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Metabolic Dysfunction and Cardiovascular Risk in Aging Populations with Chronic HIV Infection

Nasira A. Sitar

Department of Pharmacy Kampala International University Uganda
Satar.nasira@studwc.kiu.ac.ug

ABSTRACT

Advances in antiretroviral therapy transformed HIV infection into a chronic condition, resulting in a rapidly growing population of older adults living with HIV who experience a disproportionate burden of metabolic and cardiovascular comorbidities. This review examined the biological mechanisms, clinical manifestations, and therapeutic implications of metabolic dysfunction and cardiovascular risk among aging populations with chronic HIV infection. A narrative and critical review of peer-reviewed literature was conducted, synthesizing epidemiological, clinical, and mechanistic studies relevant to HIV-associated metabolic and cardiovascular disease. Persistent immune activation, chronic inflammation, antiretroviral therapy–related metabolic effects, and age-related physiological changes synergistically contributed to insulin resistance, dyslipidemia, visceral adiposity, and accelerated atherosclerosis in older adults with HIV. These abnormalities significantly elevate cardiovascular risk, often exceeding that observed in HIV-negative populations of similar age. Conventional cardiovascular risk prediction tools frequently underestimate risk in this population, complicating clinical management. Metabolic dysfunction and cardiovascular disease represented major determinants of morbidity and mortality in aging individuals with chronic HIV infection, necessitating integrated, mechanism-informed prevention and management strategies tailored to this population.

Keywords: HIV aging, Metabolic dysfunction, Cardiovascular risk, Antiretroviral therapy, Chronic inflammation.

INTRODUCTION

The widespread availability of effective antiretroviral therapy has dramatically improved survival among people living with HIV, shifting the disease trajectory from acute fatality to chronic long-term management [1, 2]. As a result, the global HIV population is aging, with an increasing proportion of individuals over the age of fifty years. This demographic transition has been accompanied by a rising prevalence of non-communicable diseases, particularly metabolic disorders and cardiovascular disease, which now constitute the leading causes of morbidity and mortality in this population. Metabolic dysfunction, including insulin resistance, dyslipidemia, altered body fat distribution, and mitochondrial impairment, has emerged as a critical driver of cardiovascular risk among older adults with chronic HIV infection [3].

Despite sustained viral suppression, individuals living with HIV experience persistent immune activation and low-grade systemic inflammation that resembles accelerated biological aging [4, 5]. These processes interact with traditional cardiovascular risk factors and age-related physiological decline, amplifying cardiometabolic vulnerability. Importantly, the burden of cardiovascular disease in this population often exceeds that observed in HIV-negative individuals [6], even after adjustment for conventional risk determinants. This disparity highlights critical gaps in current risk assessment models and preventive strategies. This review explores the

pathophysiological mechanisms underlying metabolic dysfunction in chronic HIV infection, examines the complex interaction between aging and cardiometabolic regulation, and analyzes cardiovascular risk profiles specific to older adults living with HIV. It further evaluates the long-term metabolic and cardiovascular effects of antiretroviral therapy and discusses emerging clinical and public health implications. The purpose of this review is to synthesize current evidence to inform more effective, integrated approaches to cardiovascular risk reduction in aging populations with chronic HIV infection.

Pathophysiology of Metabolic Dysfunction in Chronic HIV Infection

Metabolic dysfunction in individuals with chronic HIV infection arises from a convergence of viral, host, and treatment-related factors that disrupt normal biochemical homeostasis [7]. Even in the context of effective viral suppression, persistent immune activation remains a defining feature of HIV infection. This chronic inflammatory state is characterized by elevated pro-inflammatory cytokines, altered adipokine signaling, and sustained oxidative stress, all of which interfere with insulin signaling pathways and lipid metabolism.

Mitochondrial dysfunction plays a central role in HIV-associated metabolic abnormalities [8, 9]. Both HIV proteins and certain antiretroviral agents impair mitochondrial DNA replication and oxidative phosphorylation, leading to reduced energy efficiency and increased reactive oxygen species generation. These alterations contribute to insulin resistance and dyslipidemia while promoting ectopic lipid deposition in visceral adipose tissue and skeletal muscle.

Additionally, HIV infection alters adipose tissue biology, resulting in abnormal fat redistribution and impaired adipocyte differentiation [10]. Visceral adiposity, in particular, is strongly associated with systemic inflammation and adverse cardiometabolic outcomes. Collectively, these mechanisms establish a biochemical environment conducive to metabolic dysfunction, laying the foundation for accelerated cardiovascular disease in aging populations with chronic HIV infection.

Aging, HIV, and Altered Cardiometabolic Homeostasis

Aging is intrinsically associated with progressive metabolic and cardiovascular changes, including reduced insulin sensitivity, endothelial dysfunction, and altered lipid handling [11, 12]. In individuals with chronic HIV infection, these age-related processes are markedly intensified through mechanisms often described as immunosenescence and inflammaging. Persistent immune dysregulation accelerates biological aging, resulting in earlier onset and increased severity of metabolic disorders.

The interaction between HIV-related inflammation and age-associated hormonal changes further disrupts glucose and lipid metabolism. Declining anabolic hormone levels, combined with chronic cytokine exposure, exacerbate sarcopenia and visceral fat accumulation [13]. These changes impair metabolic flexibility and promote a pro-atherogenic lipid profile.

Furthermore, aging individuals with HIV often experience cumulative exposure to metabolic stressors, including long-term antiretroviral therapy and lifestyle-related risk factors [14]. The convergence of these influences results in a distinct cardiometabolic phenotype characterized by heightened vulnerability to cardiovascular disease. Understanding this interaction is essential for developing age-appropriate prevention and management strategies tailored to people living with HIV.

Cardiovascular Risk Profiles in Older Adults Living with HIV

Cardiovascular disease risk among older adults living with HIV is shaped by both traditional and HIV-specific determinants [15]. Epidemiological studies consistently demonstrate increased rates of myocardial infarction, stroke, and subclinical atherosclerosis in this population compared with HIV-negative counterparts. Endothelial dysfunction, arterial stiffness, and accelerated plaque formation are frequently observed, reflecting the cumulative impact of metabolic and inflammatory insults.

Standard cardiovascular risk assessment tools often underestimate risk in individuals with HIV, as they do not adequately account for chronic inflammation, immune activation, or antiretroviral exposure [16]. This limitation poses significant challenges for early detection and preventive intervention. Moreover, comorbid conditions such as chronic kidney disease and hepatic dysfunction further complicate cardiovascular risk stratification.

Sex-specific differences, socioeconomic factors, and disparities in access to healthcare also influence cardiovascular outcomes among aging populations with HIV, particularly in low- and middle-income settings. These complexities underscore the need for HIV-specific cardiovascular risk models and individualized clinical decision-making.

Impact of Antiretroviral Therapy on Metabolic and Cardiovascular Outcomes

Antiretroviral therapy has been instrumental in prolonging life expectancy among people living with HIV; however, its long-term metabolic consequences remain a critical concern. Earlier antiretroviral regimens were strongly associated with insulin resistance, dyslipidemia, and lipodystrophy [17]. Although newer agents exhibit improved metabolic profiles, long-term exposure continues to influence cardiometabolic risk.

Different antiretroviral drug classes exert distinct effects on lipid metabolism, glucose homeostasis, and body fat distribution. Protease inhibitors and some nucleoside reverse transcriptase inhibitors have been linked to adverse metabolic outcomes [18], whereas integrase strand transfer inhibitors present emerging concerns regarding weight

gain and adiposity. These effects are particularly pronounced in aging individuals, who may have reduced metabolic reserve.

Optimizing antiretroviral therapy requires careful consideration of metabolic and cardiovascular risk, especially in older adults [19]. Regimen selection should balance virologic efficacy with long-term cardiometabolic safety, emphasizing individualized treatment strategies informed by biochemical and clinical monitoring.

Clinical and Public Health Implications

The growing burden of metabolic dysfunction and cardiovascular disease among aging populations with chronic HIV infection has significant clinical and public health implications. Integrated care models that combine HIV management with cardiometabolic risk assessment are essential for improving long-term outcomes [20]. Early screening for metabolic abnormalities, lifestyle interventions, and appropriate pharmacologic therapy should be incorporated into routine HIV care.

At the public health level, aging populations with HIV represent an emerging priority, particularly in resource-limited settings where healthcare systems are often ill-equipped to manage complex chronic comorbidities. Strengthening healthcare infrastructure, improving access to preventive services, and developing context-specific guidelines are critical steps toward mitigating cardiovascular risk in this vulnerable population.

CONCLUSION

Aging populations with chronic HIV infection face a unique and escalating burden of metabolic dysfunction and cardiovascular disease that extends beyond traditional risk paradigms. Persistent immune activation, chronic inflammation, mitochondrial impairment, and long-term antiretroviral therapy collectively disrupt metabolic homeostasis and accelerate cardiovascular pathology. These mechanisms interact synergistically with age-related physiological changes, resulting in heightened vulnerability to insulin resistance, dyslipidemia, visceral adiposity, and atherosclerotic disease. Evidence consistently demonstrates that conventional cardiovascular risk assessment tools inadequately capture this complex risk profile, underscoring the need for HIV-specific approaches to prevention and management. Addressing cardiometabolic risk in older adults living with HIV requires a comprehensive strategy that integrates mechanistic understanding with clinical vigilance and public health planning. Such an approach must prioritize early detection, individualized antiretroviral therapy selection, and coordinated management of metabolic and cardiovascular comorbidities across the lifespan. Future clinical guidelines should incorporate HIV-specific cardiovascular risk stratification models to optimize prevention and improve long-term outcomes in aging populations with chronic HIV infection.

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