REVIEW

The Columbia University
JOURNAL of
GLOBAL HEALTH

Selected Markers of Development of Diabetes (Type- 2) among HIV-positive Individuals Receiving Anti-Retroviral Treatment in Ghana; A Narrative Review of risk factors and determinants

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ABSTRACT An increasing focus on the HIV epidemic and chronic diseases like diabetes (Type 2) has made it crucial to have a comprehensive understanding of the existing research on these subjects. This narrative review specifically examines the development of diabetes (Type 2) in HIV-positive individuals in Ghana who are undergoing antiretroviral treatment (ART). The review covers various aspects including the immuno-pathogenesis of HIV, randomized trials of ART, the occurrence of diabetes during ART, factors associated with diabetes after ART, prevalence of HIV-related illnesses in Ghana, socio-demographic characteristics, and behavioral characteristics. The analysis is based on 60 articles published, written in English. The study reveals consistent links between determinants such as employment, immunological status, symptoms, depression, social support, and medication adherence among HIV-positive individuals. It emphasizes the need to integrate diabetic screening into existing HIV care programs, enhance healthcare provider training, involve community-based initiatives, and utilize technology to improve access to diabetic screening for HIV patients in Ghana. The objective of this study is to provide an overview of HIV research in Ghana, raise awareness about the increasing prevalence of diabetes among people living with HIV, identify any research gaps, and recommend new research themes to guide future interventions.

KEY WORDS Ghana, HIV-positive, Anti-Retroviral Treatment, Diabetes (Type 2), Selected Markers, Socio-demographic and Behavioral factors

INTRODUCTION

HIV (Human Immunodeficiency Virus) infection attacks the immune system by targeting CD4 cells, which are crucial for the body's defense against infections [14]. As the virus multiplies, it weakens the immune system, leaving individuals more vulnerable to opportunistic infections and illnesses [27]. Without treatment, HIV can progress to AIDS (Acquired Immunodeficiency Syndrome), leading to severe immune system failure. However,

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the introduction of antiretroviral therapy (ART) has transformed HIV/AIDS from a fatal illness to a manageable chronic condition by suppressing the viral load in the body [20]. ART prevents the virus from replicating, which helps restore and protect immune function, reduces the risk of opportunistic infections, and improves overall quality of life for people living with HIV (PLHIV) [69].

Combined antiretroviral therapy/ anti-retroviral therapy (cART/ART) is a treatment approach that uses multiple antiretroviral drugs to effectively suppress HIV and prevent the virus from developing resistance [23]. This combination typically includes drugs from various classes, such as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors, and protease inhibitors, which work together to keep viral loads low [67]. Advances in HIV treatment have led to the widespread adoption of cART, offering therapeutic benefits like reduced viral loads, improved CD4 cell counts, lower AIDS-related mortality, and fewer opportunistic infections [52]. By 2016, nearly 19.5 million people in low- and middle-income countries were receiving ART as part of HIV prevention, care, and treatment programs [33]. However, long-term use of ART has been linked to adverse effects, such as mitochondrial toxicity, which can lead to complications like pancreatitis, lipodystrophy, lactic acidosis, dyslipidemia, and blood glucose abnormalities, including dysglycemia [45]. As a result, the health challenges for HIV-positive individuals are increasingly shifting toward age-related comorbidities due to extended life expectancy and prolonged ART use [17].

Emerging evidence suggests that some individuals on ART develop autoimmune diabetes [6], and there is an elevated prevalence of pre-diabetes among people living with HIV, often marked by impaired fasting blood glucose or glucose tolerance [42]. Sub-Saharan Africa (SSA), home to 80% of the global HIV burden [50], exhibits considerable variation in diabetes and pre-diabetes rates, highlighting an urgent need for further research in the region.

In Ghana, where non-communicable diseases account for 43% of all fatalities [64], HIV affects 1.7% of the population, with over 340,000 individuals living with the virus, but only 46% receiving ART [32]. Limited access to ART underscores the need to expand treatment coverage to improve health outcomes and reduce transmission. Furthermore, understanding the potential link between ART and diabetes (Type 2) is critical for developing strategies to prevent and manage diabetes within this vulnerable population. This study aims to support future research addressing the rising prevalence of diabetes among individuals living with HIV in Ghana and the need for comprehensive interventions as ART coverage expands in the region.

MATERIALS AND METHODS

The narrative review employed a global search strategy using specific keywords like "Socio-demographic characteristics", "Behavioral Characteristics", "HIV", "ART", and "Diabetes (Type 2)" in the titles. The databases Google Scholar, PubMed, and PAHO were searched for relevant articles covering topics such as the immuno-pathogenesis of HIV, randomized trials of ART, and diabetes (Type 2) emerging while on ART. The review also examined factors related to the development of diabetes after taking ART for HIV, the prevalence of HIV-related illnesses in the Ghana population, and sociodemographic and behavioral characteristics. Inclusion criteria were carefully assessed by reviewing titles, abstracts, and full texts. Papers that did not meet the requirements were rejected without further review (Figure 1).

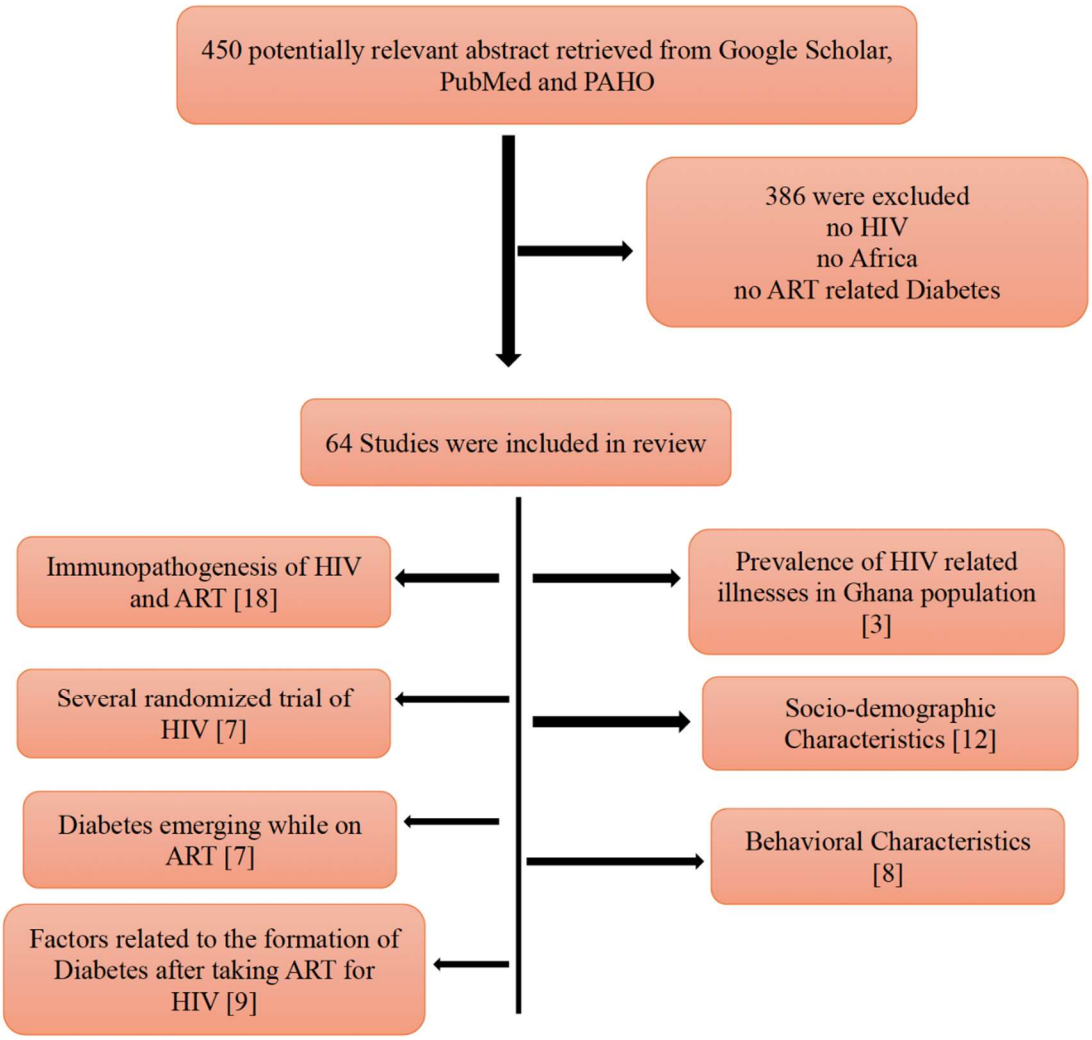

FIGURE 1: DISTRIBUTION OF RESEARCH TOPICS OF NARRATIVE REVIEW

The evaluation included 60 research manuscripts conducted in various regions of Ghana, which were categorized based on a public health study analogy. All the reviews including demographic information, HIV details, adherence to care and treatment, lifestyle and risk behaviors, sexually transmitted infection/diseases risk assessment, diet/nutrition, physical activity, and diabetes history was used for evaluation. Only studies covered with inclusion criteria were included in the review.

LITERATURE REVIEW

Immunopathogenesis of HIV and the Impact of ART

The immunopathogenesis of HIV involves complex interactions that progressively weaken the immune system, laying the groundwork for the opportunistic infections and cancers that characterize AIDS. HIV targets CD4+ T cells—central coordinators of immune response—and directly leads to their destruction, a primary driver of immune system dysfunction [24]. The virus induces chronic immune activation and inflammation, both of which lead to immune cell exhaustion, impaired cytokine production, and overall immune dysregulation [46]. This chronic inflammation is associated with the development of secondary health conditions in people living with HIV (PLHIV), including cardiovascular disease, liver and kidney damage, neurological disorders, and an increased risk of cancer [13].

Chronic immune activation is a hallmark of HIV infection, resulting in persistent inflammation and immune cell depletion [38]. Biomarkers of immune activation and inflammation, such as Interleukin-6 (IL-6), soluble Cluster

of Differentiation 14 (sCD14), soluble Cluster of Differentiation 163 (sCD163), D-dimer, and soluble tumor necrosis factor (TNF) receptors 1 and 2, are often associated with the development and progression of HIV-related comorbidities [7]. Chronic immune activation contributes to tissue damage across multiple organs, particularly the cardiovascular system, liver, kidneys, and central nervous system. This ongoing inflammation also accelerates immune system exhaustion, impairing the body's ability to respond to infections effectively [5, 18].

HIV disrupts immune homeostasis, creating an imbalance between immune activation and regulation [24]. The virus establishes latent reservoirs within various tissues, including gut-associated lymphoid tissue (GALT), which leads to further systemic inflammation and immune activation [63]. Damage to GALT promotes bacterial translocation and amplifies systemic immune activation, further depleting immune resources and contributing to the persistence of HIV in the body [59]. The formation of these reservoirs remains a major barrier to complete viral eradication and long-term immune recovery [16].

Antiretroviral therapy (ART) aims to suppress viral replication, reducing viral load to undetectable levels, typically fewer than 20 or 50 copies/mL [56]. This viral suppression minimizes further immune damage and lowers the risk of developing both AIDS-related and non-AIDS-related conditions [43]. By effectively controlling HIV replication, ART reduces immune activation and inflammation, helping to slow the progression of immune dysfunction in PLHIV [36]. However, while ART helps manage these pathogenic effects, it does not fully restore immune function or eliminate HIV reservoirs [5].

Although ART has transformed HIV into a manageable chronic condition, prolonged use is associated with adverse metabolic effects and organ-specific risks [62]. Metabolic complications include mitochondrial toxicity, dyslipidemia, insulin resistance, and lipodystrophy, all of which increase the risk of diabetes (Type 2), cardiovascular disease, and other comorbidities [39]. Long-term ART use can also impact liver and kidney function, necessitating careful monitoring and management to minimize potential adverse effects [55].

Several randomized trials of ART

Multi-Month Dispensing (MMD) is a model in HIV care that allows stable patients who have successfully suppressed their viral load after at least a year of therapy to receive several months' worth of medication at once, reducing the need for frequent clinic visits [10]. This approach has gained traction, particularly in sub-Saharan Africa, where healthcare resources are limited, and there are significant logistical barriers to regular access [15]. Observational studies in this region suggest MMD has improved clinical outcomes, though the quality of evidence is limited due to selection bias. Additionally, initial findings from adherence groups in South Africa show promise for MMD in supporting viral suppression and reducing the burden on patients and clinics. However, large-scale trials to establish optimal scheduling and intervals for MMD are still limited [29].

MMD has demonstrated various benefits, including fewer clinic visits, better treatment adherence, cost savings for patients, and improved autonomy [26]. On the other hand, the model requires careful management to avoid stockouts and risks due to less frequent patient monitoring [30]. In terms of ART medications, drugs such as Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and certain protease inhibitors (PIs) are associated with adverse metabolic effects, including lipodystrophy and mitochondrial toxicity, which can increase the risk of diabetes (Type 2) [35]. However, newer PIs- atazanavir and darunavir, along with Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) like Efavirenz, show minimal impact on glucose metabolism, although ART regimens contribute to increases in body weight, BMI, and fat distribution [28].

Diabetes emerging while on ART

Higher glucose levels in HIV patients on ART can be attributed to pancreatic beta-cell lipotoxicity, which is caused by drug-induced factors, lipodystrophy-related factors, or a combination of both [39]. In terms of blood glucose regulation, insulin activates insulin receptors on cell surfaces to stimulate glucose absorption [34]. This leads to the phosphorylation of important cell substrates, resulting in the movement of glucose transporter 4 (GLUT4) from the cytosol to the cell surface, facilitating glucose entry into the cell [37]. However, insulin resistance can occur at various points along this pathway, inhibiting insulin activity. Protease inhibitors (PIs), a type of medication commonly used in antiretroviral therapy, such as Atazanavir, Darunavir, Saquinavir, and Ritonavir, have been found to increase insulin resistance, particularly early PIs like indinavir [28]. These PIs can impede the movement of GLUT4 from the cell cytoplasm to the surface and also affect adipocyte differentiation, which plays a role in insulin sensitivity [37]. Interestingly, studies have shown correlations between leptin, blood

lipids, obesity, and insulin resistance in individuals without HIV, suggesting a potential link between these factors and insulin sensitivity in PLWHIV on ART [37,9].

Factors relating to the formation of diabetes after taking ART for HIV

Long-term untreated HIV can result in significant non-AIDS-related health issues and clinical complications, often leading to inflammation and immune system dysfunction [68]. Initiating antiretroviral therapy (ART) early, particularly within the initial days or weeks, has been linked to a reduction in latently infected cells [60]. The effectiveness of ART has redefined HIV as a chronic condition, shifting the focus from acute treatment to long-term management, which requires healthcare professionals to be adept in handling comorbidities, preventing cardiovascular diseases, and administering ART [11].

Certain antiretroviral medications, notably nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs), can adversely impact glucose metabolism, resulting in mitochondrial toxicity and conditions such as lipodystrophy [41]. The chronic nature of HIV infection can induce inflammation that disrupts glucose metabolism and leads to insulin resistance [53]. Additionally, ART may alter body fat distribution and contribute to lipodystrophy, which is associated with an increased risk of diabetes (Type 2) [39]. Individuals with pre-existing diabetes risk factors, including family history, obesity, or metabolic syndrome, are more susceptible to developing diabetes (Type 2) while on ART [47]. Furthermore, older age and extended ART use correlate with a heightened diabetes (Type 2) risk, while HIV itself may exacerbate insulin resistance [51]. Lifestyle choices, such as poor nutrition and insufficient physical activity, can further intensify the metabolic side effects of ART, making it essential to address these factors for effective diabetes (Type 2) prevention and management in HIV-positive individuals [66].

Association between socio-demographic and behavioral characteristics and prevalence of diabetes (Type 2) among HIV patients receiving ART in Ghana

Prevalence of HIV-related illnesses in Ghana populations

In 2020, Ghana reported 346,120 individuals living with HIV, 19,267 new infections, and 11,797 AIDS-related deaths, with the western region contributing 7.37% of the total population and 25,620 HIV-positive individuals. Despite free antiretroviral medication availability, challenges persist in achieving viral suppression, with Ghana aiming for a 90-90-90 goal of 64% awareness, 96% treatment, and 73% viral suppression [12]. Studies suggest Ghana's HIV prevalence is approximately 2.14%, listing HIV as a top 10 leading cause of death, although recent years have seen a decline in general adult HIV prevalence [3]. Secondary data from the 2019 National Health Surveillance Survey (NHSS) and 2014 Ghana Demographic and Health Survey (DHS), focusing on pregnant women and evaluating health programs, aimed to monitor key health indicators through questionnaire-based interviews with 347,555 respondents aged 18-59 years [2].

Socio-demographic characteristics

Studies show that social support significantly improves the quality of life for people living with HIV/AIDS in disadvantaged regions like Ghana, though its impact has been underexplored [1, 40]. Men benefit more from support groups despite lower participation, as men often hesitate to seek help [22]. Younger men with higher STD knowledge and older men with more HIV-related stigma are less likely to use condoms for oral sex [49]. Women experience heightened HIV-related stigma and have higher waist circumferences than HIV-negative individuals when diabetic [8, 54]. High baseline body weights (>70 kg) are linked to greater diabetes risk among HIV patients on ART [48]. Education plays a critical role in shaping HIV perceptions, particularly by reducing stigma through informed understanding, while employment positively impacts self-esteem, though stigma concerns persist for HIV-positive women [4]. Migration and poverty exacerbate the challenges, particularly for women and children [31, 13]. High rates of pre-diabetes and diabetes among HIV-positive Ghanaians highlight the need for metabolic disorder management despite ART advances [58, 64].

Behavioral Characteristics and HIV Care in Ghana

As the HIV-infected population ages, chronic conditions like diabetes (Type 2) and hypertension become more prevalent, contributing to morbidity and mortality [44]. Tensions between traditional and orthodox healthcare systems in Ghana hinder effective care [52]. Men who have sex with men (MSM) in Ghana face high HIV infection rates, and social stigma exacerbates discrimination against HIV-positive individuals [49]. Gender norms act as barriers to reproductive healthcare and HIV transmission prevention. Engagement in HIV care among MSM is crucial for improving outcomes, though many HIV-positive individuals struggle with glycemic control (the maintenance of appropriate levels of blood sugar, measured through the self-monitoring of blood glucose)

[21] despite antiretroviral therapy (ART) [61]. Cognitive behavioral therapy (CBT) has shown promise in reducing depression and improving viral load suppression [57]. Additionally, longer lifespans and the emergence of non-AIDS comorbidities, like diabetes and hypertension, pose challenges to ART adherence [40]. Public insurance barriers also impact medication access, complicating adherence and intervention evaluation [44].

DISCUSSION

The findings of this study highlight the complex interplay between HIV treatment and the emergence of comorbidities like diabetes among individuals living with HIV (PLHIV) in Ghana. As HIV-positive individuals age and ART becomes more effective in suppressing viral replication, the focus of care is shifting from acute treatment to managing long-term health outcomes, particularly the increasing prevalence of non-AIDS-related conditions such as diabetes, hypertension, and cardiovascular disease.

The immunopathogenesis of HIV involves chronic immune activation and inflammation, which not only contributes to immune dysfunction but also accelerates the development of secondary health conditions. ART has been transformative in managing HIV, reducing viral loads, and preventing AIDS-related deaths. However, the metabolic side effects of ART, with antiretroviral medications, remain a significant challenge. Nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) can lead to insulin resistance, dyslipidemia, and lipodystrophy, contributing to an increased risk of diabetes (Type 2). These metabolic complications are compounded by lifestyle factors, such as poor diet and insufficient physical activity, as well as socio-demographic factors including obesity, age, and pre-existing diabetes risk factors like family history.

Despite ART's ability to suppress HIV replication, it does not fully restore immune function or eliminate latent HIV reservoirs, contributing to ongoing inflammation and immune system dysfunction. This chronic immune activation is linked to various comorbidities, which may be worsened by ART itself. The relationship between HIV-related inflammation and diabetes (Type 2) is an evident, as insulin resistance and lipotoxicity are often observed in PLHIV on ART.

Social and behavioral factors also play a significant role in the health outcomes of HIV-positive individuals. Social support networks were found to improve the quality of life for PLHIV in Ghana, though their role in diabetes prevention has been underexplored. Stigma remains a significant barrier to accessing care, for men who have sex with men (MSM) and women, who experience higher levels of HIV-related stigma. Moreover, younger men with better knowledge of sexually transmitted diseases (STDs) and older men with higher levels of HIV-related stigma tend to engage in risky sexual behaviors. Educational interventions that reduce stigma and increase awareness of HIV transmission could improve prevention and treatment outcomes, particularly in addressing comorbidities such as diabetes.

While multi-month dispensing (MMD) of ART has shown potential in improving adherence and reducing the burden on healthcare systems, particularly in sub-Saharan Africa, more research is needed to establish the optimal schedules and intervals for this approach. MMD offers benefits like clinic visits, better treatment adherence, and reduced healthcare costs, but it also requires careful management to prevent medication stockouts and ensure patient safety.

The high prevalence of pre-diabetes and diabetes among HIV-positive individuals in Ghana highlights the need for integrated care models that address both HIV and metabolic comorbidities. Interventions focusing on early identification and management of diabetes risk factors, along with comprehensive health education and access to care, could significantly improve health outcomes. Additionally, policy efforts to improve access to healthcare services, reduce stigma, and support lifestyle changes are essential to addressing the growing burden of diabetes among PLHIV in Ghana.

In conclusion, while ART has made significant strides in managing HIV, the emergence of diabetes and other non-AIDS comorbidities poses a substantial challenge. Addressing the metabolic side effects of ART, enhancing social support systems, reducing stigma, and promoting healthy behaviors are key strategies for improving the long-term health outcomes of PLHIV in Ghana.

Strengths and weaknesses of the study

In the fight against the infection, our study's practical conclusions can help HIV clinicians and policymakers. However, this review is narrative, and narrative reviews have several drawbacks. Because the literature review

was not completely documented, it cannot be replicated, and the inclusion of the research could have been influenced by personal preferences. Additionally, stigma and discrimination surrounding HIV/AIDS are sensitive issues, finding a real report of this circumstance creates prejudice. A difficulty to the completeness of the data was that we depended on publicly available hospital data, community-based data, articles particularly those reporting patient viral load results.

CONCLUSION

In Ghana, addressing the significant public health concern of the HIV epidemic requires effective strategies to enhance diabetic screening for HIV patients. Various approaches can be implemented to ensure widespread coverage and effective implementation of diabetic screening programs. Integrating diabetic screening into existing HIV care and treatment programs can improve efficiency and ensure comprehensive care for both HIV and diabetes management. Strengthening healthcare provider training on diabetic screening and management is crucial for effective identification and management of diabetes (Type 2) in HIV patients. Community-based initiatives involving health workers and peer educators can raise awareness and provide support for individuals testing positive for diabetes (Type 2) among HIV patients. Leveraging technology and telemedicine can improve access to diabetic screening for HIV patients in remote or underserved areas, overcoming geographical barriers and ensuring equal access to screening services. Overall, it is essential for HIV patients receiving ART in Ghana to be aware of the importance of diabetic screening and management.

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