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Antiretroviral Therapy-Induced Metabolic Alterations and Risk of Type 2 Diabetes in People Living With HIV

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ABSTRACT

Antiretroviral therapy has transformed HIV from a fatal disease into a manageable chronic condition. However, metabolic complications, including insulin resistance, dyslipidemia, and type 2 diabetes mellitus (T2DM) have emerged as major concerns in long-term management of people living with HIV (PLWH). Global prevalence estimates suggest that up to 15–20% of PLWH develop T2DM during chronic therapy, a rate significantly higher than in HIV-uninfected populations. This review examined the mechanisms, risk factors, and clinical consequences of antiretroviral therapy–associated metabolic alterations contributing to T2DM in PLWH. This review synthesized peer-reviewed studies from PubMed, Scopus, and Web of Science, focusing on clinical, molecular, and pharmacokinetic reports published between 2010 and 2025. Protease inhibitors and certain nucleoside reverse transcriptase inhibitors alter glucose transporter function, mitochondrial energetics, and adipokine signaling, producing insulin resistance. Chronic immune activation and adipose tissue inflammation further amplify metabolic risk. Host factors, including age, sex, ethnicity, and pre-existing obesity, interact with therapy-specific pharmacokinetics to increase susceptibility. Quantitative data indicate that protease inhibitor exposure increases diabetes incidence by approximately 1.5–2.0-fold, while integrase inhibitor regimens confer a lower but significant risk. Antiretroviral therapy remains essential but carries a measurable risk of T2DM mediated by drug-specific and host-related mechanisms. Integrative management strategies, including risk stratification, lifestyle modification, and pharmacovigilance, are needed.

Keywords: Antiretroviral therapy, HIV, Type 2 diabetes, Metabolic alterations, Insulin resistance.

INTRODUCTION

The advent of antiretroviral therapy (ART) has transformed the prognosis of HIV infection, reduced mortality and extended life expectancy to near-normal levels for many individuals. As of 2023, more than 29 million people worldwide were receiving ART, with coverage particularly high in sub-Saharan Africa [1]. Despite this progress, the clinical management of HIV has become increasingly complicated by chronic comorbidities, including cardiovascular disease, liver disease, and metabolic disorders. Type 2 diabetes mellitus (T2DM) is among the most significant of these comorbidities, with major implications for morbidity and health system costs. A recent study estimated that the financial burden of HIV/AIDS management in East Africa has risen sharply, with non-communicable disease complications accounting for nearly 20% of long-term care expenditures [2].

Epidemiological evidence demonstrates that PLWH on ART are disproportionately affected by T2DM. Meta-analyses indicate prevalence rates of 8–15% depending on regimen and geography, compared with approximately 6–8% in the general population [3]. A large cohort analysis reported that ART exposure increased the risk of T2DM by 1.7-fold relative to HIV-negative controls [4]. Mechanistic explanations implicate drug-induced insulin resistance, mitochondrial dysfunction, and chronic immune activation [5-7]. This review aims to provide a

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comprehensive synthesis of evidence on ART-induced metabolic alterations and their contribution to T2DM risk in PLWH. Following this introduction, Section 1 evaluates molecular and cellular mechanisms linking specific antiretroviral agents to glucose dysregulation. Section 2 discusses host and environmental risk factors that modulate susceptibility. Section 3 presents pharmacokinetic and clinical trial data quantifying incidence and relative risks across therapeutic classes. Section 4 addresses the pathophysiological role of immune activation and adipose tissue dysfunction. Section 5 evaluates the clinical impact of T2DM in HIV populations. Section 6 explores current strategies for monitoring and mitigating metabolic risk, while Section 7 outlines future directions and clinical implications. The purpose of this review is to integrate mechanistic and clinical evidence to inform therapeutic decision-making and guide research priorities.

Antiretroviral Therapy and Molecular Mechanisms of Metabolic Alterations

i. **Protease Inhibitors and Glucose Transporter Dysfunction:** Protease inhibitors (PIs) such as indinavir and lopinavir were among the first agents associated with marked metabolic toxicity. In vitro studies demonstrated that indinavir directly inhibits GLUT4-mediated glucose uptake in adipocytes and skeletal muscle, resulting in acute insulin resistance within hours of exposure [8]. Clinical pharmacokinetic studies report that indinavir-treated patients exhibit a 25–30% reduction in insulin sensitivity measured by hyperinsulinemic-euglycemic clamp [9]. PIs also increase hepatic gluconeogenesis through altered AKT signaling, compounding hyperglycemia [10].

ii. **Nucleoside Reverse Transcriptase Inhibitors and Mitochondrial Toxicity:** Older nucleoside reverse transcriptase inhibitors (NRTIs), particularly stavudine and didanosine, are linked with mitochondrial DNA polymerase-γ inhibition, leading to mitochondrial depletion, oxidative stress, and reduced ATP generation [11]. These alterations impair insulin signaling and promote lipodystrophy. Patients on stavudine regimens exhibit a 2.3-fold higher incidence of diabetes relative to tenofovir-based therapies [12].

iii. **Integrase and Non-Nucleoside Reverse Transcriptase Inhibitors:** Integrase strand transfer inhibitors (INSTIs) such as dolutegravir have been associated with weight gain and incident diabetes. Data from longitudinal cohorts show mean weight increases of 5–6 kg after 96 weeks of dolutegravir therapy [13]. Although the exact mechanisms remain unclear, alterations in adipocyte differentiation and central appetite regulation have been proposed [14]. In contrast, non-nucleoside reverse transcriptase inhibitors (NNRTIs) display a relatively favorable metabolic profile, though efavirenz may induce hepatic cytochrome P450-mediated lipid perturbations [15].

Host and Environmental Risk Factors

i. **Demographic Influences:** Age is a strong determinant of ART-associated diabetes risk. Patients over 50 years have double the incidence compared with younger cohorts [16]. Sex differences are also observed, with women demonstrating greater susceptibility to weight gain on INSTI regimens [17]. Ethnic variation is notable; African and Hispanic populations show higher rates of ART-associated T2DM compared to European cohorts [18].

ii. **Obesity and Lifestyle:** Pre-existing obesity amplifies ART-related risk. In a Ugandan cohort, patients with baseline body mass index (BMI) >30 kg/m² had a 3.1-fold increased likelihood of incident diabetes when treated with PIs [19]. Sedentary lifestyle, dietary changes, and urbanization further exacerbate metabolic vulnerability [20].

iii. **Genetic Predisposition:** Variants in genes encoding adipokines and glucose transporters have been implicated. A study of South African PLWH identified polymorphisms in SLC2A4 (GLUT4) that conferred heightened susceptibility to PI-induced insulin resistance [21].

Clinical and Pharmacokinetic Evidence

i. **Incidence and Relative Risk Estimates:** Prospective cohort analyses demonstrate consistent associations between ART and T2DM. A French cohort reported incidence rates of 14.1 per 1000 person-years in PI-treated patients versus 7.9 per 1000 in non-PI regimens [22]. In North American studies, dolutegravir exposure was linked with a 1.3-fold increased hazard of diabetes [23].

ii. **Pharmacokinetic Parameters:** Drug concentration profiles influence metabolic risk. For instance, high trough levels of lopinavir/ritonavir (Cmin >5 mg/L) correlate with greater insulin resistance [24]. Similarly, stavudine's mitochondrial toxicity shows dose-dependence, with higher cumulative exposure producing more severe glucose intolerance [25].

iii. **Combination Effects:** Combination regimens often produce additive effects. Patients on PI plus thymidine analogue NRTIs demonstrate the highest risk, with hazard ratios exceeding 2.0 for incident diabetes compared with integrase-based therapies [26].

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Immune Activation and Adipose Tissue Dysfunction

Chronic HIV infection, even under viral suppression, is characterized by persistent immune activation. Elevated cytokines such as TNF-α and IL-6 impair insulin receptor signaling and promote hepatic gluconeogenesis [27]. Adipose tissue biopsy studies reveal macrophage infiltration and reduced adiponectin levels in PLWH, correlating with insulin resistance indices [28]. Bone marrow alterations also contribute indirectly to systemic metabolic imbalance through dysregulated erythropoiesis and altered energy demands [29]. These inflammatory processes interact with ART-induced mitochondrial and transporter defects, amplifying diabetes risk.

Clinical Impact of Diabetes in HIV Populations

The coexistence of T2DM and HIV compounds risks for cardiovascular disease, renal impairment, and neuropathy. Data from the D: A:D cohort demonstrate that PLWH with diabetes have a 1.9-fold higher risk of myocardial infarction compared to non-diabetic counterparts [30]. Furthermore, T2DM complicates ART adherence and efficacy, as polypharmacy and pill burden reduce treatment consistency [31]. The psychosocial impact is significant, with patients reporting reduced quality of life and increased financial strain, particularly in resource-limited settings [2,32].

Strategies for Monitoring and Mitigating Risk

i. **Screening and Early Detection:** Routine screening for fasting plasma glucose and HbA1c is recommended for all ART-exposed individuals. However, HbA1c underestimates glycemia in PLWH due to altered erythrocyte turnover; thus, oral glucose tolerance testing is more reliable [33].
ii. **Lifestyle and Behavioral Interventions:** Structured patient education and lifestyle counseling have demonstrated efficacy in reducing incidence. A trial in Nigeria showed a 30% reduction in new-onset diabetes with diet and exercise interventions integrated into HIV clinics. Sustainable self-management approaches, including culturally tailored patient education, are increasingly recognized as essential [34].
iii. **Pharmacologic Interventions:** Switching from high-risk to metabolically favorable regimens is a common strategy. Transition from stavudine to tenofovir has been shown to normalize insulin sensitivity within six months [35]. Pharmacologic prevention with metformin has demonstrated benefits, reducing insulin resistance by 20–25% in high-risk PLWH [36].

Future Directions and Clinical Implications

Future research should address mechanistic gaps, including the precise pathways by which INSTIs induce weight gain and diabetes. Pharmacogenomic studies could identify high-risk individuals and guide personalized therapy. Novel therapeutic approaches targeting adipose inflammation, such as IL-1β antagonists, warrant exploration. Large-scale clinical trials are needed to compare long-term metabolic outcomes across ART classes in diverse global populations.

Clinically, integration of HIV and non-communicable disease management is critical. Task-shifting models, where diabetes screening is embedded into HIV care platforms, may optimize resource use. Health policy frameworks should prioritize surveillance systems to monitor long-term ART toxicity. The ultimate goal is to sustain viral suppression while minimizing the burden of metabolic disease.

CONCLUSION

Antiretroviral therapy has transformed HIV into a chronic condition, but its metabolic complications pose new challenges. Evidence indicates that protease inhibitors, certain nucleoside analogues, and integrase inhibitors alter glucose metabolism through mechanisms including transporter inhibition, mitochondrial toxicity, and adipose tissue dysfunction. Host factors such as age, ethnicity, obesity, and genetic predisposition amplify this risk. Clinical data consistently demonstrate a higher incidence of type 2 diabetes among people living with HIV receiving ART, with significant consequences for cardiovascular and renal health. Screening, lifestyle modification, and strategic regimen selection are essential components of comprehensive management. The key lesson from this synthesis is that the benefits of ART must be balanced with vigilant monitoring of metabolic health. A practical recommendation is that clinicians should incorporate routine diabetes risk assessment and early lifestyle interventions into HIV care protocols for all patients initiating antiretroviral therapy.

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