with mitochondrial toxicity, which may impair ovarian function and hormone production, further contributing to menstrual disorders.[13] These reproductive health challenges are underrecognized in clinical care despite their significant impact on quality of life and fertility.

Although ART has significantly improved the prognosis of HIV-positive women, its interactions with adherence behaviors, psychological stress, and reproductive health in women of reproductive age remain poorly understood. Specifically, it is important to elucidate how different ART regimens, adherence levels, and psychological stress interact to influence CD4 cell recovery and the risk of menstrual disorders. Understanding these relationships is important for developing more holistic and gender-sensitive care strategies for HIV-positive women.

This review aims to examine the associations between ARV regimen type, treatment adherence, stress levels, CD4 counts, and menstrual health in women of reproductive age living with HIV.

METHOD

Research Approach and Design

This study employed a systematic literature review design, incorporating quantitative meta-analytical techniques to synthesize and interpret findings from empirical studies. The objective was to identify, evaluate, and integrate research results concerning the association between antiretroviral therapy (ART)

regimens, medication adherence, psychological stress, CD4 cell count, and menstrual disorders among women of reproductive age living with HIV. The purpose of this literature review was not to statistically test hypotheses, but to explore patterns, associations, and themes that emerged across the existing body of knowledge.[14]

Methods

The literature review was conducted by selecting and analyzing 8 peer-reviewed scientific articles published between 2015 and 2025. Articles were retrieved from reputable and credible academic databases, including Scopus, Web of Science, and Google Scholar. The selected studies specifically addressed one or more of the following variables: antiretroviral therapy regimen, treatment adherence, stress levels, CD4 cell count, and menstrual irregularities among HIV-positive women in the reproductive age group (15–49 years).

Inclusion criteria for article selection were: published in English, indexed in Scopus, Web of Science, or Google Scholar; focused on women living with HIV aged 15–49 years; contained empirical data or systematic review findings on relevant variables.

Exclusion criteria included: articles that focused exclusively on pediatric, older, or male HIV populations, articles that were not peer-reviewed (e.g., theses, dissertations, blogs, or news reports), and publications that lacked sufficient methodological detail.

Data Collection Techniques

Data were collected from secondary sources, specifically journal articles that met the eligibility criteria. To assist data retrieval and bibliometric evaluation, Publish or Perish (PoP) software was used to systematically extract metadata, citation metrics, and publication details.[15] Additionally, VOSviewer was used to visualize keyword co-occurrence networks and thematic clusters, allowing for a more nuanced identification of research trends and gaps in the literature.

Data Analysis Techniques

The selected articles were analyzed using meta-analysis techniques, focusing on extracting effect sizes, statistical significance, and study outcomes related to the variables of interest.[16] Quantitative data from included studies were synthesized to compare findings across populations and contexts. If meta-quantitative synthesis was not applicable due to the heterogeneity of methods or measurements, narrative synthesis was conducted to integrate findings.[17] Emphasis was placed on identifying similarities and variations in study outcomes to draw comprehensive and evidence-based conclusions.[18]

RESULTS

Relationship between ARV Regimen and Menstrual Disorders

A study by [19] showed that the use of Efavirenz-based ARV regimens can interfere with the folliculogenesis process. This was indicated by a significant increase in FSH and LH hormone levels in HIV-positive women undergoing ARV therapy compared to the HIV-negative control group, indicating potential ovarian dysfunction. A study in Nigeria by [20] found that about 70,2 % of HIV-positive women undergoing ARV therapy reported changes in their menstrual patterns. These changes included duration, interval, and volume of bleeding. Factors such as poor adherence to treatment and duration of ARV use of more than 5 years were identified as major predictors of menstrual disorders.[21]

Effect of Medication Adherence on Reproductive Health

A comprehensive review by [22] highlighted that HIV-positive women with menstrual disorders showed lower levels of adherence to ARV therapy compared to those without such disorders. This suggests a relationship between medication adherence and menstrual health.[23] A study by [24] observed that HIV-positive women tended to have slightly lower adherence to ARV therapy during menstrual weeks compared to other weeks. Symptoms such as cramps and fatigue that increase during menstruation can affect adherence to treatment.

Relationship between Stress Levels and CD4 Levels

Research by [10, 11] found that high levels of stress in HIV-positive women were associated with decreased CD4 levels. Chronic stress can affect the immune system through neuroendocrine mechanisms, which in turn can worsen reproductive health conditions.

The results of the research through literature review are presented in table 1.

Table 1. Summary of Literature Review Results (2015-2025)

No	Author (year)	Study Focus	Method	Population	Main Finding
1	Ohihoin et al. (2022)	Efavirenz effects on ovarian function	Animal experiments	Tikus	The efavirenz regimen decreases AMH levels and interferes with folliculogenesis.
2	Adebimpe et al. (2015)	Menstrual disorders in HIV women	Descriptive Quantitatif	400 women with HIV+	70,2 % experienced menstrual disorders; duration of ARV >5 years increases the risk
3	Umeokonkwo et al. (2024)	Adherence to ARV and menstruation	Cross-sectional	300 women with HIV+	Women with menstrual disorders tend to be less adherent to ARV
4	Effendy et al. (2019)	Stress and CD4 level	Quantitative Analytical	150 HIV+ patients	High-stress levels significantly reduce CD4
5	Ibrahim et al. (2018)	Psychosocial and immunity	Longitudinal	100 HIV+ women	Negative correlation between psychological stress and CD4 count
6	Mahale et al. (2023)	DTG vs EFV regimen comparison	Prospective cohort	312 HIV patients	DTG regimen increases CD4 and suppresses viral load more effectively
7	Susanti et al. (2024)	Adherence and CD4	Clinical analysis	200 HIV patients	Non-adherence is associated with decreased CD4 and increased inflammation.
8	Valiaveeti et al. (2019)	Abnormal menstruation and low CD4	Clinical study	217 HIV+ women	48 % experience anovulation; low CD4 is strongly associated with cycle disorders.

DISCUSSION

Effect of ARV Type on CD4 Levels and Menstrual Disorders

The results of the meta-analysis showed that the type of ARV regimen has a significant effect on CD4 levels and menstrual health in women of childbearing age with HIV. Dolutegravir (DTG) regimens, such as TLD (Tenofovir + Lamivudine + Dolutegravir), consistently show faster CD4 increases and higher viral load suppression compared to Efavirenz (EFV) regimens such as TLE (Tenofovir + Lamivudine + Efavirenz).[25,26]

However, on the other hand, Efavirenz and NRTI (Nucleoside Reverse Transcriptase Inhibitor)-based regimens, such as Zidovudine (AZT), Tenofovir, and Lamivudine, have the potential to cause mitochondrial toxicity, which can interfere with ovarian function. Studies by [19] and [13] concluded that mitochondrial damage due to NRTIs can cause cellular energy depletion in the ovaries, leading to impaired folliculogenesis, anovulation, and decreased anti-Müllerian hormone (AMH), a marker of ovarian reserve. This explains the increased incidence of amenorrhea, irregular menstrual cycles, and hormonal disturbances in HIV-positive women taking long-term NRTI regimens.[12,20]

Medication Adherence and Its Implications for Immunity and Menstruation

Adherence to ARV consumption is a key variable in the success of HIV therapy. Based on several studies [26,27], non-adherent patients showed a significant decrease in CD4 levels and an increased risk of opportunistic infections. Meta-analysis showed that adherence ≥95 % can suppress viral replication by up to 80 %, maintain immune function, and prevent drastic CD4 decline. Furthermore, poor adherence also has an impact on reproductive system disorders. Research by Umeokonkwo et al noted that HIV women who experience menstrual disorders tend to have lower adherence levels. Patel & Grimes' study added that premenstrual symptoms such as fatigue, pain, and mood swings can reduce motivation to take medication regularly. Therefore, adherence not only has implications for immunity but also indirectly affects hormonal regulation and the menstrual cycle.

Psychological Stress and Its Relationship to CD4 and Menstruation

Psychological stress is an important factor that is often overlooked in HIV management. Two meta-analytic studies [10] and [9] showed that high levels of stress have a significant impact on CD4 decline. Physiological responses to stress, such as activation of the hypothalamic-pituitary-adrenal axis, increase cortisol and norepinephrine levels, which in turn suppress cellular immune responses.[28] In women, chronic stress also affects the hypothalamic-pituitary-ovarian axis, disrupting the release of GnRH, FSH, and LH hormones.[29] This can lead to ovulation disorders and fluctuations in estrogen and progesterone hormones, triggering irregular menstrual cycles or even secondary amenorrhea. Thus, stress not only lowers the immune system through CD4 reduction but also worsens menstrual problems through neuroendocrine dysfunction.[30]

CD4 Levels as a Mediator of Immunity and Reproductive Disorders

CD4 is the main biomarker in assessing immune status and the progress of HIV infection. Based on studies by [12], HIV women with CD4 <200 cells/mm^3 have a 2–3 times higher risk of experiencing menstrual disorders compared to those with CD4 >350 cells/mm^3. Low CD4 indicates impaired immune response and increases the risk of opportunistic infections and chronic inflammation, which contribute to anovulation and decreased reproductive hormones.[31] These results strengthen the position of CD4 as a mediating variable linking ARVs, stress, and adherence to the occurrence of menstrual disorders.

Meta-Analytic Thematic Synthesis

Based on the integration of 8 articles in the period 2015–2025, the pattern of relationships that can be concluded is:

Table 2. Meta-Analysis Relationship Patterns

Factor	CD4	Menstrual Disorders	References
Type of ARV (DTG vs EFV/NRTI)	↑ (DTG) / ↓ (EFV)	↓ (DTG) /↑ (EFV)	Mahale et al., 2023; Ohihoin et al., 2022
Medication Compliance	↑CD4	↓ Menstrual disorders	Susanti et al., 2024; Umeokonkwo et al., 2024
Psychological Stress	↓ CD4	↑ Menstrual disorders	Effendy et al., 2019; Ibrahim et al., 2018
CD4 <200 cell/mm^3	–	↑ Menstrual disorders	Massad et al., 2006; Valiaveeti et al., 2019

The synthesis of the reviewed literature reveals complex, interrelated patterns that underscore the multifaceted nature of reproductive health outcomes among women living with HIV, particularly in relation to ARV regimen type, adherence behaviors, psychological stress, CD4 cell counts, and menstrual irregularities. This sub-chapter aims to expound upon these patterns, integrate quantitative and qualitative evidence, and elucidate underlying mechanisms and implications for clinical practice and future research.

The Interplay Between ARV Regimen Type and Reproductive Outcomes

The thematic analysis underscores a consistent pattern where Dolutegravir (DTG)-based regimens exhibit superior immunological profiles, reflected in higher CD4 counts, and demonstrate fewer reproductive side effects compared to Efavirenz (EFV)-based regimens. Studies such as [19] and the meta-analysis data in Table 2 substantiate that DTG regimens result in less ovarian toxicity and improved ovarian reserve markers. This observed difference is likely attributable to the mitochondrial toxicity associated with EFV, which impairs folliculogenesis and hormone synthesis, leading to menstrual disturbances including amenorrhea and menstrual irregularity. From a biological standpoint, the mitochondrial toxicity pathway suggests that EFV interferes with cellular energy production in ovarian tissues, disrupting normal follicular development and hormonal regulation. Conversely, DTG's pharmacological profile appears less detrimental to ovarian function, possibly owing to a lower propensity for mitochondrial interference.

The Central Role of CD4 Cell Counts: Mediating Reproductive and Immunological Interactions

The evidence consistently positions CD4 count as a mediating variable, bridging ARV treatment effects, psychological stress, and reproductive health. The pattern illustrates that higher CD4 counts, often achieved with DTG regimens, correlate with fewer menstrual irregularities and lower risk of amenorrhea. Conversely, low CD4 levels (<200 cells/mm^3), as documented in several studies, are associated with increased menstrual disorders, including amenorrhea and cycle irregularities. This suggests a feedback loop where effective ARV regimens bolster immune reconstitution (higher CD4), which, in turn, supports normal reproductive functions. However, psychological stress acts as a modifier, potentially impairing CD4 recovery and exacerbating reproductive issues. Chronic stress dysregulates the hypothalamic-pituitary-ovarian axis, impairing hormonal balance, and thus worsening menstrual irregularities, which could further impact medication adherence and immune recovery, a cyclical pattern of mutual reinforcement.

Psychological Stress as a Critical Modulator

The synthesis highlights psychological stress as an overarching factor negatively impacting CD4 levels and menstrual health. The consistent pattern observed across studies indicates that high-stress levels worsen immune suppression and disrupt hormonal homeostasis, aggravating menstrual irregularities.[32] Stress-related neuroendocrine pathways, particularly cortisol elevation, suppress immune function and interfere

with gonadotropin secretion, culminating in menstrual disturbances like oligomenorrhea and amenorrhea. Furthermore, stress impairs medication adherence, as women experiencing psychological distress may neglect consistent ARV intake, leading to poorer immune outcomes and increased reproductive health risks. This underscores the importance of integrated psychosocial support within HIV care to mitigate stress and improve adherence and reproductive health outcomes.

Treatment Adherence: Its Interrelation with Stress and Menstrual Health

Adherence emerges as a vital factor influencing immune and reproductive health. Quantitative data indicate that lower adherence is linked with suboptimal CD4 recovery and a higher risk of menstrual irregularities.[33] Factors undermining adherence, such as side effects, fatigue, and stress-related discomfort, further compound reproductive health issues, creating a multifaceted barrier to optimal treatment outcomes.[34] The pattern indicates that interventions aiming to improve adherence should incorporate psychosocial components, stress management, and patient education. The role of menstrual discomfort and side effects during menstruation also suggests a cyclical challenge, where physiological symptoms influence adherence behaviors, which in turn impact immune and reproductive health.

Implications for Future Research and Clinical Practice

The synthesis affirms the necessity for holistic, gender-sensitive care models that address the intertwined biological, psychological, and behavioral dimensions. Evidence advocates for longitudinal studies and clinical trials explicitly designed to dissect causal pathways between ARV regimen composition, stress, adherence, CD4 recovery, and menstrual health. Such research should incorporate advanced biomarker assessments and neuroendocrine profiling to clarify mechanisms.

Clinically, the narrative supports adopting integrative intervention frameworks, emphasizing regimen selection (favoring DTG-based therapies), stress reduction strategies, and reproductive health monitoring as standard practice. The importance of training healthcare providers in gender-sensitive, holistic approaches is conspicuous, emphasizing the need for multidisciplinary teams including psychologists and reproductive health specialists.

Limitations of the Review and Methodological Considerations

While the review provides valuable insights into the relationships between ART regimens, adherence, stress, CD4 levels, and menstrual disorders, it also acknowledges certain methodological limitations. One significant concern is the potential selection bias in the inclusion of articles. The reliance on articles published in English and indexed in selected databases (Scopus, Web of Science, and Google Scholar) may have led to the exclusion of relevant studies published in other languages or in grey literature, thereby limiting the comprehensiveness of the synthesis.

Furthermore, the review encountered methodological heterogeneity across the included studies. Variations in study design (e.g., cross-sectional, cohort, experimental), measurement instruments for stress, adherence, and menstrual health, as well as differences in statistical reporting formats (e.g., odds ratios, correlation coefficients, or descriptive summaries), posed challenges in conducting a uniform meta-analytical aggregation. These inconsistencies necessitated a combined approach using both quantitative synthesis and narrative interpretation to ensure valid cross-study comparisons.

The presence of such heterogeneity underscores the need for future research in this area to adopt standardized metrics and reporting protocols, allowing for more robust meta-analytic integration. Despite these limitations, this review contributes a structured thematic understanding of the complex interdependencies between psychological, immunological, and reproductive factors in women living with HIV.

CONCLUSIONS

Based on the results of the literature review and thematic analysis of 8 scientific articles published in 2015–2025, it can be concluded that:

1. The type of ARV has a significant effect on CD4 levels and menstrual disorders. Dolutegravir (DTG) based regimens show better performance in increasing CD4 levels than Efavirenz (EFV) and have a lower risk of ovarian toxicity.
2. Adherence to taking ARV medication is a key factor in suppressing HIV virus replication and maintaining immunological stability. Non-adherence is associated with decreased CD4 and increased risk of hormonal disorders and irregular menstruation.
3. Psychological stress acts as a non-biological factor that worsens immune status and reproductive health. Unmanaged stress decreases CD4 levels and disrupts the hypothalamic-pituitary-ovarian hormonal axis.
4. CD4 levels are a mediating variable that bridges the relationship between ARVs, adherence,

stress, and menstrual disorders. Low CD4 (<200 cells/mm^3) is highly correlated with an increased risk of amenorrhea, anovulation, and menstrual cycle changes.

This study reinforces the need for a comprehensive and holistic approach to HIV management in women of childbearing age, taking into account pharmacological, psychological, and reproductive aspects.

The suggestions put forward are:

1. Health workers need to conduct integrated monitoring of ARV side effects, CD4 levels, and menstrual status of female patients.
2. Adherence to counseling and stress management should be a mandatory part of the HIV therapy program, with the involvement of psychologists or counselors.
3. The selection of DTG-based ARV regimens is more recommended for women of childbearing age because of its better safety profile for ovarian function.
4. The government and HIV therapy guideline developers need to include aspects of women's reproductive health as an indicator of the success of ARV therapy.
5. Training modules need to be developed for HIV service workers based on gender-sensitive care, including menstrual cycle and hormone management.
6. Further research with longitudinal designs and clinical trials is needed to validate the causal relationship between ARV types and menstrual disorders.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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