**UDC 616.98:578.828:577.12** *https://doi.org/10.31861/biosystems2026.02.327*

# VIRUS-INDUCED DISRUPTIONS OF CELLULAR METABOLISM IN HIV INFECTION AND THE EFFECTS OF ANTIRETROVIRAL THERAPY

O. V. KETSA

*Fedkovich Chernovtsy National University,*
*2 Kotsyubinskogo Str., Chernovtsy, 58012, Ukraine*
*o.ketsa@chnu.edu.ua*

*This study provides a comprehensive analysis of current scientific evidence on the mechanisms underlying virus-induced alterations in cellular metabolism during human immunodeficiency virus (HIV) infection and the effects of antiretroviral therapy (ART) on metabolic processes and cellular function The review focuses on alterations in energy metabolism, glucose, lipid, and amino acid metabolism, mitochondrial dysfunction, redox imbalance, and the regulation of cellular responses. The aim of this study was to assess the main mechanisms of virus-induced alterations in cellular metabolism during HIV infection and to elucidate the effects of ART on metabolic processes and cellular function. To achieve this aim, systematic, comparative, and critical analyses, as well as a synthesis of scientific publications, were employed. The evidence base was established using studies retrieved from the international bibliographic and scientometric databases PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The analysis revealed that HIV infection is accompanied by alterations in metabolic pathways involved in meeting cellular energy demands, biomolecule synthesis, and immune response regulation. In particular, changes in glucose metabolism and mitochondrial function may affect productive viral replication, the maintenance of latency, and the resistance of infected cells to oxidative stress. The review also highlights the interplay between energy, lipid, and amino acid metabolism and cellular signaling pathways, including mechanistic target of rapamycin complex 1 (mTORC1), which regulates anabolic processes, autophagy, and cellular activation. Particular attention was also given to mitochondrial dysfunction, the production of reactive oxygen species (ROS), and metabolic alterations associated with ART use. Thus, the analysis of the scientific literature indicates that metabolic disturbances are an important component of HIV–host cell interactions. Their investigation contributes to a deeper understanding of the mechanisms underlying viral persistence, impaired immune function, and the potential metabolic consequences of treatment.*

*Keywords: human immunodeficiency virus, metabolism, glycolysis, mitochondria, redox imbalance, lipids, amino acids, antiretroviral therapy*

**Introduction.** Human immunodeficiency virus (HIV) is the causative agent of a chronic infection characterized by progressive changes in immune system function and complex alterations in cellular metabolism (Siripurapu et al., 2023). The interaction of HIV with human cells is accompanied by changes in key biochemical processes, including energy metabolism, carbohydrate, lipid, and amino acid metabolism, as well as mitochondrial function (Wik et al., 2022; Kalra et al., 2023; Hulgan et al., 2021; Rozzi et al., 2017). These metabolic alterations may affect the viability of infected cells, their functional activity, and their ability to mount an adequate immune response (Mbonye et al., 2017).

The relevance of investigating HIV-induced metabolic disturbances stems from the complexity of the mechanisms underlying viral interactions with host cells and their effects on intracellular biochemical processes. Of particular importance are changes in the metabolism of $CD4^+$ T lymphocytes, the primary cellular targets of HIV, as well as monocytes, macrophages, and other immune cells (De Masson d'Autume et al., 2026). The reprogramming of energy metabolism, alterations in enzyme system activity, and disturbances in the metabolism of biologically active compounds may be associated with the characteristics of viral replication, immune cell activation, and the progression of infection.

An important aspect of metabolic alterations during HIV infection is the impairment of mitochondrial function. Mitochondria play a key role in cellular energy production and the regulation of intracellular signaling processes. Changes in mitochondrial metabolism may be accompanied by disturbances in redox homeostasis and alterations in the activity of antioxidant systems (Roca-Bayerri et al., 2021). These processes are considered in the context of cellular dysfunction, inflammatory responses, and changes in immune function. At the same time, their nature and severity may depend on the stage of infection, individual host characteristics, and the effects of antiretroviral therapy.

Investigating HIV-induced metabolic alterations is important for understanding the pathogenesis of HIV infection. Cellular metabolic reprogramming

may be associated not only with the direct effects of the virus but also with prolonged immune system activation, systemic inflammation, and changes in the functional state of various tissues (Capendale et al., 2026). Particular attention should be paid to the metabolic effects of antiretroviral therapy (ART), as its long-term use may be accompanied by alterations in lipid and carbohydrate metabolism, as well as other metabolic disturbances. Distinguishing between changes associated with the infection itself and those related to its treatment is essential for a comprehensive understanding of the biochemical mechanisms underlying the disease.

Despite significant progress in investigating the molecular mechanisms of HIV infection, the relationships between viral replication, alterations in cellular metabolism, mitochondrial dysfunction, and immune responses require further systematic analysis. A comprehensive investigation of these processes, taking into account cell type, the stage of infection, and the effects of antiretroviral therapy, is of particular importance. Therefore, synthesizing current scientific evidence on the main mechanisms of HIV-induced alterations in cellular metabolism is highly relevant, particularly with regard to changes in energy metabolism, lipid and carbohydrate metabolism, mitochondrial function, and their significance for immune system function and the course of HIV infection.

The aim of this study was to assess the main mechanisms of virus-induced alterations in cellular metabolism during HIV infection and to elucidate the effects of ART on metabolic processes and cellular function.

**Materials and methods.** This article presents a comprehensive narrative review of the scientific literature on the mechanisms underlying HIV-induced alterations in cellular metabolism and the metabolic effects of ART. The review synthesizes current scientific evidence on HIV-associated metabolic changes and their potential implications for immune cell function. The review incorporates comparative analysis, critical appraisal, and synthesis of findings from experimental and clinical studies, systematic reviews, and meta-analyses.

The evidence base consisted of scientific publications retrieved from the international bibliographic and scientometric databases PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The literature search was conducted using keywords and their combinations in English, including “HIV infection,” “cellular metabolism,” “energy metabolism,” “glucose metabolism,” “lipid metabolism,” “amino acid metabolism,” “mitochondrial dysfunction,” “immunometabolism,” and “oxidative stress.”

Peer-reviewed scientific publications addressing the mechanisms by which HIV affects intracellular metabolic processes, the functional state of immunocompetent cells, and the relationship between metabolic alterations and the course of HIV infection were included in the analysis. Preference was given to original experimental and clinical studies, systematic reviews, and meta-analyses reporting changes in energy metabolism, carbohydrate, lipid, and amino acid metabolism, mitochondrial function, and the regulation of cellular immune responses. Publications addressing the effects of systemic inflammation and ART on the metabolic status of individuals with HIV infection were also considered.

The materials were analyzed according to the following thematic areas: HIV-induced reprogramming of cellular metabolism; alterations in energy metabolism and glucose metabolism; disturbances in lipid and amino acid metabolism; changes in mitochondrial function and redox homeostasis; the relationship between metabolic processes and $CD4^+$ T lymphocyte function; and the metabolic effects of systemic inflammation and ART. This approach made it possible to examine metabolic disturbances not as isolated phenomena but as interconnected components of the cellular response to HIV infection.

The selected sources were synthesized by comparing the mechanisms described, identifying common patterns and discrepancies among study findings, and determining their potential significance for the functional state of immune cells and the course of the infectious process. Figures illustrating the main mechanisms and interrelationships were created using the BioRender online platform (https://www.biorender.com/).

**Results and their discussion.** ***Disruption of Energy Metabolism and Glucose Metabolism in HIV-Infected Cells.*** HIV-induced alterations in energy metabolism and glucose metabolism in infected cells represent one of the mechanisms that establish intracellular conditions favorable for viral replication. These changes have been investigated most extensively in $CD4^+$ T lymphocytes, in which increased glucose uptake and activation of specific components of the glycolytic pathway have been observed following HIV infection.

HIV can alter the energy metabolism of infected cells by affecting glucose transport, the activity of glycolytic enzymes, and mitochondrial energy pathways. In a study by Williamson et al. (Williamson et al., 2018) conducted using primary human $CD4^+$ T lymphocytes, HIV-1 infection was found to increase glucose uptake, enhance hexokinase activity, and upregulate the expression of the glucose transport proteins – GLUT1, GLUT3, GLUT4, and

GLUT6. Increased expression of hexokinase 1 (HK1) (Sen et al., 2015) and the mitochondrial protein VDAC (Zhong et al., 2020) was also observed. These changes were associated with the kinetics of viral replication, indicating a relationship between the infectious process and the reprogramming of glucose metabolism in host cells (Williamson et al., 2018).

The functional significance of these changes is supported by the study by Hegedus et al. (2014), which demonstrated an increase in glycolytic flux in primary $CD4^+$ T lymphocytes following HIV-1 infection. Viral particle output decreased when glucose was substituted with galactose, thereby limiting glycolytic activity. However, similar metabolic changes were not observed in all cell lines examined, highlighting the dependence of the metabolic response on cell type and experimental conditions (Hegedus et al., 2014).

The energy supply of infected cells also depends on the interaction between glycolysis and mitochondrial metabolism. Clerc et al. (2019) showed that glutamine-derived carbon enters the tricarboxylic acid (TCA) cycle, contributing to its metabolic activity and sustaining oxidative phosphorylation in $CD4^+$ T cells. The authors showed that glucose and glutamine utilization, as well as the balance between glycolysis and mitochondrial respiration, are associated with cellular susceptibility to HIV-1 and the early stages of infection (Clerc et al., 2019). Thus, the metabolic support of the viral life cycle is not limited to a single energy pathway but depends on the interaction of several interconnected biochemical processes.

An important factor is the level of viral activity. During productive infection, increased glycolysis may help meet the metabolic demands of viral replication, whereas reduced glycolytic activity has been reported in latently infected cells. Shytaj et al. (2021) associated HIV-1 latency with glycolytic reprogramming and alterations in the metabolic mechanisms involved in maintaining redox homeostasis. This indicates that the metabolic profile of an infected cell depends not only on its type but also on whether active viral replication is occurring (Shytaj et al., 2021).

Thus, HIV-1-infected cells exhibit changes in glucose uptake, glycolytic activity, and the utilization of mitochondrial energy pathways. These processes may support the metabolic requirements of the viral life cycle; however, their characteristics depend on cell type and the state of infection. Taken together, these findings support the view that energy metabolism is an important component of HIV–host cell interactions.

***Mitochondrial dysfunction and redox imbalance.*** Mitochondria play a key role in maintaining cellular energy supply, regulating redox processes, intracellular calcium homeostasis, and programmed cell death (König et al., 2024). During HIV infection, mitochondrial function may be altered by viral proteins, disturbances in cellular metabolism, and prolonged activation of signaling pathways. These changes are not limited to reduced energy production but also involve the regulation of mitochondrial dynamics, organelle quality control, and the maintenance of intracellular redox homeostasis (Rozzi et al., 2017; Fields et al., 2019).

One of the important mechanisms underlying mitochondrial alterations is the effect of viral proteins on organelle structure and function. HIV-1 proteins Tat, Vpr, and Nef, together with the envelope glycoprotein gp120, have been implicated in mitochondrial alterations, including shifts in membrane potential, disruption of respiratory chain activity, dysregulation of calcium balance, and changes in the mechanisms controlling mitochondrial fusion and fission (Avdoshina et al., 2016). These effects have been described in various cellular models, including lymphocytes and cells of the central nervous system; however, their extent depends on cell type and experimental conditions (Rozzi et al., 2017; Fields et al., 2019).

Mitochondrial dysfunction is closely associated with the production of ROS. During HIV infection, oxidative stress is enhanced, which is attributed not only to mitochondrial disturbances but also to the activation of other intracellular sources of ROS, including NADPH oxidases, and the effects of specific viral proteins on redox signaling (Ivanov et al., 2016).

Redox imbalance, in turn, may alter the functioning of antioxidant systems and signaling pathways that regulate cellular stress responses. When the oxidative burden cannot be adequately compensated for, damage to mitochondrial components may sustain further ROS production, establishing an interconnected cycle of mitochondrial dysfunction and oxidative stress (Kidwell et al., 2023). However, ROS should not be regarded exclusively as mediators of cellular damage: depending on their concentration, localization, and signal duration, they may influence the regulation of antiviral mechanisms and HIV-1 replication (Ivanov et al., 2016). Therefore, the significance of redox

alterations is determined not only by the intensity of ROS production but also by the cell's ability to maintain controlled redox signaling (Muccilli et al., 2025).

Changes in redox homeostasis may be accompanied by the reprogramming of energy substrate utilization pathways, particularly those involving glucose and glutamine, thereby affecting the fulfillment of cellular energy demands and the course of viral replication (Fig. 1).

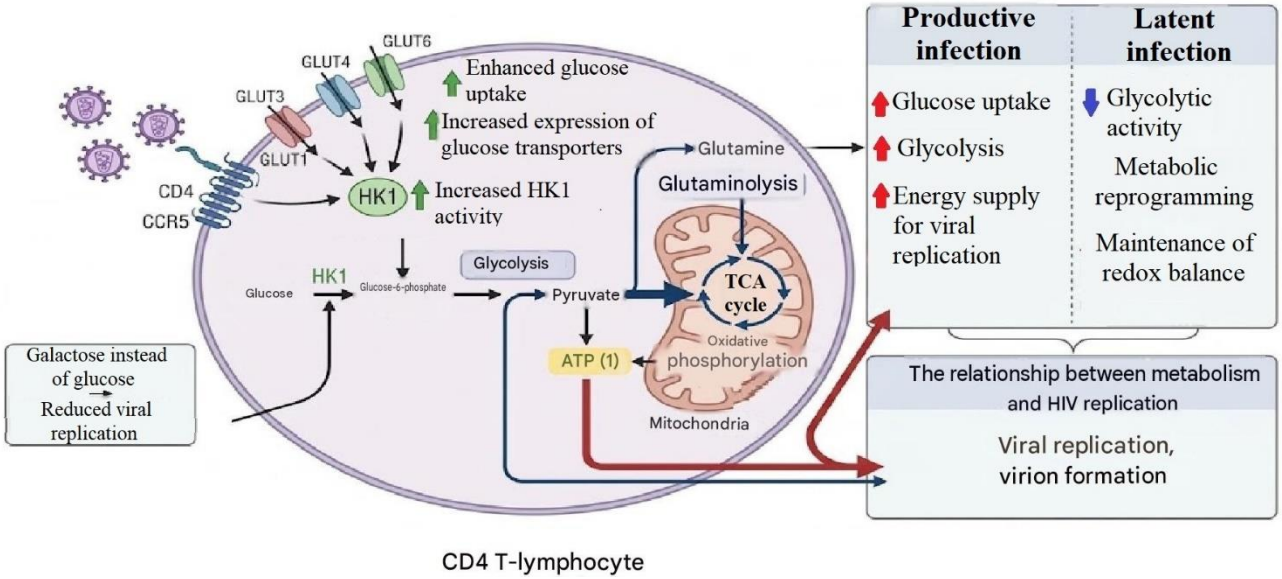



***Fig. 1. Schematic representation of HIV-induced alterations in energy metabolism in CD4⁺ T lymphocytes***

*Note: HK1 – hexokinase 1; CCR5 – C-C chemokine receptor type 5; GLUT – glucose transporter; TCA cycle – tricarboxylic acid cycle*

The initial binding of HIV-1 to the CD4 receptor and the CCR5 co-receptor is accompanied by increased expression and glucose transport via GLUT transporters, as well as enhanced HK1 activity (Yu et al., 2025). This stimulates glycolytic flux in the cytosol, resulting in pyruvate production. In parallel, the activation of glutaminolysis supplies carbon substrates to the mitochondrial TCA cycle, thereby supporting oxidative phosphorylation and increasing ATP production.

However, the nature of these changes may vary depending on the stage of infection, particularly between productive infection and latency. During productive infection, the upregulation of glycolysis and mitochondrial respiration directly supports the biosynthetic and energy requirements of HIV-1 replication and virion production (Crater et al., 2022; Kayode et al., 2025). In contrast, latent infection is characterized by reduced glycolytic activity, which is associated with the reprogramming of redox homeostasis and the survival of the latent reservoir (Fig. 1). The functional dependence of the virus on glucose metabolism is further supported by evidence that restricting glycolysis through the replacement of glucose with galactose substantially suppresses viral replication.

It should be noted that mitophagy, the selective removal of damaged mitochondria by the cellular autophagic machinery, is an important component of mitochondrial homeostasis. Impairment of this process may lead to the accumulation of functionally compromised organelles, increased ROS production, and alterations in intracellular signaling responses (Teodorof-Diedrich et al., 2018). In particular, experimental models have linked the effects of the Tat protein to disturbances in mitochondrial dynamics and mitophagy in microglia, accompanied by microglial activation and enhanced inflammatory responses. These findings suggest a potential link between impaired mitochondrial quality control and the maintenance of cellular inflammation, although the underlying mechanisms may differ among cell types (Rawat et al., 2019; Thangaraj et al., 2018).

Thus, mitochondrial dysfunction, excessive ROS production, and impaired cellular organelle quality control mechanisms represent interconnected components of metabolic alterations during HIV infection. Their significance lies in their potential to disrupt energy production, alter the regulation of intracellular signaling processes, and sustain inflammatory responses. However, these changes are not universal and depend on cell type, viral replication activity, and the effects of ART.

Disruptions in cellular homeostasis during HIV infection also depend on the state of the infectious process. Whereas metabolic alterations during productive infection may support the energy and biosynthetic requirements of viral replication, latently

infected cells exhibit distinct metabolic profiles. In particular, reduced glycolytic activity has been described as a characteristic of HIV-1 latency and is accompanied by changes in redox homeostasis and cellular susceptibility to oxidative stress (Tsoneva et al., 2025). Therefore, mitochondrial and redox alterations should be considered in the context of not only cell type but also the stage of infection and the metabolic state of the cells.

***Lipid and amino acid metabolic changes in HIV infection and their role in viral replication.*** Metabolic reprogramming of cells during HIV-1 infection involves not only changes in carbohydrate metabolism and mitochondrial energy production but also alterations in lipid and amino acid metabolism. These processes are important for meeting the biosynthetic demands of infected cells, regulating intracellular signaling, and maintaining the conditions required for various stages of the viral life cycle.

Lipid metabolism plays an important role in HIV-1 replication because lipids are structural components of cellular membranes and the viral envelope, and they also participate in the formation of membrane microdomains and the organization of intracellular signaling complexes. Following viral entry into the cell and the initiation of viral gene expression, the activity of specific pathways involved in lipid synthesis, transport, and redistribution changes. These alterations may affect the availability of membrane structures required for viral particle assembly, maturation, and release from the cell (Fig. 2) (Tran et al., 2022).

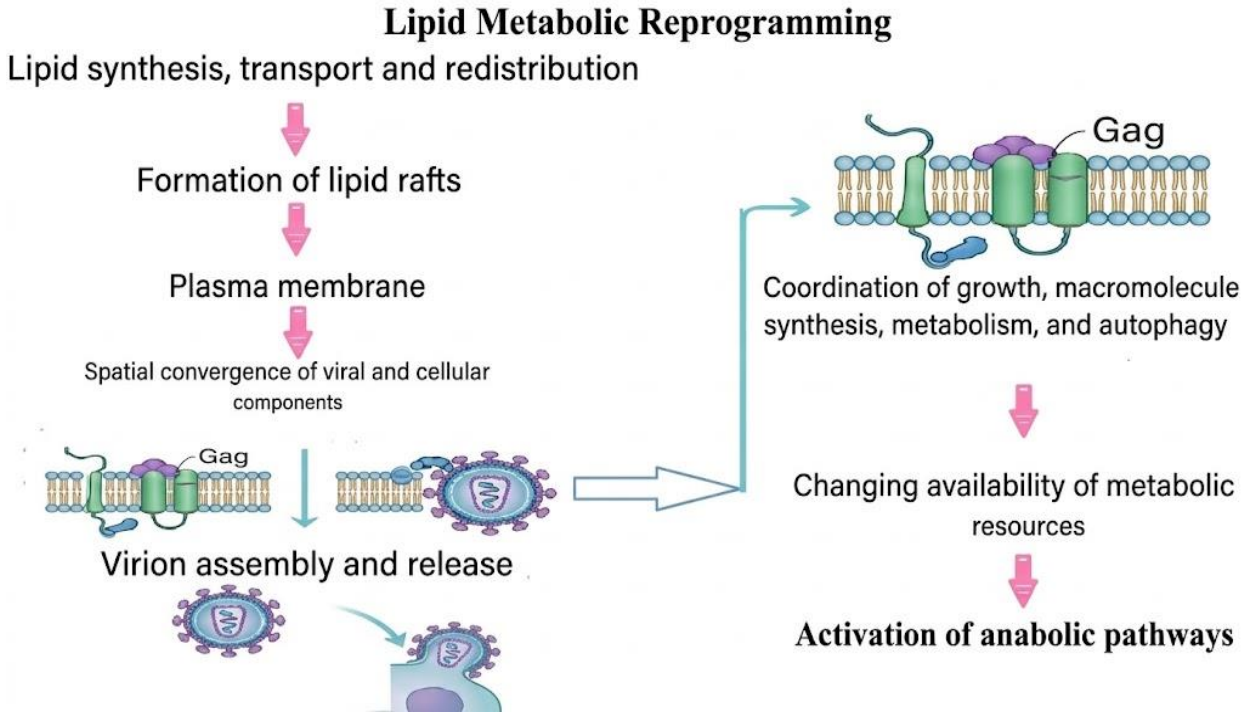



***Fig. 2. Alterations in lipid metabolism during HIV-1 infection and their role in the viral life cycle***
*Note: Gag – group-specific antigen HIV*

Cholesterol and sphingolipids are of particular importance because they contribute to the organization of plasma membrane lipid microdomains. These regions may facilitate the spatial proximity of viral and cellular components involved in virion assembly. In particular, the viral Gag protein provides the structural framework for new HIV virions and mediates their assembly at the plasma membrane of the host cell. The local lipid composition of the membrane influences the efficiency of these processes, although the extent of dependence on individual lipid components varies among cellular models. The incorporation of cholesterol and other lipids into the envelope of newly formed virions may also affect its physical properties and the subsequent infectivity of viral particles (Denieva et al., 2024).

In addition to their structural role, lipids participate in the regulation of intracellular signaling pathways, particularly PI3K/AKT/mTOR, which coordinate cell growth, macromolecule synthesis, metabolism, and autophagy. Viral proteins may modulate these signaling systems, thereby altering the availability of metabolic resources to infected cells (Cai et al., 2024). In particular, the activation of anabolic processes promotes the synthesis of fatty acids and membrane lipids required for the formation of new viral particles. However, disturbances in lipid

metabolism during HIV-1 infection are not limited to the metabolic requirements of the virus; they are also associated with immune activation, chronic inflammation, and changes in the functional state of host cells (Moezpoor et al., 2024).

Amino acid metabolism plays an important role in the course of HIV infection because amino acids are used for viral protein synthesis, participate in the biosynthesis of nucleotide bases required for viral genome replication, and contribute to the regulation of metabolic processes in the host cell. Glutamine is of particular importance, as it is used not only for protein biosynthesis but also to replenish the pool of TCA cycle intermediates. During glutaminolysis, glutamine is converted into glutamate and subsequently into α-ketoglutarate, which enters mitochondrial metabolism. In this way, glutamine supports cellular metabolic flexibility and helps sustain the biosynthetic processes required for productive viral infection.

In primary $CD4^+$ T lymphocytes, increased glutamine utilization has been associated with greater cellular susceptibility to productive HIV infection and more efficient viral particle production. Its metabolic products may be used for acetyl-CoA synthesis, which contributes to fatty acid biosynthesis and the regulation of protein acetylation. Thus, amino acid metabolism is functionally linked to lipid metabolism: the carbon skeletons of amino acids provide intermediates for biosynthetic reactions, whereas lipids are used to form membrane structures required during the late stages of the viral life cycle (Yao et al., 2022).

The mTORC1 signaling complex is an important regulator of these processes, and its activity depends, among other factors, on amino acid availability and the cellular energy status (Akbay et al., 2020). Its activation coordinates nutrient transport, protein and lipid synthesis, and other anabolic processes. During HIV infection, interactions between viral and cellular regulatory mechanisms may alter the activity of this signaling hub, thereby affecting the conditions required for viral replication. However, the role of mTORC1 is not limited to directly supporting viral replication, as this complex also participates in the regulation of autophagy, cellular activation, and mechanisms associated with HIV latency (Akbay et al., 2020; Niyomdecha et al., 2020).

Tryptophan metabolism warrants separate consideration, as it is involved in both protein synthesis and the formation of immunoregulatory metabolites. Under conditions of chronic immune activation, its catabolism via the kynurenine pathway may increase through the activity of indoleamine 2,3-dioxygenase 1 (IDO1). Changes in the ratio of tryptophan to its metabolites reflect alterations in immunometabolic regulation (Qi et al., 2018). Kynurenine metabolites can influence immune cell activity, particularly through the aryl hydrocarbon receptor (AhR). Therefore, this pathway is considered one of the links between amino acid metabolism, chronic inflammation, and impaired antiviral immune responses. However, these changes should not be interpreted exclusively as a mechanism supporting HIV replication, since their effects depend on the cellular context and stage of infection (Mehraj et al., 2015).

Thus, alterations in lipid and amino acid metabolism during HIV infection form an interconnected system that supports metabolic requirements and regulates cellular functions. Glutaminolysis replenishes TCA cycle intermediates and provides substrates for anabolic reactions, whereas lipid synthesis and redistribution contribute to the formation of membrane structures required for viral particle assembly and release. At the same time, changes in amino acid and lipid metabolism affect signaling pathways, immune responses, and cellular homeostasis. Taken together, these processes underscore that the HIV life cycle depends not on an isolated alteration in a particular metabolic pathway, but on the coordinated reprogramming of cellular metabolism.

***Effects of ART on Cellular and Systemic Metabolism.*** ART remains the cornerstone of HIV-1 management, limiting viral multiplication, facilitating immune system restoration, and lowering the likelihood of HIV-related complications. Nevertheless, prolonged exposure to antiretroviral agents can be associated with metabolic alterations at both the cellular and whole-body levels. These effects vary according to the pharmacological class of the drugs, the combination used, treatment duration, and the patient's individual metabolic characteristics (Menéndez-Arias et al., 2022).

Suppression of HIV replication reduces the intensity of infection-induced immune activation and systemic inflammation. This may mitigate the adverse effects of chronic inflammation on metabolism, although it does not always ensure complete restoration of metabolic homeostasis (Alum, 2024).

At the cellular level, the metabolic effects of ART vary substantially among individual drugs and pharmacological classes. Mitochondrial toxicity has been particularly associated with nucleoside reverse transcriptase inhibitors (NRTIs), including zidovudine (AZT; ZDV) and stavudine (d4T). One of the mechanisms underlying this toxicity is the inhibition of mitochondrial DNA polymerase γ, which may impair mitochondrial DNA replication, compromise respiratory chain function, and

contribute to increased ROS production. Clinically, these effects have been associated with lipoatrophy, hyperlactatemia, and, in some cases, lactic acidosis and hepatic steatosis. The mitochondrial toxicity of contemporary NRTIs, including tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), is substantially lower than that associated with older agents, although their metabolic profiles are not identical (Bailin et al., 2024).

Protease inhibitors (PIs) have been associated with dyslipidemia and impaired glucose homeostasis, although the magnitude of these effects differs among individual agents. Some PIs may interfere with insulin-stimulated glucose transport, including GLUT4-mediated glucose uptake, and alter lipid synthesis and processing. These effects may contribute to increased circulating triglyceride and low-density lipoprotein cholesterol levels, insulin resistance, and changes in adipose tissue distribution. Certain PI-containing regimens have also been associated with lipodystrophy, particularly when combined with older NRTIs. However, the metabolic effects of PIs are not uniform across the class, and differences between individual drugs should be taken into account (Papantoniou et al., 2024).

Integrase strand transfer inhibitors (INSTIs), including dolutegravir (DTG) and bictegravir (BIC), have become important components of contemporary ART regimens. Although these agents generally have a favorable virological efficacy and tolerability profile, greater weight gain has been observed with some INSTI-based regimens, particularly those containing DTG or BIC. Weight changes may also be influenced by the accompanying NRTI backbone, with greater weight gain reported in some studies for TAF-containing than for TDF-containing regimens (Sax et al., 2020; Mallon et al., 2021). These observations should not be interpreted as evidence that all INSTIs directly cause insulin resistance. Rather, changes in body weight and composition may contribute to the subsequent development of metabolic risk in susceptible individuals. The underlying mechanisms remain incompletely understood, and the relative contributions of the individual drugs, restoration of health following viral suppression, and patient-related factors continue to be investigated (Sax et al., 2020; Bailin et al., 2024).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) also differ in their metabolic profiles. Efavirenz (EFV) has been associated with increases in circulating lipid concentrations, whereas newer agents, including rilpivirine (RPV) and doravirine (DOR), generally exhibit more favorable lipid profiles in comparative studies. These differences indicate that metabolic effects should be assessed at the level of individual drugs rather than attributed uniformly to the entire NNRTI class. In addition, changes in lipid concentrations during ART may reflect the combined effects of the treatment regimen, HIV-associated inflammation, and individual metabolic characteristics (Tebas et al., 2014; Maggi et al., 2023).

ART-associated metabolic changes also affect lipid homeostasis. Alterations in circulating total cholesterol, LDL-C, HDL-C, and triacylglycerol levels have been reported in individuals undergoing treatment, with the magnitude and direction of these effects varying across therapeutic regimens (Bailin et al., 2024). Certain protease inhibitors and nucleoside reverse transcriptase inhibitors have been linked to dyslipidemia and changes in fat distribution. By contrast, tenofovir disoproxil fumarate has demonstrated a comparatively favorable profile for some lipid measures relative to other antiretroviral agents.

Alterations in lipid metabolism may be accompanied by disturbances in carbohydrate metabolism regulation. In some patients receiving ART, weight gain, reduced tissue sensitivity to insulin, and impaired blood glucose regulation have been reported (Bailin et al., 2024; Maggi et al., 2023). In particular, weight gain has been observed in patients receiving integrase inhibitor-based regimens, as well as tenofovir alafenamide. However, these changes are not universal and depend on the combination of drugs, baseline metabolic status, age, and other individual factors (Sax et al., 2020).

At the systemic level, the metabolic effects of ART reflect the combined influence of viral suppression, immune recovery, the pharmacological properties of individual antiretroviral agents, and patient-related factors. Older NRTIs, particularly zidovudine and stavudine, have been associated with mitochondrial toxicity and peripheral fat loss, whereas some protease inhibitor-containing regimens have been linked to dyslipidemia, impaired insulin sensitivity, and changes in adipose tissue distribution. Contemporary NRTIs generally have a more favorable mitochondrial safety profile, although differences in lipid outcomes remain relevant when comparing TDF- and TAF-containing regimens. In addition, greater weight gain has been reported with some INSTI-based regimens, particularly those containing dolutegravir or bictegravir. NNRTIs also differ in their effects on lipid metabolism. These class-specific differences underscore the importance of considering the complete treatment regimen, baseline metabolic status, and individual risk factors when evaluating the long-term metabolic consequences of ART. Although effective viral suppression reduces HIV-associated immune

activation, it does not necessarily eliminate all metabolic disturbances.

The main metabolic effects associated with different classes of antiretroviral drugs are summarized in Table 1.

***Table 1.***

***Class-specific metabolic effects of antiretroviral therapy***

| Antiretroviral drug class | Representative drugs | Main metabolic effects |
|---|---|---|
| NRTIs | Zidovudine, stavudine | Agents have been associated with mitochondrial toxicity, impaired mitochondrial DNA replication, lipoatrophy, and, in some cases, hyperlactatemia and lactic acidosis. |
| | Tenofovir disoproxil fumarate, tenofovir alafenamide | Lower mitochondrial toxicity than older NRTIs. TDF is generally associated with a more favorable lipid profile than TAF, although their effects on renal function, bone health, and other metabolic parameters differ. |
| NNRTIs | Efavirenz, rilpivirine, doravirine | Metabolic effects vary by agent. Efavirenz has been associated with less favorable lipid changes than some newer NNRTIs. |
| PIs | Selected agents within the PI class | Depending on the drug, possible effects include dyslipidemia, impaired insulin sensitivity, and alterations in adipose tissue distribution. |
| INSTIs | Dolutegravir, bictegravir | Some INSTI-based regimens have been associated with greater weight gain. The magnitude of weight change may depend on the accompanying NRTI backbone and individual patient characteristics. |

*Note: NRTIs – нуклеозидні/нуклеотидні інгібітори зворотної транскриптази; NNRTIs – ненуклеозидні інгібітори зворотної транскриптази; PIs – інгібітори протеази; INSTIs – інгібітори перенесення ланцюга інтегразою*

Overall, the metabolic effects of ART depend on the specific drugs used, the composition of the treatment regimen, and individual patient characteristics. These differences highlight the importance of monitoring metabolic parameters during long-term treatment.

**Conclusion.** HIV induces cellular metabolic reprogramming, manifested by changes in glycolytic activity, the use of glutamine to replenish TCA cycle intermediates, the involvement of lipids in the formation of new virions, and alterations in tryptophan metabolism. Mitochondrial dysfunction and increased ROS production may disrupt redox homeostasis, sustain inflammatory processes, and adversely affect immune cell function. Antiretroviral therapy suppresses HIV replication and helps reduce immune activation; however, its metabolic effects depend on the drugs used. Certain nucleoside reverse transcriptase inhibitors may affect mitochondrial function, whereas some treatment regimens are associated with changes in lipid levels, weight gain, and impaired glucose regulation. These alterations may increase cardiometabolic risk, highlighting the need to monitor metabolic parameters during long-term therapy.

Thus, HIV infection and antiretroviral therapy exert distinct effects on cellular and systemic metabolism. Understanding these changes is important for assessing metabolic disturbances and improving approaches to the long-term management of patients with HIV infection.

**References:**


1. Akbay, B., Shmakova, A., Vassetzky, Y., & Dokudovskaya, S. (2020). Modulation of mTORC1 signaling pathway by HIV-1. *Cells*, *9*(5), 1090. https://doi.org/10.3390/cells9051090
2. Alum, E. U., Uti, D. E., Ugwu, O. P., & Alum, B. N. (2024). Toward a cure – advancing HIV/AIDS treatment modalities beyond antiretroviral therapy: A review. *Medicine*, *103*(27), e38768. https://doi.org/10.1097/MD.0000000000038768
3. Avdoshina, V., Fields, J. A., Castellano, P., Dedoni, S., Palchik, G., Trejo, M., Adame, A., Rockenstein, E., Eugenin, E., Masliah, E., & Mocchetti, I. (2016). The HIV protein gp120 alters mitochondrial dynamics in neurons. *Neurotoxicity Research*, *29*(4), 583–593. https://doi.org/10.1007/s12640-016-9608-6
4. Bailin, S. S., & Koethe, J. R. (2024). Weight gain and antiretroviral therapy. *Infectious Disease Clinics of North America*, *38*(3), 499–515. https://doi.org/10.1016/j.idc.2024.04.005

5. Cai, J. F., Zhou, J. S., Meng, Z. Y., Wu, Z. Q., Zhao, J. C., Peng, H. X., Liang, X. Y., Chen, J. J., Wang, P. P., & Deng, K. (2024). Ripretinib inhibits HIV-1 transcription through modulation of PI3K-AKT-mTOR. *Acta Pharmacologica Sinica*, *45*(8), 1632–1643. https://doi.org/10.1038/s41401-024-01282-z
6. Capendale, P. E., Helgers, L. C., Ambikan, A. T., Vieira de Sá, R., Wolthers, K. C., Geijtenbeek, T. B. H., Sridhar, A., Neogi, U., & Pajkrt, D. (2026). Microglia cause HIV-induced transcriptional and metabolic changes in human neural organoids. *Communications Biology*, *9*(1), 436. https://doi.org/10.1038/s42003-026-09864-9
7. Clerc, I., Moussa, D. A., Vahlas, Z., Tardito, S., Oburoglu, L., Hope, T. J., Sitbon, M., Dardalhon, V., Mongellaz, C., & Taylor, N. (2019). Entry of glucose- and glutamine-derived carbons into the citric acid cycle supports early steps of HIV-1 infection in CD4 T cells. *Nature Metabolism*, *1*(7), 717–730. https://doi.org/10.1038/s42255-019-0084-1
8. Crater, J. M., Nixon, D. F., & Furler O'Brien, R. L. (2022). HIV-1 replication and latency are balanced by mTOR-driven cell metabolism. *Frontiers in Cellular and Infection Microbiology*, *12*, 1068436. https://doi.org/10.3389/fcimb.2022.1068436
9. De Masson d'Autume, V., LeDouce, V., Dutilleul, A., O'Reilly, S., François, N., Formiconi, E., Angieladis, M., Pilosio, L., Bendoumou, M., Leon, A. G., Alalwan, D., Moore, E., McGinty, T., Valle-Casuso, J. C., Macken, A., Rohr, O., Van Lint, C., Sáez-Cirión, A., Cotter, A., Feeney, E., Mallon, P. W. G., & Gautier, V. W. (2026). Metabolic reprogramming of CD4+ T cells by Zaprinast induces HIV-1 latency reversal ex vivo. *Retrovirology*, *23*(1), 10. https://doi.org/10.1186/s12977-026-00680-x
10. Denieva, Z. G., Kuzmin, P. I., Galimzyanov, T. R., Datta, S. A. K., Rein, A., & Batishchev, O. V. (2024). Human immunodeficiency virus type 1 Gag polyprotein modulates membrane physical properties like a surfactant: Potential implications for virus assembly. *ACS Infectious Diseases*, *10*(8), 2870–2885. https://doi.org/10.1021/acsinfecdis.4c00251
11. Fields, J. A., & Ellis, R. J. (2019). HIV in the cART era and the mitochondrial: immune interface in the CNS. *International Review of Neurobiology*, *145*, 29–65. https://doi.org/10.1016/bs.irn.2019.04.003
12. Hegedus, A., Kavanagh Williamson, M., & Huthoff, H. (2014). HIV-1 pathogenicity and virion production are dependent on the metabolic phenotype of activated CD4+ T cells. *Retrovirology*, *11*, 98. https://doi.org/10.1186/s12977-014-0098-4
13. Hulgan, T., & Samuels, D. C. (2021). Mitochondria and human immunodeficiency virus: A troubled relationship enters its fourth decade. *Clinical Infectious Diseases*, *73*(2), e474–e476. https://doi.org/10.1093/cid/ciaa983
14. Ivanov, A. V., Valuev-Elliston, V. T., Ivanova, O. N., Kochetkov, S. N., Starodubova, E. S., Bartosch, B., & Isaguliants, M. G. (2016). Oxidative stress during HIV infection: Mechanisms and consequences. *Oxidative Medicine and Cellular Longevity*, *2016*, 8910396. https://doi.org/10.1155/2016/8910396
15. Kalra, D. K., Vorla, M., Michos, E. D., Agarwala, A., Virani, S., Duell, P. B., & Raal, F. J. (2023). Dyslipidemia in human immunodeficiency virus disease: JACC review topic of the week. *Journal of the American College of Cardiology*, *82*(2), 171–181. https://doi.org/10.1016/j.jacc.2023.04.050
16. Kavanagh Williamson, M., Coombes, N., Juszczak, F., Athanasopoulos, M., Khan, M. B., Eykyn, T. R., Srenathan, U., Taams, L. S., Dias Zeidler, J., Da Poian, A. T., & Huthoff, H. (2018). Upregulation of glucose uptake and hexokinase activity of primary human CD4+ T cells in response to infection with HIV-1. *Viruses*, *10*(3), 114. https://doi.org/10.3390/v10030114
17. Kayode, Y. I., Clemmer, D. C., Owolabi, A. A., AlShaheeb, A. A., McMahon, E. K., Tangiyan, A., Clark, L., Simmons, G. E., Bosque, A., McReynolds, M. R., & Taylor, H. E. (2025). Glucose-fueled histone modifications drive HIV-1 latency reversal at hypoxia. *bioRxiv* [Preprint]. https://doi.org/10.1101/2025.09.14.676169
18. Kidwell, C. U., Casalini, J. R., Pradeep, S., Scherer, S. D., Greiner, D., Bayik, D., Watson, D. C., Olson, G. S., Lathia, J. D., Johnson, J. S., Rutter, J., Welm, A. L., Zangle, T. A., & Roh-Johnson, M. (2023). Transferred mitochondria accumulate reactive oxygen species, promoting proliferation. *eLife*, *12*, e85494. https://doi.org/10.7554/eLife.85494
19. König, T., & McBride, H. M. (2024). Mitochondrial-derived vesicles in metabolism, disease, and aging. *Cell Metabolism*, *36*(1), 21–35. https://doi.org/10.1016/j.cmet.2023.11.014
20. Maggi, P., Ricci, E. D., Martinelli, C. V., De Socio, G. V., Squillace, N., Molteni, C., Masiello, A., Orofino, G., Menzaghi, B., Bellagamba, R., Vichi, F., Celesia, B. M., Madeddu, G., Pellicanò, G. F., Carleo, M. A., Cascio, A., Parisini, A., Taramasso, L., Valsecchi, L., Calza, L., & CISAI Study Group. (2023). Lipids and transaminase in antiretroviral-treatment-experienced people living with HIV, switching to a doravirine-based vs. a rilpivirine-based regimen: Data from a real-life setting. Viruses, 15(7), 1612. https://doi.org/10.3390/v15071612
21. Mallon, P. W., Brunet, L., Hsu, R. K., Fusco, J. S., Mounzer, K. C., Prajapati, G., Beyer, A. P., Wohlfeiler, M. B., & Fusco, G. P. (2021). Weight gain before and after switch from TDF to TAF in a U.S. cohort study. *Journal of the International AIDS Society*, 24(4), e25702. https://doi.org/10.1002/jia2.25702
22. Mbonye, U., & Karn, J. (2017). The molecular basis for human immunodeficiency virus latency. *Annual Review of Virology*, *4*(1), 261–285. https://doi.org/10.1146/annurev-virology-101416-041646

23. Mehraj, V., & Routy, J. P. (2015). Tryptophan catabolism in chronic viral infections: Handling uninvited guests. *International Journal of Tryptophan Research*, *8*, 41–48. https://doi.org/10.4137/IJTR.S26862
24. Menéndez-Arias, L., & Delgado, R. (2022). Update and latest advances in antiretroviral therapy. *Trends in Pharmacological Sciences*, *43*(1), 16–29. https://doi.org/10.1016/j.tips.2021.10.004
25. Moezpoor, M. R., & Stevenson, M. (2024). Help or hinder: Protein host factors that impact HIV-1 replication. *Viruses*, *16*(8), 1281. https://doi.org/10.3390/v16081281
26. Muccilli, S. G., Schwarz, B., Shue, B., Jessop, F., Shannon, J. G., Larson, C. L., Hage, A., Hong, S. H., Bohrnsen, E., Hsu, T., Ashbrook, A. W., Sturdevant, G. L., Robertson, S. J., Guarnieri, J. W., Lack, J., Wallace, D. C., Bosio, C. M., MacDonald, M. R., Rice, C. M., Yewdell, J. W., & Best, S. M. (2025). Mitochondrial hyperactivity and reactive oxygen species drive innate immunity to the yellow fever virus-17D live-attenuated vaccine. *PLOS Pathogens*, *21*(4), e1012561. https://doi.org/10.1371/journal.ppat.1012561
27. Niyomdecha, N., Suptawiwat, O., Boonarkart, C., Jitobaom, K., & Auewarakul, P. (2020). Inhibition of human immunodeficiency virus type 1 by niclosamide through mTORC1 inhibition. *Heliyon*, *6*(6), e04050. https://doi.org/10.1016/j.heliyon.2020.e04050
28. Papantoniou, E., Arvanitakis, K., Markakis, K., Papadakos, S. P., Tsachouridou, O., Popovic, D. S., Germanidis, G., Koufakis, T., & Kotsa, K. (2024). Pathophysiology and clinical management of dyslipidemia in people living with HIV: Sailing through rough seas. *Life*, 14(4), Article 449. https://doi.org/10.3390/life14040449
29. Qi, Q., Hua, S., Clish, C. B., Scott, J. M., Hanna, D. B., Wang, T., Haberlen, S. A., Shah, S. J., Glesby, M. J., Lazar, J. M., Burk, R. D., Hodis, H. N., Landay, A. L., Post, W. S., Anastos, K., & Kaplan, R. C. (2018). Plasma tryptophan-kynurenine metabolites are altered in human immunodeficiency virus infection and associated with progression of carotid artery atherosclerosis. *Clinical Infectious Diseases*, *67*(2), 235–242. https://doi.org/10.1093/cid/ciy053
30. Rawat, P., Teodorof-Diedrich, C., & Spector, S. A. (2019). Human immunodeficiency virus type-1 single-stranded RNA activates the NLRP3 inflammasome and impairs autophagic clearance of damaged mitochondria in human microglia. *Glia*, *67*(5), 802–824. https://doi.org/10.1002/glia.23568
31. Roca-Bayerri, C., Robertson, F., Pyle, A., Hudson, G., & Payne, B. A. I. (2021). Mitochondrial DNA damage and brain aging in human immunodeficiency virus. *Clinical Infectious Diseases*, *73*(2), e466–e473. https://doi.org/10.1093/cid/ciaa984
32. Rozzi, S. J., Avdoshina, V., Fields, J. A., Trejo, M., Ton, H. T., Ahern, G. P., & Mocchetti, I. (2017). Human immunodeficiency virus promotes mitochondrial toxicity. *Neurotoxicity Research*, *32*(4), 723–733. https://doi.org/10.1007/s12640-017-9776-z
33. Sax, P. E., Erlandson, K. M., Lake, J. E., McComsey, G. A., Orkin, C., Esser, S., Brown, T. T., Rockstroh, J. K., Wei, X., Carter, C. C., Zhong, L., Brainard, D. M., Melbourne, K., Das, M., Stellbrink, H. J., Post, F. A., Waters, L., & Koethe, J. R. (2020). Weight gain following initiation of antiretroviral therapy: Risk factors in randomized comparative clinical trials. *Clinical Infectious Diseases*, *71*(6), 1379–1389. https://doi.org/10.1093/cid/ciz999
34. Sen, S., Kaminiski, R., Deshmane, S., Langford, D., Khalili, K., Amini, S., & Datta, P. K. (2015). Role of hexokinase-1 in the survival of HIV-1-infected macrophages. *Cell Cycle*, *14*(7), 980–989. https://doi.org/10.1080/15384101.2015.1006971
35. Shytaj, I. L., Procopio, F. A., Tarek, M., Carlon-Andres, I., Tang, H. Y., Goldman, A. R., Munshi, M., Kumar Pal, V., Forcato, M., Sreeram, S., Leskov, K., Ye, F., Lucic, B., Cruz, N., Ndhlovu, L. C., Bicciato, S., Padilla-Parra, S., Diaz, R. S., Singh, A., Lusic, M., Karn, J., Alvarez-Carbonell, D., & Savarino, A. (2021). Glycolysis downregulation is a hallmark of HIV-1 latency and sensitizes infected cells to oxidative stress. *EMBO Molecular Medicine*, *13*(8), e13901. https://doi.org/10.15252/emmm.202013901
36. Siripurapu, R., & Ota, Y. (2023). Human immunodeficiency virus: Opportunistic infections and beyond. *Neuroimaging Clinics of North America*, *33*(1), 147–165. https://doi.org/10.1016/j.nic.2022.07.014
37. Tebas, P., Sension, M., Arribas, J., Duiculescu, D., Florence, E., Hung, C. C., Wilkin, T., Vanveggel, S., Stevens, M., Deckx, H., & ECHO and THRIVE Study Groups. (2014). Lipid levels and changes in body fat distribution in treatment-naive, HIV-1-infected adults treated with rilpivirine or efavirenz for 96 weeks in the ECHO and THRIVE trials. *Clinical Infectious Diseases*, 59(3), 425–434. https://doi.org/10.1093/cid/ciu234
38. Teodorof-Diedrich, C., & Spector, S. A. (2018). Human immunodeficiency virus type 1 gp120 and tat induce mitochondrial fragmentation and incomplete mitophagy in human neurons. *Journal of Virology*, *92*(22), e00993-18. https://doi.org/10.1128/JVI.00993-18
39. Thangaraj, A., Periyasamy, P., Liao, K., Bendi, V. S., Callen, S., Pendyala, G., & Buch, S. (2018). HIV-1 TAT-mediated microglial activation: Role of mitochondrial dysfunction and defective mitophagy. *Autophagy*, *14*(9), 1596–1619. https://doi.org/10.1080/15548627.2018.1476810
40. Tran, N., Oh, Y., Sutherland, M., Cui, Q., & Hong, M. (2022). Cholesterol-mediated clustering of the HIV fusion protein gp41 in lipid bilayers. *Journal of Molecular Biology*, *434*(2), 167345. https://doi.org/10.1016/j.jmb.2021.167345

41. Wik, J. A., & Skålhegg, B. S. (2022). T cell metabolism in infection. *Frontiers in Immunology*, *13*, 840610. https://doi.org/10.3389/fimmu.2022.840610
42. Yao, W., Strebel, K., Yamaoka, S., & Yoshida, T. (2022). Simian immunodeficiency virus SIVgsn-99CM71 Vpu employs different amino acids to antagonize human and greater spot-nosed monkey BST-2. *Journal of Virology*, *96*(4), e01527-21. https://doi.org/10.1128/JVI.01527-21
43. Yu, X., Zhou, J., Lei, J., Ge, H., Zhang, Z., Fu, Y., Han, X., Hu, Q., Ding, H., Geng, W., Shang, H., & Jiang, Y. (2025). Impaired natural killer cell migration in HIV-infected individuals is caused by TIGIT-mediated inhibition of HIF-1alpha-dependent glycolysis. *Cell Death & Disease*, *16*(1), 805. https://doi.org/10.1038/s41419-025-08039-4
44. Zhong, P., Liu, C. H., Chen, Y. T., & Yu, T. Y. (2020). The study of HIV-1 Vpr-membrane and Vpr-hVDAC-1 interactions by graphene field-effect transistor biosensors. *ACS Applied Bio Materials*, *3*(9), 6351–6357. https://doi.org/10.1021/acsabm.0c00783
45. Tsoneva, E., & Yordanov, A. (2025). HPV oncoproteins and mitochondrial reprogramming: The central role of ROMO1 in oxidative stress and metabolic shifts. Cells, 14(20), 1629. https://doi.org/10.3390/cells14201629

# ВІРУС-ІНДУКОВАНІ ПОРУШЕННЯ КЛІТИННОГО МЕТАБОЛІЗМУ ПРИ ВІЛ-ІНФЕКЦІЇ ТА ВПЛИВ АНТИРЕТРОВІРУСНОЇ ТЕРАПІЇ

**О.В. Кеца**

*Чернівецький національний університет імені Юрія Федьковича,*
*вул. Коцюбинського, 2, Чернівці, 58012, Україна*
*o.ketsa@chnu.edu.ua*

*У роботі проведено комплексний аналіз сучасних наукових даних щодо механізмів вірус-індукованих порушень клітинного метаболізму при інфекції вірусу імунодефіциту людини (ВІЛ) та впливу антиретровірусної терапії (АРТ) на метаболічні процеси й функціональний стан клітин. Основну увагу приділено змінам енергетичного обміну, метаболізму глюкози, ліпідів і амінокислот, порушенням функціонування мітохондрій, розвитку окисно-відновного дисбалансу та регуляції клітинної відповіді. Мета роботи – оцінити основні механізми вірус-індукованих порушень клітинного метаболізму при ВІЛ-інфекції та з'ясувати особливості впливу АРТ на метаболічні процеси й функціональний стан клітин. Для досягнення мети використано методи системного, порівняльного та критичного аналізу, узагальнення наукових публікацій. Інформаційну базу дослідження сформовано на основі праць, відібраних у міжнародних наукометричних і бібліографічних ресурсах PubMed, Scopus, Web of Science, ScienceDirect та Google Scholar. Встановлено, що ВІЛ-інфекція супроводжується змінами метаболічних шляхів, які беруть участь у забезпеченні енергетичних потреб клітини, синтезі біомолекул і регуляції імунної відповіді. Зокрема, зміни метаболізму глюкози та мітохондріальної функції можуть впливати на продуктивну реплікацію вірусу, підтримання латентного стану та стійкість інфікованих клітин до окисного стресу. Показано взаємозв'язок енергетичного, ліпідного й амінокислотного обміну з клітинними сигнальними шляхами, зокрема mTORC1, які беруть участь у регуляції анаболічних процесів, аутофагії та клітинної активації. Окрему увагу приділено мітохондріальній дисфункції, утворенню активних форм кисню (АФК) та метаболічним змінам, пов'язаним із застосуванням АРТ. Отже, аналіз наукових джерел засвідчує, що метаболічні порушення є важливим компонентом взаємодії ВІЛ із клітинами-господаря, а їхнє вивчення дає змогу поглибити розуміння механізмів вірусної персистенції, порушення імунної функції та потенційних метаболічних наслідків лікування.*

*Ключові слова: вірус імунодефіциту людини, метаболізм, гліколіз, мітохондрії, окисно-відновний дисбаланс, ліпіди, амінокислоти, антиретровірусна терапія*

*Отримано редколегією 15.08.2026 р.*
*Підписано до друку 15.10.2026 р.*
*Дата публікації 31.10.2026 р.*

**ORCID ID**
Oksana Ketsa: https://orcid.org/0000-0002-2695-1790