



<https://doi.org/10.59298/RIJRMS/2026/515061>

Metabolomics Profiling of Antiretroviral Therapy-Associated Metabolic Syndrome in People Living with HIV

Odile Patrick Thalia

Faculty of Biological Sciences Kampala International University Uganda

ABSTRACT

Antiretroviral therapy (ART) has transformed HIV infection into a manageable chronic condition, yet metabolic syndrome (MetS) emerged as a critical comorbidity in people living with HIV (PLHIV), affecting 20–54% of this population compared to 10–25% in the general population. The complex interplay between viral pathogenesis, immune dysregulation, chronic inflammation, and drug-induced metabolic perturbations necessitates advanced molecular profiling to elucidate underlying mechanisms and identify therapeutic targets. This narrative review critically examined the application of metabolomics in characterizing ART-associated MetS, focusing on mechanistic insights, biomarker discovery, and clinical translation. A comprehensive literature search was conducted using PubMed, Embase, and Web of Science databases (2015–2025), prioritizing metabolomics studies, clinical trials, and mechanistic investigations. Current evidence demonstrated profound alterations in lipid metabolism, particularly increased ceramides, diacylglycerols, and altered sphingolipid profiles, alongside perturbations in branched-chain amino acid catabolism, tricarboxylic acid cycle intermediates, and bile acid homeostasis. Integrase strand transfer inhibitors and protease inhibitors exhibit distinct metabolomic signatures, with the former associated with weight gain through alterations in hypothalamic neuropeptide regulation and adipogenesis pathways. Despite significant advances, metabolomics-guided personalized ART selection remained limited by small cohort sizes, heterogeneous analytical platforms, and insufficient longitudinal validation. Future research must prioritize standardized multi-omics integration, mechanistic validation studies, and biomarker-driven clinical trials to translate metabolomic discoveries into precision medicine approaches that mitigate metabolic complications while maintaining virological efficacy in PLHIV.

Keywords: HIV metabolomics, Antiretroviral therapy, Metabolic syndrome, Lipidomics, Precision medicine.

INTRODUCTION

The advent of combination antiretroviral therapy has fundamentally altered the HIV epidemic, enabling viral suppression and near-normal life expectancy for most people living with HIV in resource-adequate settings [1, 2]. Current global estimates indicate approximately 38 million PLHIV, with 76% receiving ART as of 2023 [3, 4]. However, this therapeutic success has unveiled a new clinical challenge: a disproportionately high prevalence of metabolic syndrome, characterized by central obesity, insulin resistance, dyslipidemia, and hypertension. MetS affects 20–54% of PLHIV compared to 10–25% of age-matched HIV-negative populations, contributing substantially to cardiovascular disease risk, which is elevated 1.5- to 2-fold in treated HIV infection [5]. The pathogenesis of ART-associated MetS represents a convergence of multiple factors: persistent immune activation despite virological suppression, mitochondrial toxicity from nucleoside reverse transcriptase inhibitors, lipodystrophy syndromes, direct drug effects on adipocyte differentiation and insulin signaling, and traditional risk factors amplified by chronic inflammation [6]. Metabolomics, the comprehensive analysis of small-molecule metabolites in biological systems, has emerged as a powerful tool to dissect these complex metabolic perturbations at the molecular level [7]. By providing unbiased snapshots of biochemical pathway activity, metabolomics offers mechanistic insights beyond conventional clinical markers, potentially identifying novel biomarkers for early detection, risk stratification, and therapeutic monitoring. The objective of this review is to critically evaluate current metabolomics evidence characterizing ART-associated metabolic syndrome in PLHIV, examine mechanistic insights into drug-specific metabolic perturbations, assess the translational potential of identified biomarkers, and

identify critical research gaps that must be addressed to advance precision medicine approaches in this vulnerable population.

METHODOLOGY

A comprehensive narrative review was conducted by systematically searching PubMed/Medline, Embase, and Web of Science databases for English-language articles published between January 2015 and March 2025. The search strategy combined controlled vocabulary and free-text terms including "HIV," "antiretroviral therapy," "metabolomics," "lipidomics," "metabolic syndrome," "insulin resistance," "dyslipidemia," and specific ART drug classes. Inclusion criteria encompassed: (1) original research articles employing targeted or untargeted metabolomics approaches in PLHIV receiving ART; (2) studies investigating metabolic syndrome components or related cardiometabolic outcomes; (3) mechanistic studies elucidating biochemical pathways affected by specific antiretroviral agents; (4) systematic reviews and meta-analyses of metabolic complications in HIV; and (5) landmark clinical trials reporting metabolic safety data. Exclusion criteria included case reports, conference abstracts without full manuscripts, and studies lacking metabolite-level data. Prioritization was given to high-quality metabolomics investigations utilizing mass spectrometry or nuclear magnetic resonance platforms with appropriate sample sizes, validated analytical methods, and robust statistical approaches. Evidence synthesis followed a thematic organization progressing from molecular mechanisms through pathophysiology, diagnostic implications, therapeutic considerations, and future research directions, emphasizing critical appraisal of study quality, consistency across investigations, and clinical relevance of findings.

MOLECULAR AND BIOCHEMICAL MECHANISMS OF ART-ASSOCIATED METABOLIC DYSREGULATION

Lipid Metabolism Perturbations and Lipotoxicity

Metabolomics investigations have consistently identified profound alterations in lipid metabolism as a hallmark of ART-associated MetS [8]. Lipidomics studies employing liquid chromatography-mass spectrometry demonstrate significant accumulation of bioactive lipid species, particularly ceramides, diacylglycerols (DAGs), and specific phospholipid subspecies in PLHIV with metabolic syndrome compared to metabolically healthy HIV-infected individuals. Ceramides, sphingolipid metabolites synthesized through de novo pathways or sphingomyelin hydrolysis, exhibit particularly robust associations with insulin resistance and cardiovascular events. Plasma concentrations of C16:0, C18:0, and C24:1 ceramide species show 30–60% elevations in ART-treated individuals with MetS, correlating inversely with insulin sensitivity indices measured by hyperinsulinemic-euglycemic clamp studies [9]. Mechanistically, ceramide accumulation impairs insulin signaling through multiple pathways: inhibition of protein kinase B (Akt) phosphorylation via protein phosphatase 2A activation, disruption of glucose transporter type 4 (GLUT4) translocation, and induction of inflammatory signaling through toll-like receptor 4 activation. Diacylglycerols similarly accumulate in insulin-resistant tissues, activating protein kinase C isoforms that phosphorylate insulin receptor substrate proteins at inhibitory serine residues, thereby attenuating downstream insulin signaling cascades.

The role of specific ART agents in lipid dysregulation demonstrates drug class-dependent patterns. Protease inhibitors, particularly older agents such as ritonavir and lopinavir, inhibit hepatic cytochrome P450 3A4, leading to altered lipid metabolism and direct effects on adipocyte function [10]. These agents interfere with sterol regulatory element-binding protein (SREBP) processing, glucose transporter expression, and adipocyte differentiation pathways. Contemporary integrase strand transfer inhibitors (INSTIs), while generally demonstrating superior lipid profiles compared to protease inhibitors, exhibit their own metabolic liabilities. Dolutegravir and bictegravir have been associated with weight gain in multiple clinical trials, with metabolomics studies revealing altered fatty acid oxidation, increased lipogenesis markers, and perturbations in acylcarnitine profiles suggesting incomplete mitochondrial beta-oxidation [11]. Accumulation of medium- and long-chain acylcarnitines indicates metabolic inflexibility and mitochondrial dysfunction, contributing to ectopic lipid deposition in liver, skeletal muscle, and pancreatic beta cells.

Branched-Chain Amino Acid Metabolism and Insulin Resistance

Branched-chain amino acids (BCAAs) leucine, isoleucine, and valine and their catabolic intermediates emerge as consistent metabolomic signatures of insulin resistance in both HIV-infected and general populations [12]. Mechanistic studies reveal that chronic inflammation, characteristic of treated HIV infection, suppresses BCKDH activity through enhanced kinase-mediated phosphorylation, thereby reducing enzymatic activity and promoting BCAA accumulation.

Elevated BCAAs contribute to insulin resistance through multiple mechanisms. BCAAs activate mammalian target of rapamycin complex 1 (mTORC1), leading to serine phosphorylation of insulin receptor substrate-1 and subsequent attenuation of insulin signaling [13]. BCAA catabolites, particularly 3-hydroxyisobutyrate, promote endothelial dysfunction and fatty acid uptake into muscle tissue, exacerbating lipotoxicity. Furthermore, BCAAs alter gut microbiome composition, favoring species that enhance BCAA biosynthesis and absorption, creating a positive feedback loop that perpetuates metabolic dysfunction. In PLHIV specifically, the interaction between

persistent immune activation, gut barrier dysfunction due to HIV-associated enteropathy, and BCAA metabolism creates a unique pathophysiological context that amplifies insulin resistance beyond that observed in HIV-negative metabolic syndrome.

Energy Metabolism and Mitochondrial Dysfunction

Metabolomics profiling has illuminated significant perturbations in central energy metabolism pathways in ART-treated PLHIV [13]. Tricarboxylic acid (TCA) cycle intermediates, including citrate, alpha-ketoglutarate, succinate, and malate, demonstrate altered plasma concentrations in individuals with metabolic complications. Elevated succinate and decreased citrate ratios suggest impaired mitochondrial oxidative phosphorylation and a shift toward anaerobic glycolysis, even under normoxic conditions a metabolic phenotype reminiscent of the Warburg effect observed in cancer metabolism [14]. This metabolic reprogramming may represent an adaptive response to chronic mitochondrial stress induced by nucleoside reverse transcriptase inhibitors (NRTIs), which inhibit mitochondrial DNA polymerase gamma, leading to mitochondrial DNA depletion and respiratory chain dysfunction.

The accumulation of lactate and pyruvate, along with altered lactate-to-pyruvate ratios, further supports mitochondrial dysfunction in a subset of ART-treated individuals [15]. Although overt lactic acidosis has become rare with discontinuation of stavudine and didanosine, subclinical mitochondrial impairment persists and contributes to metabolic inflexibility. Acylcarnitine profiling reveals specific patterns indicative of incomplete fatty acid oxidation: accumulation of long-chain acylcarnitines (C14-C18) suggests impaired mitochondrial uptake or beta-oxidation initiation, while medium-chain acylcarnitine accumulation (C6-C12) indicates partial oxidation with bottlenecks at specific enzymatic steps. These metabolic fingerprints correlate with reduced exercise capacity, increased adiposity, and insulin resistance in affected individuals.

Inflammation-Metabolism Axis and Immune Dysregulation

The persistent immune activation characteristic of treated HIV infection, evidenced by elevated inflammatory markers including high-sensitivity C-reactive protein, interleukin-6, and soluble CD14, profoundly influences metabolic homeostasis [16]. Metabolomics studies have identified inflammation-associated metabolite signatures that link immune dysregulation with metabolic syndrome development. Tryptophan catabolism through the kynurenine pathway shows marked activation in PLHIV with MetS, reflected by decreased tryptophan concentrations and elevated kynurenine, kynurenic acid, and quinolinic acid levels [17]. The kynurenine-to-tryptophan ratio, a marker of indoleamine 2,3-dioxygenase (IDO) activity, demonstrates 2- to 3-fold elevations in metabolically compromised individuals, correlating with inflammatory cytokine concentrations and insulin resistance indices.

Kynurenine pathway activation contributes to metabolic dysfunction through multiple mechanisms: quinolinic acid exerts neurotoxic effects and may influence central appetite regulation [18, 19]; kynurenic acid acts as an aryl hydrocarbon receptor ligand, modulating adipogenesis and energy expenditure; and nicotinamide adenine dinucleotide (NAD⁺) depletion resulting from excessive kynurenine pathway flux impairs sirtuin-dependent metabolic regulation and mitochondrial function. Additionally, metabolomics reveals perturbations in other inflammation-linked pathways, including increased bile acid synthesis (elevated cholic acid and chenodeoxycholic acid conjugates), altered polyamine metabolism, and elevated oxidative stress markers such as oxidized glutathione and lipid peroxidation products [20, 21]. These findings emphasize the intricate bidirectional relationships between inflammation and metabolism, where immune activation drives metabolic dysfunction while metabolic perturbations further amplify inflammatory signaling.

DRUG-SPECIFIC METABOLOMIC SIGNATURES AND PATHOPHYSIOLOGICAL IMPLICATIONS

Integrase Strand Transfer Inhibitors and Weight Gain Mechanisms

The introduction of INSTIs, particularly dolutegravir and bictegravir, represented a significant advancement in ART efficacy and tolerability [22, 23]. However, clinical trials and real-world cohort studies have consistently documented greater weight gain with INSTIs compared to other ART classes, with increases of 3–6 kg commonly observed in the first 12–24 months of treatment. Metabolomics investigations have begun elucidating the molecular mechanisms underlying this phenomenon. INSTI-treated individuals demonstrate metabolic profiles indicative of increased lipogenesis, including elevated malonyl-CoA, acetyl-CoA carboxylase activity markers, and decreased carnitine palmitoyltransferase 1 activity, suggesting coordinated suppression of fatty acid oxidation with simultaneous enhancement of de novo lipogenesis.

Emerging evidence suggests INSTI effects on central nervous system appetite regulation [24]. Dolutegravir crosses the blood-brain barrier and may interfere with hypothalamic melanocortin signaling, which governs energy homeostasis [25]. Metabolomics studies in cerebrospinal fluid, though limited, show alterations in neuropeptide Y, pro-opiomelanocortin-derived peptides, and neurotransmitter precursors in INSTI-treated individuals with significant weight gain. Additionally, INSTIs may affect adipocyte biology directly; in vitro studies demonstrate that dolutegravir enhances adipocyte differentiation through peroxisome proliferator-activated receptor gamma (PPAR γ) activation and increases expression of lipogenic enzymes including fatty acid synthase and acetyl-CoA

carboxylase. The metabolic consequences extend beyond simple weight gain: INSTI-associated adiposity preferentially affects visceral depots, increasing cardiometabolic risk despite improved virological outcomes. Metabolomics reveals that individuals experiencing excessive weight gain on INSTIs exhibit more pronounced insulin resistance markers, including elevated BCAA concentrations, increased ceramide species, and perturbations in adipokine profiles with decreased adiponectin and increased leptin concentrations.

Protease Inhibitors and Dyslipidemia

Protease inhibitors have long been associated with dyslipidemia, characterized by elevated triglycerides, increased low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, and qualitative lipoprotein alterations [26]. Lipidomics studies reveal that PI-associated dyslipidemia extends far beyond conventional lipid panel abnormalities, encompassing profound changes in lipid subspecies and lipoproteins composition. PI treatment associates with 40–80% increases in very-low-density lipoprotein (VLDL) particle concentrations, particularly triglyceride-rich remnant particles that possess high atherogenic potential [27, 28]. Nuclear magnetic resonance spectroscopy demonstrates shifts toward small, dense LDL particles and decreased large HDL particles, creating a highly atherogenic lipid profile despite total cholesterol concentrations that may appear only modestly elevated.

At the molecular level, PIs interfere with multiple aspects of lipid metabolism. Ritonavir and lopinavir inhibit apolipoprotein B degradation through proteasomal pathways, increasing VLDL secretion from hepatocytes. These agents also impair lipoprotein lipase activity and hepatic lipase function, reducing triglyceride clearance. Metabolomics reveals accumulation of specific triglyceride species enriched in saturated and monounsaturated fatty acids, reflecting both increased hepatic lipogenesis and impaired lipolysis [29]. Free fatty acid profiles show elevations in palmitic acid (C16:0) and stearic acid (C18:0), substrates for ceramide synthesis, thereby linking PI-induced dyslipidemia with insulin resistance through lipotoxic mechanisms. Contemporary boosted PI regimens, particularly darunavir/cobicistat, demonstrate somewhat improved lipid profiles compared to older agents, yet metabolomics still reveals subtle perturbations in bile acid metabolism, cholesterol synthesis intermediates (increased lanosterol and desmosterol), and oxysterol concentrations, indicating ongoing disruption of cholesterol homeostasis.

Nucleoside Reverse Transcriptase Inhibitors and Mitochondrial Consequences

Although contemporary NRTI backbones (tenofovir alafenamide/emtricitabine or abacavir/lamivudine) demonstrate markedly reduced mitochondrial toxicity compared to older agents such as stavudine, subtle metabolic perturbations remain detectable through sensitive metabolomics approaches [30]. Tenofovir alafenamide, despite superior renal and bone safety profiles compared to tenofovir disoproxil fumarate, associates with modest weight gain and lipid elevations in some individuals. Metabolomics investigations reveal that TAF-containing regimens produce metabolite profiles suggesting enhanced adipogenesis and altered bile acid homeostasis, with increased primary bile acids and decreased secondary bile acid formation, possibly reflecting changes in gut microbiome composition.

Abacavir presents a distinct metabolic profile characterized by cardiovascular safety concerns that remain controversial despite extensive investigation [31, 32]. Metabolomics studies have identified potential mechanistic links: abacavir associates with elevated inflammatory metabolites, particularly leukotriene B4 and other arachidonic acid-derived eicosanoids, suggesting enhanced inflammatory pathway activation. Additionally, abacavir induces oxidative stress markers, including increased oxidized LDL epitopes and decreased antioxidant capacity (reduced glutathione, vitamin E). These alterations may contribute to endothelial dysfunction and accelerated atherosclerosis in susceptible individuals. Acylcarnitine profiling in abacavir-treated individuals occasionally reveals patterns consistent with subtle mitochondrial dysfunction, though far less pronounced than with older NRTIs. The incomplete fatty acid oxidation signatures may contribute to ectopic lipid accumulation and insulin resistance in long-term treatment.

DIAGNOSTIC AND BIOMARKER APPLICATIONS OF METABOLOMICS

Early Detection and Risk Stratification

Conventional diagnostic criteria for metabolic syndrome rely on threshold-based clinical measurements waist circumference, blood pressure, fasting glucose, and lipid panel that identify established metabolic dysfunction but lack sensitivity for detecting early pathophysiological changes [33]. Metabolomics offers potential for earlier detection through identification of subtle metabolic perturbations preceding clinically apparent disease. Several studies have developed metabolomic risk scores for predicting metabolic syndrome development in PLHIV. A composite biomarker panel including ceramide species (C16:0, C18:0, C24:1), BCAA concentrations, kynurenine-to-tryptophan ratio, and specific acylcarnitine ratios demonstrated 78–85% sensitivity and 72–80% specificity for identifying individuals who developed MetS within 2–3 years of ART initiation, significantly outperforming traditional risk factors alone.

For insulin resistance detection specifically, BCAA-based metabolite scores show correlation coefficients of 0.65–0.75 with gold-standard hyperinsulinemic-euglycemic clamp-derived insulin sensitivity indices, comparable to homeostasis model assessment (HOMA-IR) but providing additional mechanistic information [34]. Ceramide

profiling demonstrates particular promise for cardiovascular risk stratification: the ceramide risk score, combining C16:0 ceramide, C18:0 ceramide, and C24:1 ceramide normalized to C24:0 ceramide, predicts major adverse cardiovascular events with hazard ratios of 2.3–3.8 in the highest versus lowest quartiles in HIV-negative populations, with emerging evidence suggesting similar predictive value in PLHIV [35]. However, translation of these biomarkers into clinical practice faces significant barriers, including analytical standardization challenges, need for large prospective validation cohorts, cost considerations, and establishment of appropriate reference intervals for HIV-infected populations across diverse demographics and ART regimens.

Therapeutic Response Monitoring and Treatment Personalization

Metabolomics holds potential for guiding individualized ART selection and monitoring metabolic treatment responses [36, 37]. Baseline metabolomic profiling before ART initiation reveals that individuals with pre-existing elevations in ceramides, BCAAs, and inflammatory metabolites experience greater metabolic complications during subsequent treatment, suggesting value in pre-treatment risk assessment. For individuals requiring ART switches due to metabolic complications, metabolomics can track biochemical changes following regimen modifications. Studies examining switches from PI-based to INSTI-based regimens demonstrate rapid improvements in triglyceride-rich lipoprotein metabolism (within 4–12 weeks) but variable effects on ceramide concentrations and insulin resistance markers, with some individuals showing improvement while others demonstrate worsening insights not captured by conventional lipid panels alone.

Pharmacometabolomics integrating drug concentration measurements with metabolomic profiles reveals inter-individual variability in drug metabolism and metabolic responses that may guide dosing optimization or drug selection [38]. For example, individuals who are slow metabolizers of efavirenz (due to CYP2B6 polymorphisms) demonstrate distinct metabolomic profiles including altered steroid hormone metabolism and enhanced oxidative stress markers, potentially indicating need for alternative agents. Similarly, metabolomic signatures may identify individuals at highest risk for INSTI-associated excessive weight gain before initiation, enabling prospective selection of alternative regimens. Despite this potential, implementation requires prospective clinical trials demonstrating that metabolomics-guided treatment decisions improve clinical outcomes compared to standard management, evidence that remains limited.

Limitations of Current Biomarker Approaches

Despite promising findings, several limitations constrain clinical translation of metabolomics biomarkers. Analytical variability across platforms represents a major challenge: different mass spectrometry methods, sample preparation protocols, and data processing pipelines generate incompatible datasets, hindering meta-analysis and external validation. Efforts toward analytical standardization, including certified reference materials for key metabolites and inter-laboratory proficiency testing programs, remain incomplete for most metabolites of interest [39]. Sample stability and pre-analytical factors introduce additional variability; many metabolites are sensitive to collection conditions, processing delays, storage temperatures, and freeze-thaw cycles, necessitating rigorous standard operating procedures that may be difficult to implement in diverse clinical settings.

Biological variability, influenced by diet, physical activity, circadian rhythms, and concurrent medications, substantially affects metabolite concentrations, potentially obscuring disease-specific signals [40]. Fasting status particularly impacts lipid and amino acid measurements, yet standardizing fasting duration in clinical practice remains challenging. Moreover, most metabolomics investigations in PLHIV involve modest sample sizes (typically 50–300 participants), utilize cross-sectional designs that cannot establish causality, and lack ethnic diversity, with most studies conducted in European or North American cohorts. The paucity of longitudinal data tracking metabolite changes from ART initiation through development of metabolic complications limits understanding of temporal dynamics and critical windows for intervention. Finally, the incremental value of metabolomics biomarkers beyond readily available clinical measurements requires formal evaluation through decision curve analysis and health economic assessment to justify implementation costs.

THERAPEUTIC INTERVENTIONS TARGETING METABOLIC PATHWAYS

Lifestyle Modifications and Metabolic Response

Lifestyle interventions including dietary modification, exercise training, and behavioral counseling constitute first-line management for ART-associated metabolic syndrome, yet metabolomics reveals substantial heterogeneity in individual responses [41]. Exercise intervention studies employing pre- and post-training metabolomics demonstrate that aerobic and resistance training improve metabolic health through multiple mechanisms [42]: reduced BCAA concentrations (10–25% decreases), increased fatty acid oxidation markers (decreased long-chain acylcarnitines), improved TCA cycle function (normalized citrate and succinate concentrations), and reduced inflammation-associated metabolites (decreased kynurenine-to-tryptophan ratios). However, approximately 20–30% of individuals demonstrate minimal metabolomic responses to standardized exercise interventions, a phenomenon termed "exercise resistance."

Metabolomics may identify characteristics of exercise responders versus non-responders: baseline elevations in ceramides and specific phosphatidylcholines associate with attenuated responses to exercise, while individuals with

primarily BCAA-driven metabolic dysfunction show greater improvements. Dietary interventions similarly produce heterogeneous responses identifiable through metabolomics [43]. Mediterranean dietary patterns reduce inflammatory metabolites and improve lipid subspecies profiles, while ketogenic diets alter energy metabolism pathways with shifts toward ketone body production (elevated beta-hydroxybutyrate and acetoacetate) and reduced glycolytic intermediates. Time-restricted eating and intermittent fasting approaches demonstrate metabolomic changes suggesting enhanced autophagy, improved mitochondrial function, and reduced oxidative stress [44]. Personalized nutrition approaches guided by baseline metabolomics tailoring macronutrient composition, meal timing, and specific dietary components based on individual metabolic signatures represent an emerging research area with preliminary evidence of superior outcomes compared to standard dietary advice.

Pharmacological Interventions and Metabolic Targets

Several pharmacological agents demonstrate efficacy for managing specific components of ART-associated metabolic syndrome, with metabolomics providing mechanistic insights and identifying treatment responders [45]. Statins, the cornerstone of dyslipidemia management, effectively reduce cardiovascular risk in PLHIV, yet metabolomics reveals that lipid-lowering effects extend beyond LDL cholesterol reduction. Statin therapy normalizes triglyceride subspecies profiles, reduces ceramide concentrations (particularly atherogenic species), and improves the balance between anti-inflammatory and pro-inflammatory lipid mediators [46]. However, statins also produce adverse metabolic effects in some individuals, including reduced coenzyme Q10 concentrations and increased 3-hydroxy-3-methylglutaryl-CoA, potentially contributing to myopathy risk. Metabolomic monitoring may identify individuals requiring coenzyme Q10 supplementation or alternative lipid-lowering strategies.

Metformin, widely prescribed for insulin resistance and type 2 diabetes prevention, demonstrates pleiotropic metabolic effects in PLHIV beyond glucose lowering [47]. Metabolomics studies reveal that metformin reduces BCAA concentrations through enhanced catabolism, improves mitochondrial function markers, alters bile acid profiles toward more favorable compositions (increased secondary bile acids reflecting improved gut microbiome function), and reduces inflammation-associated metabolites. Metformin's effects on AMP-activated protein kinase activation and subsequent metabolic reprogramming provide mechanistic rationale for its benefits beyond glycemic control. GLP-1 receptor agonists, increasingly investigated for obesity management in PLHIV, produce profound metabolomic changes including reduced appetite-stimulating metabolites, enhanced fatty acid oxidation, improved insulin sensitivity markers, and favorable alterations in adipokine profiles. Randomized controlled trials incorporating metabolomics endpoints are needed to determine whether specific metabolomic signatures predict treatment response and identify optimal candidates for these costly interventions.

Emerging Therapeutic Approaches

Novel therapeutic strategies targeting specific metabolic pathways identified through metabolomics investigations are under development. Ceramide-lowering agents, including myriocin (serine palmitoyltransferase inhibitor) and fenretinide (dihydroceramide desaturase inhibitor), demonstrate preclinical efficacy for improving insulin sensitivity and reducing cardiovascular risk, though clinical development in HIV populations remains early-stage [47]. BCAA-lowering strategies, including dietary BCAA restriction and pharmacological enhancement of BCAA catabolism, show promise in animal models but require clinical validation. Bile acid sequestrants and farnesoid X receptor agonists, which modulate bile acid signaling pathways perturbed in ART-associated MetS, are being investigated for metabolic benefits beyond their traditional cholesterol-lowering indications.

Mitochondrial-targeted antioxidants, such as MitoQ and SS-31 peptide, aim to ameliorate mitochondrial dysfunction and oxidative stress that persist despite contemporary ART [48]. Small pilot studies demonstrate improvements in mitochondrial function biomarkers and exercise capacity, though metabolomic endpoints were not assessed. Microbiome modulation through probiotics, prebiotics, or fecal microbiota transplantation represents another emerging approach, as gut dysbiosis contributes to metabolic dysfunction in PLHIV. Metabolomics-microbiome integration studies reveal that beneficial microbiome interventions correlate with increased short-chain fatty acid production (butyrate, propionate, acetate), improved bile acid metabolism, and reduced inflammatory metabolites. However, optimal probiotic formulations, treatment duration, and patient selection criteria remain undefined. Finally, switching ART regimens based on metabolomic profiles selecting agents less likely to exacerbate identified metabolic vulnerabilities represents a precision medicine approach requiring prospective validation through clinical trials demonstrating improved long-term cardiometabolic outcomes.

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Multi-Omics Integration and Systems Biology Approaches

The integration of metabolomics with genomics, transcriptomics, proteomics, and microbiomics data collectively termed multi-omics offers unprecedented opportunity to comprehensively characterize ART-associated metabolic syndrome pathophysiology [49]. Systems biology approaches that model interactions across biological layers can identify key regulatory nodes, feedback loops, and network perturbations driving metabolic dysfunction. For example, integrating host genomics (particularly genes involved in drug metabolism, lipid homeostasis, and inflammation) with metabolomics reveals gene-metabolite associations that explain inter-individual variability in

ART metabolic responses. Polymorphisms in ABCB1 (encoding P-glycoprotein), SLCO1B1 (organic anion transporter), and CYP enzymes influence drug exposure and metabolic consequences, detectable through pharmacometabolomics [50, 51].

Transcriptomics-metabolomics integration identifies dysregulated pathways at both gene expression and metabolite levels, providing stronger evidence for pathway involvement than either approach alone [52]. Studies combining RNA sequencing of peripheral blood mononuclear cells or adipose tissue with plasma metabolomics reveal that inflammatory gene expression signatures correlate with specific metabolite perturbations, including kynurenine pathway activation, oxidative stress markers, and altered lipid metabolism. Proteomics adds functional protein information, identifying post-translational modifications and protein-metabolite interactions that regulate metabolic pathways. Microbiome-metabolomics integration demonstrates that gut microbial composition influences host metabolism through production of microbial metabolites (short-chain fatty acids, secondary bile acids, trimethylamine) and metabolism of dietary components. [53] Sophisticated computational approaches, including machine learning algorithms, network analysis, and pathway modeling, are essential for extracting meaningful insights from these high-dimensional multi-omics datasets. Future research must prioritize well-designed cohort studies that systematically collect multi-omics data longitudinally, employ rigorous analytical workflows, and validate findings in independent populations.

Technological Advances and Analytical Innovations

Continued advancement in analytical technologies will enhance metabolomics capabilities for studying ART-associated metabolic complications. Ultra-high-resolution mass spectrometry systems enable detection of low-abundance metabolites and resolution of isobaric compounds, expanding metabolome coverage [54, 55]. Ion mobility spectrometry adds a separation dimension based on molecular shape, improving identification confidence and resolving complex mixtures. Advances in targeted metabolomics panels, offering absolute quantification of hundreds of metabolites with high reproducibility, facilitate clinical translation through standardized assays amenable to regulatory approval and clinical laboratory implementation. Development of point-of-care metabolite sensors, leveraging microfluidics and biosensor technologies, could enable real-time monitoring of key biomarkers during clinic visits, facilitating immediate treatment decisions.

Spatial metabolomics including matrix-assisted laser desorption/ionization mass spectrometry imaging allows tissue-level metabolite mapping, revealing heterogeneous metabolic states within adipose tissue, liver, and vascular tissues affected by ART-associated MetS [56]. This approach may identify critical cellular populations and tissue microenvironments driving disease progression. Single-cell metabolomics, though technically challenging, promises to resolve metabolic heterogeneity within cell populations, potentially identifying rare cell subsets with aberrant metabolism that initiate or perpetuate disease processes. Integration of metabolomics with imaging modalities combining metabolite measurements with magnetic resonance spectroscopy, positron emission tomography, or advanced ultrasound provides complementary functional and metabolic information. Finally, computational advances including artificial intelligence-driven metabolite identification, pathway prediction algorithms, and personalized metabolic modeling may accelerate translation from biomarker discovery to clinical implementation.

Critical Knowledge Gaps and Research Needs

Despite substantial progress, major knowledge gaps impede translation of metabolomics discoveries into improved clinical management of ART-associated metabolic syndrome. Longitudinal studies tracking metabolomic changes from ART initiation through metabolic syndrome development remain sparse, limiting understanding of temporal dynamics, critical time windows for intervention, and causal versus consequential metabolite alterations [57]. Most investigations involve prevalent cases with established metabolic complications, potentially identifying consequences rather than drivers of disease. Prospective cohorts with serial metabolomics assessments, ideally beginning before ART initiation and continuing throughout treatment, are essential for identifying predictive biomarkers and elucidating pathogenic mechanisms.

The scarcity of metabolomics data from diverse populations including individuals of African, Asian, and Hispanic ancestry, women, transgender individuals, adolescents, and older adults limits generalizability of current findings, which derive predominantly from cisgender male European cohorts. Given substantial population differences in baseline metabolic profiles, genetic variants affecting drug metabolism, dietary patterns, and comorbidity burdens, dedicated studies in underrepresented populations are critically needed. Similarly, investigations in low- and middle-income countries, where most PLHIV reside and where different ART regimens, nutritional contexts, and coinfections prevail, remain virtually absent from the metabolomics literature [58].

Mechanistic validation of metabolomic associations represents another critical gap. Most identified metabolite alterations represent associations rather than proven causal relationships [59]. Functional studies employing cell culture models, animal experiments, and human mechanistic trials with metabolomic endpoints are necessary to definitively establish whether specific metabolite perturbations drive metabolic syndrome development or represent epiphenomena. For example, while ceramide elevations strongly associate with insulin resistance and cardiovascular risk, interventional studies demonstrating that ceramide reduction (through dietary, pharmacological, or genetic

approaches) improves clinical outcomes would strengthen causal inference and justify therapeutic targeting. Similarly, the mechanistic links between INSTI use, central nervous system metabolite alterations, and weight gain require cerebrospinal fluid metabolomics, neuroimaging studies, and controlled feeding experiments to definitively establish causality.

The lack of metabolomics-guided randomized controlled trials represents perhaps the most significant barrier to clinical translation [60]. While biomarker discovery studies proliferate, few investigations have prospectively tested whether metabolomics-informed treatment decisions improve outcomes compared to standard care. Pragmatic clinical trials comparing metabolomics-guided ART selection or metabolomics-directed lifestyle/pharmacological interventions versus usual care are essential for demonstrating clinical utility and cost-effectiveness. Such trials must include diverse populations, adequate sample sizes for robust subgroup analyses, long-term follow-up assessing hard clinical endpoints (cardiovascular events, diabetes incidence, mortality) rather than surrogate biomarkers alone, and health economic evaluations. Regulatory pathways for metabolomic biomarker qualification and clinical laboratory test approval require navigation, potentially necessitating collaboration between academic investigators, diagnostic companies, pharmaceutical industry partners, and regulatory agencies.

Finally, ethical considerations surrounding metabolomics implementation deserve attention. The generation of extensive metabolic profiling data raises privacy concerns, particularly if metabolite patterns reveal sensitive information about dietary habits, substance use, medication adherence, or genetic predispositions. Frameworks for informed consent, data security, appropriate result disclosure, and prevention of discrimination based on metabolomic profiles must be established. The potential for metabolomics-based risk stratification to exacerbate health disparities if access to advanced testing or personalized interventions remains limited to privileged populations requires proactive mitigation through equitable implementation strategies and health policy considerations.

CONCLUSION

Metabolomics has emerged as a powerful technology for dissecting the complex pathophysiology of antiretroviral therapy-associated metabolic syndrome in people living with HIV, revealing mechanistic insights far beyond conventional biochemical assessments. Current evidence demonstrates consistent perturbations across multiple metabolic domains: profound alterations in lipid metabolism featuring ceramide and diacylglycerol accumulation that mechanistically links to insulin resistance; dysregulated branched-chain amino acid catabolism reflecting chronic inflammation and contributing to metabolic inflexibility; mitochondrial dysfunction evidenced by incomplete fatty acid oxidation and altered energy metabolism; and activation of inflammation-associated pathways including tryptophan-kynurenine metabolism. Drug-specific metabolomic signatures have been identified, with integrase inhibitors demonstrating effects on adipogenesis and central appetite regulation underlying weight gain, protease inhibitors producing profound dyslipidemia extending to bioactive lipid species, and residual effects of nucleoside analogues on mitochondrial metabolism. The translational potential for metabolomics in early detection, risk stratification, treatment response monitoring, and personalized ART selection remains substantial yet incompletely realized. Critical barriers include analytical standardization challenges, limited prospective validation in diverse populations, modest cohort sizes, and absence of metabolomics-guided intervention trials demonstrating clinical benefit. Future progress requires multi-omics integration to comprehensively characterize disease mechanisms, technological advances enabling robust clinical implementation, longitudinal investigations establishing temporal relationships and causality, dedicated studies in underrepresented populations, and pragmatic randomized trials evaluating metabolomics-directed management strategies. As the field matures, metabolomics holds promise to transform HIV care from one-size-fits-all ART approaches toward precision medicine strategies that optimize virological efficacy while minimizing metabolic complications, ultimately improving long-term health outcomes and quality of life for people living with HIV. Healthcare systems and research funding agencies should prioritize investment in prospective metabolomics-guided clinical trials that directly test whether personalized antiretroviral therapy selection and metabolic intervention strategies based on individual metabolomic profiles improve cardiovascular and metabolic outcomes compared to standard management in people living with HIV.

REFERENCES

1. Obeagu, E.I., Obeagu, G.U., Alum, E.U., Ugwu, O.P.-C.: Comprehensive Review of Antiretroviral Therapy Effects on Red Blood Cells in HIV Patients. *INOSR Experimental Sciences*. 12, 63–72 (2023). <https://doi.org/10.59298/INOSRES/2023/6.3.21322>
2. Katz, I.T., Maughan-Brown, B.: Improved life expectancy of people living with HIV: who is left behind? *Lancet HIV*. 4, e324 (2017). [https://doi.org/10.1016/S2352-3018\(17\)30086-3](https://doi.org/10.1016/S2352-3018(17)30086-3)
3. Alum, E.U., Ugwu, O.P.C., Obeagu, E.I., Okon, M. Ben: Curtailing HIV/AIDS Spread: Impact of Religious Leaders. *Newport International Journal of Research in Medical Sciences (NIJRMS)*. 2, 28–31 (2023)
4. Payagala, S., Pozniak, A.: The global burden of HIV. *Clin Dermatol*. 42, 119–127 (2024). <https://doi.org/10.1016/J.CLINDERMATOL.2024.02.001>

5. Enriquez, R., Ssekubugu, R., Ndyababo, A., Marrone, G., Gigante, B., Chang, L.W., Reynolds, S.J., Nalugoda, F., Ekstrom, A.M., Sewankambo, N.K., Serwadda, D.M., Nordenstedt, H.: Prevalence of cardiovascular risk factors by HIV status in a population-based cohort in South Central Uganda: a cross-sectional survey. *J Int AIDS Soc.* 25, e25901 (2022). <https://doi.org/10.1002/JIA2.25901>
6. Ge, L., Tian, X., Sun, C., Hu, P., Yu, M.: Pathogenesis of HIV-Associated Metabolic Syndrome and Clinical Management Recommendations. *Int J Gen Med.* 18, 5213–5232 (2025). <https://doi.org/10.2147/IJGM.S528870>
7. Muthubharathi, B.C., Gowripriya, T., Balamurugan, K.: Metabolomics: small molecules that matter more. *Mol Omics.* 17, 210–229 (2021). <https://doi.org/10.1039/D0MO00176G>
8. Astarita, G., Kelly, R.S., Lasky-Su, J.: Metabolomics and lipidomics strategies in modern drug discovery and development. *Drug Discov Today.* 28, 103751 (2023). <https://doi.org/10.1016/J.DRUDIS.2023.103751>
9. Haus, J.M., Kashyap, S.R., Kasumov, T., Zhang, R., Kelly, K.R., Defronzo, R.A., Kirwan, J.P.: Plasma Ceramides Are Elevated in Obese Subjects With Type 2 Diabetes and Correlate With the Severity of Insulin Resistance. *Diabetes.* 58, 337 (2009). <https://doi.org/10.2337/DB08-1228>
10. Marin, R.C., Behl, T., Negrut, N., Bungau, S.: Management of Antiretroviral Therapy with Boosted Protease Inhibitors—Darunavir/Ritonavir or Darunavir/Cobicistat. *Biomedicines* 2021, Vol. 9, Page 313. 9, 313 (2021). <https://doi.org/10.3390/BIOMEDICINES9030313>
11. Jemal, M.: A review of dolutegravir-associated weight gain and secondary metabolic comorbidities. *SAGE Open Med.* 12, 20503121241260612 (2024). <https://doi.org/10.1177/20503121241260612>
12. Alum, E.U. Optimizing patient education for sustainable self-management in type 2 diabetes. *Discov Public Health* 22, 44 (2025). <https://doi.org/10.1186/s12982-025-00445-5>
13. Yoon, M.S.: The Role of Mammalian Target of Rapamycin (mTOR) in Insulin Signaling. *Nutrients* 2017, Vol. 9, Page 1176. 9, 1176 (2017). <https://doi.org/10.3390/NU9111176>
14. Masina, N.B., Robertson, F.: Influence of maternal human immunodeficiency virus (HIV) and antiretroviral (ARV) drugs on neonate neurometabolism., <http://hdl.handle.net/11427/39635>, (2023)
15. Brown, K., Walsh, A., Yennemadi, A.S., Murphy, D.M., Connolly, S.A., O'Sullivan, M.P., Basdeo, S., O'Leary, S., Leisching, G., Keane, J.: HIV inhibits Warburg metabolism in human macrophages infected with *Mycobacterium tuberculosis*. *bioRxiv.* 2025.05.09.653039 (2025). <https://doi.org/10.1101/2025.05.09.653039>
16. Hileman, C.O., Funderburg, N.T.: Inflammation, Immune Activation, and Antiretroviral Therapy in HIV. *Curr HIV/AIDS Rep.* 14, 93–100 (2017). <https://doi.org/10.1007/S11904-017-0356-X/METRICS>
17. Bipath, P., Levay, P.F., Viljoen, M.: The kynurenine pathway activities in a sub-Saharan HIV/AIDS population. *BMC Infect Dis.* 15, 1–12 (2015). <https://doi.org/10.1186/S12879-015-1087-5/FIGURES/3>
18. -Rodríguez, A., Reyes-Long, A., Roldan-Valadez, S., González-Torres, E., Bonilla-Jaime, M., Bandala, H., Avila-Luna, C., Bueno-Nava, A., Cabrera-Ruiz, A., Sanchez-Aparicio, E., Alfaro-Rodríguez, A., Reyes-Long, S., Roldan-Valadez, E., González-Torres, M., Bonilla-Jaime, H., Bandala, C., Avila-Luna, A., Bueno-Nava, A., Cabrera-Ruiz, E., Sanchez-Aparicio, P., González Maciel, A., Lilia Dotor-Llerena, A., Luis Cortes-Altamirano, J.: Association of the Serotonin and Kynurenine Pathways as Possible Therapeutic Targets to Modulate Pain in Patients with Fibromyalgia. *Pharmaceuticals* 2024, Vol. 17, Page 1205. 17, 1205 (2024). <https://doi.org/10.3390/PH17091205>
19. Bernard, A., May, C. Le, Dastugue, A., Ayer, A., Blanchard, C., Martin, J.C., de Barros, J.P.P., Delaby, P., Bourgot, C. Le, Ledoux, S., Besnard, P.: The Tryptophan/Kynurenine Pathway: A Novel Cross-Talk between Nutritional Obesity, Bariatric Surgery and Taste of Fat. *Nutrients* 2021, Vol. 13, Page 1366. 13, 1366 (2021). <https://doi.org/10.3390/NU13041366>
20. Zhu, Q., Yuan, C., Dong, X., Wang, Y., Li, B., Tu, B., Chen, W., Xu, X., Gong, W., Xiao, W., Ding, Y., Hu, L., Li, W., Lu, G.: Bile acid metabolomics identifies chenodeoxycholic acid as a therapeutic agent for pancreatic necrosis. *Cell Rep Med.* 4, 101304 (2023). <https://doi.org/10.1016/J.XCRM.2023.101304>
21. El-Baz, A., El-Sayed, A.S.A., Shetaia, Y., Abaza, A.A.: Metabolic Pattern of Microbiome in Healthy Versus Patient Individuals. *Metabolic Dynamics in Host-Microbe Interaction.* 343–376 (2025). https://doi.org/10.1007/978-981-96-1305-2_14
22. Naidoo, A., Dooley, K.E., Naidoo, K., Padayatchi, N., Yende-Zuma, N., Perumal, R., Dorse, G., Boodhram, R., Osuala, E.C.: INSTIs for the management of HIV-associated TB (INSIGHT study): a phase 2b study to evaluate the efficacy, safety and pharmacokinetics of a combination of bictegravir, emtricitabine and tenofovir alafenamide fumarate for the treatment of HIV-1 infection in patients with drug-susceptible tuberculosis on a rifampicin-based treatment regimen: a phase 2b open-label randomised controlled trial. *BMJ Open.* 12, e067765 (2022). <https://doi.org/10.1136/BMJOPEN-2022-067765>

23. Foka, F.E.T., Mufhandu, H.T.: Current ARTs, Virologic Failure, and Implications for AIDS Management: A Systematic Review. *Viruses* 2023, Vol. 15, Page 1732. 15, 1732 (2023). <https://doi.org/10.3390/V15081732>
24. Farr, O.M., Li, C.S.R., Mantzoros, C.S.: Central Nervous System Regulation of Eating: Insights from Human Brain Imaging. *Metabolism*. 65, 699 (2016). <https://doi.org/10.1016/J.METABOL.2016.02.002>
25. Huang, C., Qu, Q.R., Bendayan, R.: Dolutegravir Inhibits Autophagy In Vitro in a Mouse Blood–Brain Barrier Model. *The FASEB Journal*. 39, e70751 (2025). <https://doi.org/10.1096/FJ.202500568RR>
26. Penzak, S.R., Chuck, S.K.: Management of protease inhibitor-associated hyperlipidemia. *Am J Cardiovasc Drugs*. 2, 91–106 (2002). <https://doi.org/10.2165/00129784-200202020-00003>
27. Ginsberg, H.N., Packard, C.J., Chapman, M.J., Borén, J., Aguilar-Salinas, C.A., Averna, M., Ference, B.A., Gaudet, D., Hegele, R.A., Kersten, S., Lewis, G.F., Lichtenstein, A.H., Moulin, P., Nordestgaard, B.G., Remaley, A.T., Staels, B., Stroes, E.S.G., Taskinen, M.R., Tokgözoğlu, L.S., Tybjaerg-Hansen, A., Stock, J.K., Catapano, A.L.: Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society. *Eur Heart J*. 42, 4791–4806 (2021). <https://doi.org/10.1093/EURHEARTJ/EHAB551>
28. Baba, M., Maris, M., Jianu, D., Luca, C.T., Stoian, D., Mozos, I.: The Impact of the Blood Lipids Levels on Arterial Stiffness. *Journal of Cardiovascular Development and Disease* 2023, Vol. 10, Page 127. 10, 127 (2023). <https://doi.org/10.3390/JCDD10030127>
29. Borén, J., Taskinen, M.R., Björnson, E., Packard, C.J.: Metabolism of triglyceride-rich lipoproteins in health and dyslipidaemia. *Nat Rev Cardiol*. 19, 577–592 (2022). <https://doi.org/10.1038/S41569-022-00676-Y;SUBJMETA>
30. Walker, U.A., Setzer, B., Venhoff, N.: Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse-transcriptase inhibitors. *AIDS*. 16, 2165–2173 (2002). <https://doi.org/10.1097/00002030-200211080-00009>
31. Alvarez, A., Orden, S., Andújar, I., Collado-Díaz, V., Núñez-Delgado, S., Galindo, M.J., Estrada, V., Apostolova, N., Esplugues, J. V.: Cardiovascular toxicity of abacavir: A clinical controversy in need of a pharmacological explanation. *AIDS*. 31, 1781–1795 (2017). <https://doi.org/10.1097/QAD.0000000000001547>
32. Choi, A.I., Vittinghoff, E., Deeks, S.G., Weekley, C.C., Li, Y., Shlipak, M.G.: Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. *AIDS*. 25, 1289–1298 (2011). <https://doi.org/10.1097/QAD.0b013e328347fa16>
33. Ford, E.S., Giles, W.H., Dietz, W.H.: Prevalence of the metabolic syndrome among US adults: Findings from the Third National Health and Nutrition Examination Survey. *J Am Med Assoc*. 287, 356–359 (2002). <https://doi.org/10.1001/JAMA.287.3.356>
34. Tam, C.S., Xie, W., Johnson, W.D., Cefalu, W.T., Redman, L.M., Ravussin, E.: Defining insulin resistance from hyperinsulinemic-euglycemic clamps. *Diabetes Care*. 35, 1605–1610 (2012). <https://doi.org/10.2337/DC11-2339/-/DC1>
35. Gaggini, M., Suman, A.F., Vassalle, C.: Ceramide in Coronary Artery Disease: Troublesome or Helpful Future Tools in the Assessment of Risk Prediction and Therapy Effectiveness? *Metabolites*. 15, 168 (2025). <https://doi.org/10.3390/METABO15030168>
36. Tomar, M., Mohit, M., Srivastava, A., Pateriya, A., Araniti, F., Shrivastava, A.: Metabolomics: Analytical Insights into Disease Mechanisms and Biomarker Discovery. *Med Res Arch*. 13, (2025). <https://doi.org/10.18103/MRA.V13I6.6549>
37. Jacob, M., Lopata, A.L., Dasouki, M., Abdel Rahman, A.M.: Metabolomics toward personalized medicine. *Mass Spectrom Rev*. 38, 221–238 (2019). <https://doi.org/10.1002/MAS.21548>
38. Kantae, V., Krekels, E.H.J., Esdonk, M.J.V., Lindenburg, P., Harms, A.C., Knibbe, C.A.J., Van der Graaf, P.H., Hankemeier, T.: Integration of pharmacometabolomics with pharmacokinetics and pharmacodynamics: towards personalized drug therapy. *Metabolomics*. 13, 1–11 (2017). <https://doi.org/10.1007/S11306-016-1143-1/FIGURES/2>
39. Zhang, N., Chen, Q., Zhang, P., Zhou, K., Liu, Y., Wang, H., Duan, S., Xie, Y., Yu, W., Kong, Z., Ren, L., Hou, W., Yang, J., Gong, X., Dong, L., Fang, X., Shi, L., Yu, Y., Zheng, Y.: Quartet metabolite reference materials for inter-laboratory proficiency test and data integration of metabolomics profiling. *Genome Biol*. 25, 1–21 (2024). <https://doi.org/10.1186/S13059-024-03168-Z/FIGURES/7>
40. Konakchieva, R., Mladenov, M., Konaktchieva, M., Sazdova, I., Gagov, H., Nikolaev, G.: Circadian Clock Deregulation and Metabolic Reprogramming: A System Biology Approach to Tissue-Specific Redox Signaling and Disease Development. *International Journal of Molecular Sciences* 2025, Vol. 26, Page 6267. 26, 6267 (2025). <https://doi.org/10.3390/IJMS26136267>

41. Bogaards, F.A., Gehrman, T., Beekman, M., van den Akker, E. Ben, van de Rest, O., Hangelbroek, R.W.J., Noordam, R., Mooijaart, S.P., de Groot, L.C.P.G.M., Reinders, M.J.T., Slagboom, P.E.: <sc>PLIS</sc> : A metabolomic response monitor to a lifestyle intervention study in older adults. *The FASEB Journal*. 36, (2022). <https://doi.org/10.1096/fj.202201037R>
42. Sardeli, A. V., Castro, A., Gadelha, V.B., Santos, W.M. dos, Lord, J.M., Cavaglieri, C.R., Chacon-Mikahil, M.P.T.: Metabolomic Response throughout 16 Weeks of Combined Aerobic and Resistance Exercise Training in Older Women with Metabolic Syndrome. *Metabolites*. 12, 1041 (2022). <https://doi.org/10.3390/METABO12111041/S1>
43. Garcia-Perez, I., Posma, J.M., Chambers, E.S., Mathers, J.C., Draper, J., Beckmann, M., Nicholson, J.K., Holmes, E., Frost, G.: Dietary metabolite modelling predicts individual responses to dietary interventions. *Nat Food*. 1, 355–364 (2020). <https://doi.org/10.1038/S43016-020-0092-Z;SUBJMETA>
44. Izah, S.C., Betiang, P.A., Ugwu, O.P.C., Ainebyoona, C., Uti, D.E., Echegu, D.A. The Ketogenic Diet in Obesity Management: Friend or Foe?. *Cell Biochem Biophys* (2025). <https://doi.org/10.1007/s12013-025-01878-0>
45. Armstrong, A.J.S., Quinn, K., Fouquier, J., Li, S.X., Schneider, J.M., Nusbacher, N.M., Doenges, K.A., Fiorillo, S., Marden, T.J., Higgins, J., Reisdorph, N., Campbell, T.B., Palmer, B.E., Lozupone, C.A.: Systems analysis of gut microbiome influence on metabolic disease in HIV and high-risk populations. *bioRxiv*. 2021.03.12.435118 (2021). <https://doi.org/10.1101/2021.03.12.435118>
46. Alum, E. U., Obeagu, E. I., Ugwu, O. P. C., Aja, P. M. and Okon, M. B. HIV Infection and Cardiovascular diseases: The obnoxious Duos. *Newport International Journal of Research in Medical Sciences (NIJRMS)*, 2023; 3(2): 95-99.
47. Garrib, A., Kivuyo, S., Bates, K., Ramaiya, K., Wang, D., Majaliwa, E., Simbauranga, R., Charles, G., van Widenfelt, E., Luo, H., Alam, U., Nyirenda, M.J., Jaffar, S., Mfinanga, S.: Metformin for the prevention of diabetes among people with HIV and either impaired fasting glucose or impaired glucose tolerance (prediabetes) in Tanzania: a Phase II randomised placebo-controlled trial. *Diabetologia*. 66, 1882–1896 (2023). <https://doi.org/10.1007/S00125-023-05968-7/TABLES/4>
48. Apostolova, N., Victor, V.M.: Molecular Strategies for Targeting Antioxidants to Mitochondria: Therapeutic Implications. <https://home.liebertpub.com/ars>. 22, 686–729 (2015). <https://doi.org/10.1089/ARS.2014.5952>
49. Jendoubi, T.: Approaches to Integrating Metabolomics and Multi-Omics Data: A Primer. *Metabolites*. 11, 184 (2021). <https://doi.org/10.3390/METABO11030184>
50. Wolking, S., Schaeffeler, E., Lerche, H., Schwab, M., Nies, A.T.: Impact of Genetic Polymorphisms of ABCB1 (MDR1, P-Glycoprotein) on Drug Disposition and Potential Clinical Implications: Update of the Literature. *Clin Pharmacokinet*. 54, 709–735 (2015). <https://doi.org/10.1007/S40262-015-0267-1/METRICS>
51. Rakhmanina, N.Y., Neely, M.N., Van Schaik, R.H.N., Gordish-Dressman, H.A., Williams, K.D., Soldin, S.J., Van Den Anker, J.N.: CYP3A5, ABCB1 and SLCO1B1 Polymorphisms and Pharmacokinetics and Virologic Outcome of Lopinavir/Ritonavir in HIV-infected Children. *Ther Drug Monit*. 33, 417 (2011). <https://doi.org/10.1097/FTD.0B013E318225384F>
52. Yin, X., Bose, D., Kwon, A., Hanks, S.C., Jackson, A.U., Stringham, H.M., Welch, R., Oravilahti, A., Fernandes Silva, L., Locke, A.E., Fuchsberger, C., Service, S.K., Erdos, M.R., Bonnycastle, L.L., Kuusisto, J., Stitzel, N.O., Hall, I.M., Morrison, J., Ripatti, S., Palotie, A., Freimer, N.B., Collins, F.S., Mohlke, K.L., Scott, L.J., Fauman, E.B., Burant, C., Boehnke, M., Laakso, M., Wen, X.: Integrating transcriptomics, metabolomics, and GWAS helps reveal molecular mechanisms for metabolite levels and disease risk. *Am J Hum Genet*. 109, 1727–1741 (2022). <https://doi.org/10.1016/j.ajhg.2022.08.007>
53. Lyu, Y., Pu, J., Deng, B., Wu, C.: Gut Metabolome in Companion Animal Nutrition—Linking Diets to Health. *Animals* 2025, Vol. 15, Page 651. 15, 651 (2025). <https://doi.org/10.3390/ANI15050651>
54. Deschamps, E., Calabrese, V., Schmitz, I., Hubert-Roux, M., Castagnos, D., Afonso, C.: Advances in Ultra-High-Resolution Mass Spectrometry for Pharmaceutical Analysis. *Molecules* 2023, Vol. 28, Page 2061. 28, 2061 (2023). <https://doi.org/10.3390/MOLECULES28052061>
55. Lagoriya, D.S.: Mass Spectrometry-Based Approaches in Metabolomics. *Advances in Omics Technologies*. 247–286 (2025). https://doi.org/10.1007/978-981-95-0285-1_12
56. Sturtevant, D., Lee, Y.J., Chapman, K.D.: Matrix assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI) for direct visualization of plant metabolites in situ. *Curr Opin Biotechnol*. 37, 53–60 (2016). <https://doi.org/10.1016/j.copbio.2015.10.004>
57. Sperisen, P., Cominetti, O., Martin, F.P.J.: Longitudinal omics modeling and integration in clinical metabonomics research: Challenges in childhood metabolic health research. *Front Mol Biosci*. 2, 151246 (2015). <https://doi.org/10.3389/FMOLB.2015.00044/EPUB>

58. Dadi, T.L., Wiemers, A.M.C., Tegene, Y., Medhin, G., Spigt, M.: Experiences of people living with HIV in low- and middle-income countries and their perspectives in self-management: a meta-synthesis. *AIDS Res Ther.* 21, 1–15 (2024). <https://doi.org/10.1186/S12981-024-00595-7/FIGURES/3>
59. Koh, A., Bäckhed, F.: From Association to Causality: the Role of the Gut Microbiota and Its Functional Products on Host Metabolism. *Mol Cell.* 78, 584–596 (2020). <https://doi.org/10.1016/j.molcel.2020.03.005>
60. Mamas, M., Dunn, W.B., Neyses, L., Goodacre, R.: The role of metabolites and metabolomics in clinically applicable biomarkers of disease. *Arch Toxicol.* 85, 5–17 (2011). <https://doi.org/10.1007/s00204-010-0609-6>

CITE AS: Odile Patrick Thalia (2026). Metabolomics Profiling of Antiretroviral Therapy-Associated Metabolic Syndrome in People Living with HIV. RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 5(1):50-61. <https://doi.org/10.59298/RIJMS/2026/515061>