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Review Report

Metabolic Syndromeand Quality of Life in HIV infected patients undergoing ART

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ABSTRACT

Human Immuno-deficiency Virus (HIV) disease has affected an estimated 40 million people worldwide with 77% of them under antiretroviral therapy (ART) (2023). However, the disease has been found to cause metabolic syndrome with various abnormalities leading to increased cardiovascular disease (CVD) risk. However, this risk of metabolic syndromehas been found to develop in HIV patients even before their exposure to ART, yet the exact pathogenesis behind the subject is unclear. This syndrome in addition to the HIV complicationshas been known to compromise the quality of life of patients. This review was thus conducted to understand the metabolic abnormalities arising after exposure to ART and its level of impact on their quality of life Methods: A comprehensive literature review was conducted in research databases like PubMed, Medline, EMBASE, and Cochrane and the search was dated till 2010. The search was performed using MeSH keywords and only published articles were considered for final review. Results: Our search provided 19 articles regarding metabolic syndrome developing in HIV patients after ART and its impact on their quality of life. The adverse effects of the treatment were found to be moreamongolder age, women andobese people. The common metabolic syndrome affections were more concerned with the weight of patients, their psychological well-being, and overall health-related quality of life. Conclusion: The impact of ART on HIV affected individuals has been multi-dimensional including metabolic abnormalities and coping strategies in terms of improving quality of life needs inclusive rework to provide better outcomes.

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Introduction

Human Immuno-deficiency Virus (HIV) has been affecting millions of people worldwide for the past few decades. As per WHO, an estimated 40 million people have been affected with HIV worldwide, where 1.3 million people acquired the disease in 2023. The global mortality rate due to HIV has been around 43 million with a death rate of 630,000 people in 2023.

Also, according to WHO regions, the African region had the highest (65%) HIV global burden and the Eastern Mediterranean with the lowest (1%), yet the mortality rate was higher in that region (3.7%) (Figure 1). This increased mortality rate despitethe low prevalence in the Eastern Mediterranean region was attributed to the low coverage of anti-retroviral therapy (ART) among people with HIV.

Globally, 77% [61–89%] of people living with HIV were receiving antiretroviral therapy (2023) and to reach the second 95–90–86 testing, treatment, and viral load suppression cascade target, an additional 5.4 million people living with HIV need to know their status and access antiretroviral therapy(1).

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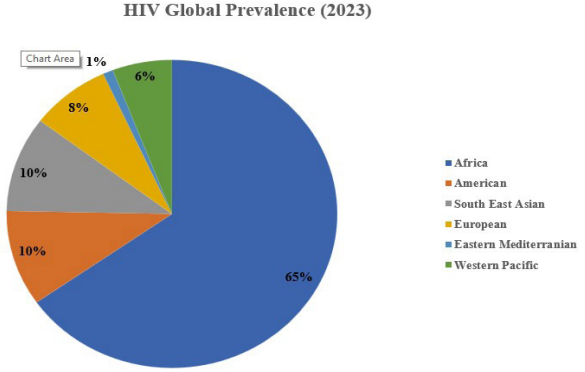
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Figure 1: HIV Prevalence worldwide according to WHO regions(Source: UNAIDS-WHO)



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The medical management of HIV has been revolutionized by the use of ART, which has improved the quality of life of patients. However, the therapy has been associated with drug-related metabolic complications which continue to constitute a major challenge to clinicians in the management of HIV/ AIDS(2).

HIV infection and ART can induce lipodystrophy, insulin resistance, and dyslipidemiawhich attribute as the key risk factors of metabolic syndrome(3).

Though ART has been beneficial in the management of HIV, its metabolic complications comprising the quality of life of patients have raised global concern for immediate action(4). This review was thus taken up to assess the metabolic complications in patients with HIV, their factors of correlation, and their impact on the quality of life.

Materials and methods

A comprehensive literature review was conducted in research databases like PubMed, Medline, EMBASE, Cochrane, and Google Scholar, and the search was dated till 2010. The search was performed using MeSH keywords and only published articles were considered for final review. Studies on metabolic syndrome affecting HIV patients undergoing ART were studied in detail.

Inclusion criteria

Studies which met the following criteria were included for final review –

- Published in peer-reviewed journals
- Available in electronic databases
- Studies were included if they described either one or all the following variables –
    - Anti-retroviral therapy and HIV patients
    - Metabolic complications in ART undergoing patients
    - Factors of correlation causing metabolic complications
    - Quality of life of HIV patients undergoing ART
    - Articles available in the English language

Exclusion criteria

Conference abstracts, books, and grey literature were excluded

Screening and data extraction

The search titles were uploaded in Zotero software andscrutinized for duplicates. Firstly, the titles were readand screened as per their relevance to the topic. Secondly,the abstracts of the relevant titles were read bythe reviewers and screened.

Thirdly, the fulltexts of the screened abstracts were read. The reviewers independently completed the screening processes at both abstract and full-text levels as per the inclusioncriteria.

The data extractions from the screened studies were donein the Excel spreadsheet. Details regarding publication,methodology, and results were extracted and recoded.

Results

Our search results revealed 724 studies (Figure 2) relevant to our research objective and on timeline limitation to articles published since 2010, 68 articles (studies and reviews) resulted.

The abstract of 68 studies were read and reviewed through full-text screening which resulted in 19 studies that focussed on metabolic syndrome among HIV patients and their quality of life. All articles were published inEnglish.

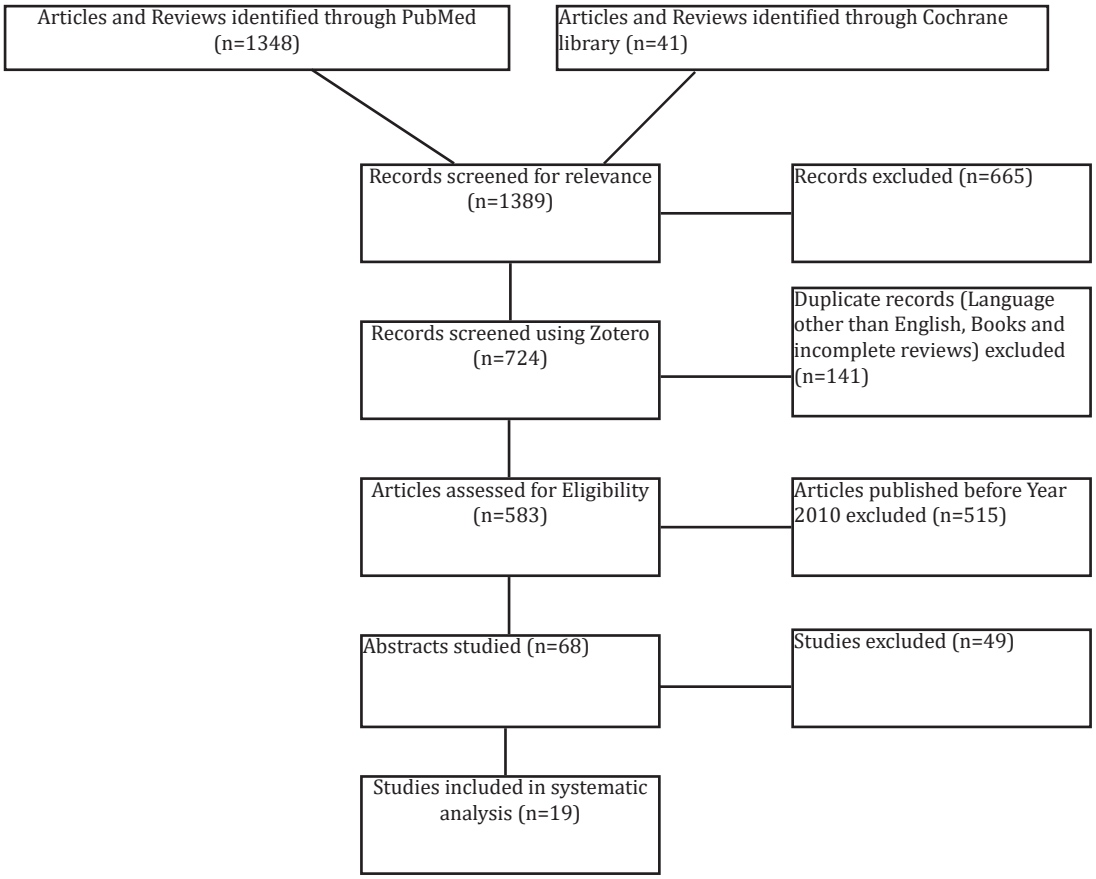
They were then reviewed in detail for the factors that determined this correlation between metabolic syndrome affecting HIV patients undergoing ART and the impact on their quality of life (Table 1).

S.No	Title of the paper	Authors	Published date and journal	Results
1	Comparing the Ability of Anthropometric Indicators in Identifying Metabolic Syndrome in HIV Patients	Beraldo RA, Meliscki GC, et al.	PLoS ONE, 2016	Waist Circumference -a good tool to identify each metabolic disorder separately: total cholesterol (only females, p<0.05), triglycerides (only males, p<0.001), HDL cholesterol (p<0.05), LDL cholesterol (p<005) and fasting glycemic (p<005).
2	Metabolic syndrome and its components among HIV/AIDS patients on Antiretroviral Therapy and ART-Naïve Patients at the University of Calabar Teaching Hospital, Calabar, Nigeria	Ojong E, Iya B, et al.	African Health Sciences, March 2022	The highest prevalence of MS was associated with HIV/AIDS patients on ART (i.e. 32.0 %, and 50.3% for NCEP-ATP III and IDF criteria respectively). Patients on ART had significant increases (p< 0.05) in waist-to-hip ratio, FPG, serum TG, and LDL-c; and a significantly higher (p< 0.05) prevalence of hypertension, diabetes, low HDL-c and hypertriglyceridemia compared to the ART-naïve patients.
3	Independent predictors of metabolic syndrome (MetS) in HIV-infected patients	Alencastro PR, Fuchs SC, et al.	AIDS Pat Care, 2011	MetS prevalence was 24.7% and was similar among men and women. Among men, age, education, physical activity, body mass index (BMI), and HAART use were independently associated with MetS, while among women, there were associations with age, BMI, and use of protease inhibitors
4	Metabolic syndrome in human immunodeficiency virus-infected patients	Duro M, Manso MC, et al.	Int J STD AIDS, Nov 2018	HIV-infected individuals diagnosed with MetS tend to be older, overweight, or obese (85% have a BMI ≥ 25), with a waist circumference > 90 cm (96.5 [88.8-105.5] cm, median [interquartile range]). Blood testing these individuals revealed high fasting levels of insulin (8.1 [5.8-21.6] pg/ml), glucose (98.0 [84.0-116.0] mg/dl), triglycerides (201.0 [142.0-267.3] mg/dl), and high-density lipoprotein cholesterol (36.5 [29.8-43.3] mg/dl) in addition with higher levels of inflammatory mediators such as high-sensitivity C-reactive protein (2.5 [1.0-4.9] mg/dl) and interleukin-6 (3.4 [2.8-3.8] pg/ml). The likelihood of HIV-infected individuals who are virally suppressed developing MetS is about 60% higher than those with acute infection.

5	Metabolic Syndrome in Children and Adolescents Living with HIV	Espiau M, Yeste D, et al.	PediatrInfec Diseases J, June 2016	An abnormally low high-density lipoprotein-cholesterol level was the most prevalent disturbance (21.05%) found. Three patients met IDF criteria for MS (1.97%), and MS was significantly associated with lipohypertrophy (P=0.029) in the analysis. When the modified NCEP-ATP III criteria were used, the prevalence of MS was 5.92% (9 patients), and MS was significantly associated with Tanner stage ≥2 (P=0.041), lipohypertrophy (P=0.001) and higher Z scores for weight and body mass index (P=0.002 and P<0.001). Insulin resistance was observed in 17 patients (11.18%) and was associated with MS (as per the modified NCEP-ATP III criteria) (P=0.03) and lower high-density lipoprotein-cholesterol values (P=0.036).
6	Associations of Cytokines, sleep patterns, and neurocognitive function in youth with HIV infection	Foster SB, Lu M, et al.	Clin Immunol Orlando Fla.,July 2012	HIV infection was significantly associated with alterations of intracellular pro-inflammatory cytokines (TNF-α, IFN-γ, IL-12), sleep factors (total time asleep and daytime sleep patterns), and neurocognitive factors (parent and patient-reported problems with socio-emotional, behavioral, and executive functions; working memory-mental fatigue; verbal memory; and sustained concentration and vigilance.
7	Metabolic syndrome (MetS) and obesity are the cornerstones of liver fibrosis in HIV-monoinfected patients	Lemoine M, Lacombe K, et al.	AIDS Lond Engl, Sept 2017	Patients with MS were older and 49% had insulin resistance. The prevalence of significant liver fibrosis (≥F2) was higher in patients with MS [25.1%, 95% confidence interval (19.3-31.2)] compared with those without MS [7.9%, (4.6-12.5), P<0.0001]. In multivariate analysis with adjustment on MS, obesity [odds ratio: 3.0 (1.1-8.4)] and homeostasis model assessment [1.1 (1.007-1.2)] were independent factors of advanced fibrosis (>= F3).
8	Metabolic Syndrome in HIV-patients in Antiretroviral Therapy	Vargas-Pacherrez D, Cotrim HP, et al	HIV Res, 2020	Patients with MS were more associated with age (OR = 1.076; 95% CI: 1.030 - 1.125), female sex (OR = 2.452; 95% CI: 1.114 - 5.374), and family history of hypertension (OR = 3.678; 95% CI: 1.431 - 9.395).
9	Change in Nutritional and Biochemical Status in People Living with HIV-1 on Antiretroviral Therapy	de Souza RG, Lima SS, et al.	Viruses,Nov 2022	PLHIV had increased measures of Triciptal Skinfold, body mass index, and arm circumference after the use of ART ($p < 0.05$). The viral load levels decreased and the CD4 levels increased after 24 months of ART use ($p < 0.05$). The change in the nutritional status in PLHIV on antiretroviral therapy seems to be a slow process, occurring in the long term
10	An Abnormal Inflammatory Pattern Associated with Long-Term Non-Progression of HIV Infection Impacts Negatively on Bone Quality	Soldado-Folgado J, Chillarón JJ, et al.	J Clinical Med, May 2022	A trend was found of lower BMSi in HIV+ progressorsconcerning the HIV-negative individuals (86 (85–89) vs. 90 (89–93), respectively; $p = 0.083$). No differences were detected in bone mineral density between groups
11	Growth hormone and HIV infection: contribution to disease manifestations and clinical implications	Falutz J, et al.	Best Pract Res ClinEndocrinolMetab,June 2011	Truncal obesity, and associated dyslipidemia and glucose homeostasis changes contribute to impaired quality of life and increased cardiovascular risk. Treatment with growth hormone and growth hormone-releasing factors leads to short-term improvement of some of these abnormalities.
12	Prevalence of Metabolic Syndrome in Patients with HIV in the Era of Highly Active Antiretroviral Therapy	Lombo B, Alkhalil I, et al.	Conn Med,May 2015	The prevalence of metabolic syndrome was 27% using IDF criteria and 26% using ATP III criteria. Logistic regression analysis found an association between treatment with the protease inhibitor darunavir and metabolic syndrome. (OR 3.32 with a 95% confidence interval between 1.54 and 7.15).
13	Increased burden and severity of metabolic syndrome and arterial stiffness in treatment-naïve HIV+ patients from Cameroon	Ngatchou W, Lemogoum D, et al.	Vasc Health Risk Manag, 2013	Fasting triglycerides and the atherogenicdyslipidemia ratio were significantly higher in HIV-UT than in controls. Hypertension prevalence was high and comparable in both groups (41% versus 44%, respectively; not significant). HIV-UT patients exhibited a twice-higher prevalence of MetS than controls (47% versus 21%; $P = 0.02$). Age- and sex-adjusted pulse wave velocity was higher in HIV-UT than in controls (7.5 ± 2.2 m/s versus 6.9 ± 1.7 m/s, respectively; $P = 0.02$), whereas aortic augmentation index was significantly lower ($6\% \pm 4\%$ versus $8\% \pm 7\%$, respectively; $P = 0.01$)
14	Characterization of gut microbiota composition in HIV-infected patients with metabolic syndrome	Villanueva-Millán MJ, et al.	J PhysiolBiochem, Aug 2019	The presence of MS was not accompanied by major changes in GM, although the reduction observed in some anti-inflammatory bacteria may be clinically useful to develop strategies to minimize inflammation and its future deleterious consequences in these HIV-infected patients.

15	Management of the metabolic effects of HIV and HIV drugs	Duro M, Manso MC, et al	Nat Rev Endocrinol, Sept 2011	Metabolic and cardiovascular diseases increase with aging, and knowledge of the optimal management of these conditions is essential for practitioners caring for HIV-infected patients, including endocrine subspecialists.
16	Association between the use of protease inhibitors (PI) in highly active antiretroviral therapy and incidence of diabetes mellitus and/or metabolic syndrome (MS) in HIV-infected patients: A systematic review and meta-analysis	Echecopar-Sabogal J, D'Angelo-Piaggio L, et al.,	Int J STD AIDS, Apr 2018	The use of PIs was associated with the development of MS (RR: 2.11; 95% CI 1.28-3.48; p-value 0.003). The incidence of DM among patients using PIs was 1.23 (95% CI 0.66-2.30; p-value: 0.51) and the RR was 1.25 (95% CI 0.99-1.58; p-value 0.06). The use of PIs in HIV-infected patients is associated with an increased risk of MS
17	Review of metabolic, immunologic, and virologic consequences of suboptimal vitamin D levels in HIV infection	Griffin AT, Arnold FW, et al.	AIDS Pat Care STD, Sep 2012	Metabolic aberrations, including obesity and hyperlipidemia, and miscellaneous risk factors, such as advanced AIDS and substance abuse, have been linked to suboptimal vitamin D in those with HIV.
18	Point prevalence of metabolic syndrome in HIV-positive patients	Hamid S, Badyal A, et al.	J Fam Prim Med Care, Apr 2024	Central obesity (47.3%) was the most common component of MS followed by hyperglycemia (43.3%), hypertriglyceridemia (38.6%), and low high-density cholesterol (HDL-C) level (38.6%). Out of 84 males with MS, 94% (79) males were having hypertriglyceridemia, 88% (74) were hypertensive, and 72% (60) were having FBS >=100. Out of 66 females with MS, 100% (66) females had central obesity and 88% (58) had hypertriglyceridemia and low HDL-C levels.
19	Impact of Metabolic Syndrome and Cardiovascular Risk on the Quality of Life of People Living with HIV	Pereira ÍI, Muto AKTM, et al.	Current HIV Res, 2024	The worst domain of QoL was concern about confidentiality (40 points), and the best was medication concerns (95 points). MetS predominated at 18.3% and a moderate CVR at 11.7%. MetS was positively associated with age >38 years, the female sex, with the lowest score in QoL for general function, and the highest for TdiagHIV and the use of ART ($p<0.05$). A moderate CRV was positively related to higher TdiagHIV and ART use, and low HDL-c and the lowest score for QoL was found for trust in a professional ($p<0.05$).

Figure 2: Flowchart of literature search and data extraction



Discussion

Metabolic syndrome of HIV patients undergoing ART

HIV/AIDS has claimed more than 40 million lives worldwide with a disproportionately higher burden in the African region (65%) and has been a significant public health burden for decades(5)(6). However, with the implementation of ART, the survival and quality of life of patients with HIV improved significantly especially if initiated early, yet has raised concern over its association with the development of metabolic syndrome(7).

Metabolic syndrome (MS) has been given different definitions by various experts, however, according to National Cholesterol Education Program–Adult Treatment Panel III 2001 criteria (NCEP ATP-III) and the International Diabetes Federation (IDF)criteria determined most recent definition of MS, its components among HIV/AIDS patients and identified the need for research in epidemiological, clinical and biochemical characterization(8)(7). The factors that could determine this development of MS among patients with HIV when studied, showed that waist circumference was one of the early key factors followed by the cholesterol profile of patients(9).

MS has received much attention in recent times due to its association with a 5-fold risk of type 2 diabetes mellitus and a 2-fold risk of cardiovascular disease(10) and the global prevalence of MSamong patients with HIV ranges from 17.0% to 45.4%. Dietary and lifestyle choices and a combination of genetic, cultural, and environmental factors may contribute to the differences in this observed prevalence(11).HIV-positive individuals frequently experienced insulin resistance, dyslipidemia, subcutaneous lipoatrophy, and cerebral lipohypertrophy and these conditions were likely known to raise the risk of type 2 diabetes and cardiovascular disease in these patients(12)(13). The impact of long-term HIV infection, the direct and secondary toxicity of highly active antiretroviral therapy (HAART), as well as genetic, behavioral, and demographic susceptibility factors, were the known contributors to the multifactorial origin of MS(14).

Chronic inflammation in HIV-infected individuals probably has an important role in the pathogenesis of their metabolic disease, but further investigation of this effect and effective intervention strategies are required(15).Understanding the mechanism behind the observed metabolic changes during an HIV infection and therapy has been a complex task. However, findings from various studieshave revealed that even 12 months of combination ART (cART) did not attenuate metabolic dysregulationdespitethe normalization of immune activation in HIV patients(16).

Sustained immune activation thus was not the complete answer to what causes co-morbidity in HIV-infected patients, like neurocognitive disorders and cardiovascular disease. Although cART has become increasingly effective over the last few years, was not enough to fully restore the metabolic profile of HIV-suppressed patients to normal(17). Thus, aggressive treatment of modifiable cardiovascular risk factors has been warranted, but interactions between HAART and medications to treat metabolic disease, such as certain statin medications, should also be considered(18).

Health-related Quality of life (HRQOL) of HIV patients undergoing ART HRQOL which determinedhow health impacts people's ability to function in daily life and their perceived well-being in physical, mental, and social domains of life has been found vcompromised to irreplaceable levels due to increasing MS in HIV patients (19). Previous studies have already shown that being diagnosed with HIV or AIDS and experiencing disease-related symptoms is associated with lower HRQOL(20). Furthermore, HRQOL was directly associated with clinically relevant outcomes in HIV-positive patients, such as treatment adherence and viral suppression. Adherence to HIV treatment and viral suppression were thus important to improve treatment effectiveness, prevent the development of drug-resistant HIV strains, and onward transmission of HIV (11).

One key study on HRQOL revealed that the worst domain of QoL among HIV patients was concern about confidentiality (40 points), and the best was medication concerns (95 points). MS predominated at 18.3% and a moderate cardiovascular risk(CVR) at 11.7% and MS was positively associated with higher age (>38 years), the female sex, with the lowest score in QoL for general function, and the highest for TdiagHIV and the use of ART ($p<0.05$). A moderate CVR was positively related to higher TdiagHIV and ART use and low HDL-c, and the lowest score for QoL was found for trust in a professional ($p<0.05$)(11).

Conclusion

It is thus evident that MS has become an inevitable condition of association for HIV patients receiving ART and the prime cause for this association has been attributed to various factors including chronic inflammation and genetic factors. Yet, the key factor behind the syndrome needs more large-scale and deeper studies to recommend appropriate medical management. Also, despite effective improvement in survival and quality of life of patients living with HIV after the implementation of ART, the development of lifestyle diseases including CVD due to metabolic syndrome that has been found to develop later, has caused impairment in key areas of QoL and needs immediate attention for appropriate medical and lifestyle management.

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