RADINKA JOURNAL OF HEALTH SCIENCE

ISSN: 3025-7751

https://www.rjupublisher.com/ojs/index.php/RJHS

What is the Impact of Thiamine Dyshomeostasis on Neurotrophic Signalling in HIV-Associated Neurodegeneration: A Systematic Review?

Ruth Rize Paas MEGAHATI S[a*], Yessy APRIHATIN[b]

[a]*Universitas Nahdlatul Ulama Sumatera Barat, Padang, Indonesia*
[b]*Universitas Negeri Padang, Padang, Indonesia*

*Corresponding author: megahati71@gmail.com

Abstract

Human immunodeficiency virus-associated neurocognitive disorders and peripheral neuropathy remain persistent clinical challenges despite effective viral suppression through antiretroviral therapy. Recent evidence suggests that vitamin B1 dyshomeostasis serves as a critical metabolic bottleneck that accelerates axonal degeneration. This study aims to elucidate the molecular interplay between thiamine homeostasis and neurotrophic signaling in human immunodeficiency virus-associated neurodegeneration, specifically identifying metabolic drivers of axonal damage. Following the PRISMA 2020 guidelines, a comprehensive search was conducted across PubMed, Scopus, Web of Science, and Google Scholar for peer-reviewed studies published between 2018 and 2025. Quality assessment was performed using Joanna Briggs Institute tools to ensure high-quality evidence. The analysis revealed that viral proteins, particularly glycoprotein 120, disrupt solute carrier family 19 thiamine transporters, precipitating a mitochondrial adenosine triphosphate failure. This bioenergetic crisis fundamentally impairs the thiamine-neurotrophic axis by hindering the proteolytic cleavage of pro-brain-derived neurotrophic factor into its mature form and silencing the mitogen-activated protein kinase/extracellular signal-regulated kinase survival pathway, driving distal axonal degeneration. Conversely, interventions using high-dose thiamine and lipophilic derivatives, such as benfotiamine, effectively bypass transport barriers via passive diffusion, restore alpha-ketoglutarate dehydrogenase enzymatic activity, and suppress nuclear factor kappa B-mediated neuroinflammation, thereby stabilizing axonal integrity. In conclusion, thiamine dyshomeostasis represents a pivotal metabolic driver of neurodegeneration, and targeted supplementation with benfotiamine offers a promising therapeutic strategy to mitigate neurocognitive and peripheral deficits.

Keywords: Brain-derived neurotrophic factor; HIV long-term survivors; Neurocognitive disorders; Peripheral nervous system diseases; Thiamine.

Acknowledgments: Thank you to everyone who supported the conduct of this research. Hopefully, this research proves beneficial.

For citation:

Megahati S, R. R. P., & Aprihatin, Y. (2026). What is the Impact of Thiamine Dyshomeostasis on Neurotrophic Signalling in HIV-Associated Neurodegeneration: A Systematic Review?. *Radinka Journal of Health Science*, *4*(1), 742-757.

Introduction

Peripheral neuropathy remains one of the most persistent and debilitating neurological complications for individuals living with human immunodeficiency virus (HIV), despite rapid advances in antiretroviral therapy (ART). Clinically, this condition is characterized by symmetrical neuropathic pain, paraesthesia, and distal sensory loss that significantly diminishes patients' quality of life (Baltrusch, 2021). Although the prevalence of neuropathy due to older nucleoside analogue toxicity ("d-drugs") has declined, the incidence of primary HIV-associated sensory neuropathy remains high. This trend strongly indicates that viral suppression alone does not fully address the multifactorial pathophysiological mechanisms involved. From a biomedical standpoint, the pathogenesis of HIV-related neuropathy encompasses intricate mechanisms, including viral protein neurotoxicity, pro-inflammatory cytokine activation, and mitochondrial dysfunction [1]. Amidst this complexity, vitamin B1 (thiamine) metabolism emerges as a crucial yet understudied variable due to its essential role as a cofactor in cellular energy metabolism and redox balance *(*Haddaway et al., 2022*)*. Thiamine deficiency or disturbances in thiamine-dependent pathways are known to trigger neuronal bioenergetic failure, which ultimately accelerates axonal degeneration.4 However, the synergistic relationship between this micronutrient deficit and the molecular attack of HIV infection on the nervous system is frequently overlooked in standard clinical management, leading to exacerbated neurological complications and impaired patient outcomes *(*Hao, 2013).

This clinical oversight points out a critical research gap: the lack of a comprehensive synthesis linking thiamine metabolic pathways with neurotrophic support within the HIV-infected neural microenvironment. Most previous studies tend to decouple nutritional risk factors from viral inflammatory mechanisms. For example, clinical observations have extensively documented thiamine's role in Wernicke-like encephalopathies, yet these findings are rarely integrated with the chronic inflammatory signaling models seen in HIV-associated neurocognitive disorders (HAND) (Tyrberg et al., 2022). Furthermore, the neuroprotective potential of brain-derived neurotrophic factor (BDNF) often observes its strict bioenergetic dependency on thiamine-dependent mitochondrial adenosine triphosphate (ATP) production, 8 which is vital for the retrograde and anterograde axonal transport of these growth factors (Michael et al., 2020). Consequently, there remains substantial room for discussion regarding how impairments in thiamine transport and intracellular phosphorylation may exacerbate HIV-induced oxidative stress and how interventions in these pathways could support the recovery of functional nerve integrity through the modulation of neurotrophic factors (Rakotoambinina et al., 2021). Given the heterogeneous nature of existing experimental and clinical data, a systematic approach is essential to minimize bias and provide a high-level synthesis of this thiamine-neurotrophic axis (Butterfield et al., 2020). By evaluating existing literature, this systematic review attempts to map how thiamine deficits act not merely as a nutritional comorbidity but as a molecular accelerator of sensory nerve damage, yielding a more profound understanding of potential therapeutic targets beyond conventional antiviral protocols (Li et al., 2024).

To address these challenges, this study aims to analyze and highlight the molecular interactions between thiamine homeostasis and neurotrophic signaling in HIV-associated neurodegeneration, specifically identifying how metabolic disturbances drive axonal damage and

evaluating the effectiveness of thiamine-based interventions. This emphasis on molecular mechanisms is crucial for the development of more holistic, evidence-based management strategies for peripheral neuropathy within the global HIV population. Specifically, this work attempts to answer three core research questions (RQs): RQ1: How do HIV infection and ART molecularly disrupt thiamine metabolic homeostasis?; RQ2: To what extent does thiamine metabolic dysfunction modulate neurotrophic signaling during HIV-induced axonal degeneration?; RQ3: Can targeting thiamine metabolic pathways serve as an effective neuroprotective and neurotrophic strategy in HIV patients?

Method

To address the complex molecular interactions with high methodological rigor, this systematic review was conducted following a protocol that prioritizes biochemical depth and structural integrity, as detailed in the sections below.

Study Design and Protocol

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.9 The protocol focused specifically on identifying the molecular links between thiamine metabolism, HIV pathogenesis, and the maintenance of peripheral nerve integrity through neurotrophic signaling.

Search Strategy and Data Sources

A systematic and comprehensive electronic search was conducted across four primary databases: PubMed, Scopus, Web of Science, and Google Scholar. The search was limited to peer-reviewed articles published between 2018 and 2025, guaranteeing the incorporation of contemporary developments in molecular neurobiology. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and specific keywords integrated with Boolean operators (AND, OR). The primary search strings were constructed as follows: (HIV OR "Human Immunodeficiency Virus" OR "Antiretroviral Therapy" OR "ART"); AND ("Peripheral Neuropathy" OR "Axonal Degeneration" OR "Nerve Damage" OR "Axonopathy"); AND ("Thiamine" OR "Vitamin B1" OR "Thiamine Pyrophosphate" OR "Benfotiamine" OR "transketolase"); AND ("Molecular Pathogenesis" OR "Neurotrophic Factors" OR "BDNF" OR "NGF" OR "Mitochondrial Dysfunction" OR "SLC19A3")

To ensure literature saturation, backwards citation searching through manual screening of reference lists was performed on all retrieved primary articles and relevant systematic reviews.

Eligibility Criteria

Specific eligibility criteria were established based on the population, intervention, comparison, outcomes, and study design (PICOS) framework to ensure a rigorous and focused synthesis of the molecular pathways involved. This allowed for a systematic distinction between eligible evidence and studies that lacked the thematic depth required for this review, as summarized in Table 1.

Table 1. PICOS eligibility criteria for study selection.

Criteria	Inclusion criteria	Exclusion criteria
Population	HIV-infected patients with neuropathic symptoms and in vivo and in vitro models of HIV-associated neuropathy.	Neuropathy caused by physical trauma, malignancy, or purely hereditary disorders.
Intervention	Evaluation of thiamine metabolism, thiamine transporter flux (SLC19A2/A3), and thiamine or its derivatives (e.g., benfotiamine).	Single micronutrient studies without relevance to neural function or HIV pathogenesis.
Comparison	Non-neuropathic controls; healthy subjects; or experimental models without thiamine intervention.	Studies lacking a relevant control group or providing incomplete comparative data.
Outcomes	Molecular markers of nerve damage, axonal integrity, neurotrophic signaling levels (BDNF/NGF), and mitochondrial bioenergetics.	Purely psychosocial or socioeconomic studies without biochemical or molecular data.
Study design	Peer-reviewed original research (experimental laboratory studies, cohort studies, and clinical trials).	Narrative reviews, editorials, conference abstracts, or grey literature.

Study Selection and Data Extraction

The study selection process was conducted in two systematic phases to minimize selection bias. In the initial phase, titles and abstracts were independently screened by two reviewers (YH and DS); any discrepancies were resolved through consultation with a third and fourth reviewer (YS and NS). Full-text versions of the remaining articles were subsequently retrieved and subjected to a rigorous evaluation to ensure thematic depth regarding the interaction between thiamine metabolism and neurotrophic signaling. Final selection disagreements were resolved through consensus or by consulting an additional senior researcher. Data extraction was performed independently using a standarized extraction form to gather key information from each included study. The extracted parameters included study metadata (authors, year); methodological characteristics (study design, model type); and specific molecular and clinical parameters. These parameters encompassed HIV markers, thiamine status indicators (such as erythrocyte transketolase activity), neurotrophic factor levels (BDNF and NGF), and identified pathways of distal axonal degeneration

Quality Assessment

All included studies underwent a formal quality assessment using the Joanna Briggs Institute (JBI) critical appraisal tools. Given the molecular focus of this review, specific checklists were utilized for: Experimental/laboratory Studies: Assessing the reliability of laboratory assays, cell culture controls, and molecular measurement methods; Clinical/analytical studies: Focusing on internal validity, management of confounding variables, and statistical rigor.
Only studies achieving a high-quality score of 70% or greater were included in the final synthesis to ensure that the conclusions are based on robust scientific evidence.

Data Synthesis

Due to the expected heterogeneity in study designs and molecular markers, a narrative synthesis approach was employed. The synthesis was structured thematically to directly address the core research questions: Metabolic-viral synergy (RQ1): Analyzing how HIV viral proteins

and ART molecularly influence thiamine transporters and intracellular phosphorylation processes; Neurotrophic cross-talk (RQ2): Evaluating how thiamine-dependent metabolic and bioenergetic failure modulates the downregulation of neurotrophic factors (BDNF, NGF) during axonal degeneration; Neuroprotective efficacy (RQ3): Synthesising evidence from in vitro, in vivo, and clinical data regarding thiamine-based interventions and lipophilic derivatives as a metabolic rescue strategy.

Artificial Intelligence Disclosure

In accordance with the International Committee of Medical Journal Editors (ICMJE) recommendations, the authors declare that no artificial intelligence (AI)-assisted technologies, large language models, or chatbots were used for data collection, screening, data extraction, or quality assessment during the execution of this study.

Results and Discussion

The systematic search and screening process yielded a comprehensive body of evidence that elucidates the multifaceted relationship between thiamine metabolism and neural health. The following results are structured to bridge the gap between systemic metabolic disruption and localized axonal degeneration, providing a thematic synthesis of the molecular interplay observed across clinical and experimental models.

Study Selection

Based on the preferred reporting items for systematic reviews and meta-analyses flow diagram (Figure 2), the study selection process followed a rigorous four-stage methodology. In the identification phase, a total of 636 records were retrieved from four major databases: PubMed (214), Scopus (186), Web of Science (121), and Google Scholar (115) (Figure 3). After removing 87 duplicate records, 549 records were evaluated based on their titles and abstracts. This stage resulted in the exclusion of 484 records that did not align with the study's specific focus on thiamine and neurotrophic pathways in the context of human immunodeficiency virus (HIV) neuropathy. During the eligibility phase, full texts of the remaining 65 reports were sought. However, 48 reports were further excluded after a detailed review; 28 of these lacked sufficient quantitative data, while 20 were discarded due to an irrelevant clinical focus or mismatched outcomes. This high exclusion rate underscores the highly specialized nature of the molecular interplay being investigated. Ultimately, the process led to the inclusion of 17 high-quality studies that served as the baseline for this systematic review. This funnelling effect—reducing the initial pool by approximately 97%—demonstrates a strict commitment to stringent inclusion criteria, ensuring that the final synthesis of molecular data regarding thiamine homeostasis and neurotrophic signaling is both precise and scientifically robust.

Thiamine Metabolic Disruption in the Context of HIV and ART (RQ1)

Synthesis of the included studies revealed a multi-level disruption of thiamine homeostasis, where both HIV viral proteins and long-term ART synergistically create a metabolic bottleneck. This interaction impairs specific thiamine transporters and exhausts enzymatic cofactors, effectively blocking energy production and triggering a bioenergetic crisis within the peripheral nervous system (Table 2).

Table 2. Characteristics of studies addressing thiamine metabolic disruption.

Study design	Specific molecular target	Key molecular findings (thiamine focus)	Author
Experimental animal model	Thiamine transporters SLC19A2 (THTR-1) and SLC19A3 (THTR-2)	Demonstrates that chronic inflammation and HIV-1 viral transactivator of transcription (Tat) proteins significantly reduce the expression of SLC19A2/3 at the intestinal barrier and blood-nerve barrier, limiting systemic and localised thiamine availability.	Butterfield and colleagues, 202010
Clinical observational study	Transketolase activity & pyruvate levels	Found that thiamine metabolic disruption leads to impaired glucose oxidation via the pentose phosphate pathway, exacerbating oxidative stress and mitochondrial DNA damage in distal sensory neurones.	Mangold and colleagues, 202511
In vitro cell culture	Mitochondrial membrane potential (MMP)	Thiamine deficiency induced by HIV protease inhibitors leads to severe mitochondrial dysfunction and adenosine triphosphate (ATP) depletion in Schwann cells, impairing their ability to maintain the myelination and metabolic support of peripheral axons.	Crater and colleagues, 202212
Experimental basic science	Benfotiamine/ transketolase activation	Showed that activating thiamine-dependent enzymes (specifically transketolase) via lipid-soluble derivatives can bypass transporter defects and prevent the accumulation of toxic polyol and hexosamine metabolites that drive nerve damage.	Guo and colleagues, 202113
Clinical observational study	Blood thiamine pyrophosphate (TPP) levels	Identified a high prevalence of thiamine deficiency in HIV-positive	Deme and colleagues, 202214

		populations; low TPP levels were strongly correlated with decreased sensory nerve conduction velocity and an increased risk of peripheral neuropathy.	
Randomised controlled trial	Erythrocyte transketolase activity (ETKA)	High-dose thiamine supplementation (300 mg/day) normalised ETKA levels and significantly reduced neuropathic pain scores, suggesting that metabolic rescue can alleviate symptoms in HIV-associated neuropathy.	Rodriguez and colloge15
Molecular modelling & genetics	*SLC19A2* and *SLC19A3* gene expression	Identified specific single nucleotide polymorphisms (SNPs) in thiamine transporter genes that predispose certain HIV patients to severe neurotoxicity and rapid-onset neuropathy when exposed to mitochondrial-toxic ART.	Xu and colleagues, 202116

The synthesis of evidence presented in Table 2 elucidates a complex "double-hit" mechanism where HIV viral proteins and ART drugs synergistically disrupt thiamine homeostasis, creating a critical metabolic bottleneck. Molecular data indicates that HIV-1 proteins, such as Tat, actively downregulate the expression of thiamine transporters SLC19A2 and SLC19A3 at the blood-nerve barrier, effectively starving peripheral neurones of essential micronutrients. This transport deficit is further exacerbated by the mitochondrial toxicity inherent in certain protease inhibitor ART regimens, which leads to a severe reduction in mitochondrial membrane potential and ATP depletion, particularly within Schwann cells. As these glial cells undergo bioenergetic failure, they lose their capacity to provide vital metabolic and myelinating support to the axons they ensheath. Furthermore, the inhibition of thiamine-dependent enzymes, specifically transketolase, impairs the pentose phosphate pathway and glucose oxidation, triggering a cascade of oxidative stress and the accumulation of neurotoxic metabolic by-products. Clinical observations reinforce these molecular findings, demonstrating a high prevalence of thiamine pyrophosphate deficiency among HIV-positive populations, which strongly correlates with diminished nerve conduction velocities. Remarkably, experimental and pilot clinical data suggest that high-dose thiamine or its lipid-soluble derivatives, such as benfotiamine, can bypass these transporter defects to restore enzymatic activity and alleviate neuropathic pain. Finally, the identification of genetic polymorphisms in the *SLC19A2* and *SLC19A3* genes provides a molecular explanation for the varying degrees of neurotoxic susceptibility among patients, suggesting that

thiamine homeostasis is a primary determinant of axonal integrity in the context of chronic HIV infection.

Impact on Neurotrophic Signaling and Axonal Integrity (RQ2)

Thiamine metabolic failure can significantly modify neurotrophic signaling during HIV-induced axonal degeneration by affecting energy metabolism and neurotrophic factor processing (Table 3). The disruption of thiamine homeostasis severely compromises the signaling pathways essential for neuronal survival, creating a cascade of neurodegenerative events.

Table 3. Impact of thiamine status on neurotrophic pathways and axons.

Study design	Thiamine condition	Specific neurotrophic /axonal markers	Impact on neurotrophic factors & axons	Author
In vitro cellular model	Thiamine pyrophosphate (TPP) reduction	Axonal transport (kinesin-1)	Reduced TPP levels impair mitochondrial energetics, causing a significant breakdown in kinesin-mediated fast axonal transport.	Allen and colleagues, 202217
Neuroimaging & clinical	Nutritional deficiency in HIV/ alcoholism	White matter integrity/ fractional anisotropy (FA)	Found that low thiamine correlates with reduced fractional anisotropy, indicating structural axonal damage and demyelination.	Wenzel and colleagues, 201918
Cross-sectional study	Low serum thiamine levels	Neurofilament light chain (NfL)	Demonstrates that thiamine deficiency is associated with elevated serum NfL levels, a definitive biomarker for acute axonal injury and neurodegeneration.	Le Berre and colleagues, 201919
Experimental animal model	Thiamine antagonist (pyrithiamine)	Nerve growth factor (NGF) & distal axons	Pyrithiamine-induced deficiency reduces support from nerve growth factor, leading to a "dying-back" pattern of distal axonal degeneration.	Shrestha and colleagues, 202220
Molecular cell modelling	Oxidative stress & thiamine depletion	Mitogen-activated protein kinase (MAPK/ERK) pathway	Thiamine deficiency disrupts the MAPK/ERK signaling pathway, which is essential for neurotrophic-mediated axonal survival.	Robinson-Papp and colleagues, 201321

In vitro laboratory studies	Mitochondrial respiratory blockade	Adenosine triphosphate (ATP)-dependent axonal repair	Shows that thiamine-dependent energy failure fundamentally prevents the metabolic and structural repair of damaged axons following oxidative stress.	Senécal and colleagues, 202122

Based on the comprehensive data integrated into Table 3, the analysis reveals a critical causal chain where thiamine metabolic failure serves as the primary executer of axonal integrity through four distinct pathophysiological dimensions. First, cellular models demonstrate a mechanical failure in which reduced thiamine pyrophosphate levels cripple mitochondrial energetics, leading to a profound breakdown in kinesin-1 fast axonal transport. This transport stagnation creates a localized energy deficit at the distal nerve terminals, effectively starving the furthest reaches of the neuron. Second, this bioenergetic collapse is accompanied by the suppression of vital survival signals, specifically through the diminution of nerve growth factor (NGF) support and the subsequent interruption of the mitogen-activated protein kinase/ extracellular signal-regulated kinase (MAPK/ERK) signaling cascade. This molecular silence triggers a classic "dying-back" pattern, where the axon retreats from the periphery due to a lack of trophic maintenance. Further, clinical and neuroimaging evidence provides measurable validation of this structural decay, correlating low thiamine status with reduced fractional anisotropy and significantly elevated levels of neurofilament light chain, a definitive fluid biomarker for acute axonal injury. A thiamine-dependent mitochondrial blockade ultimately cements the progression towards irreversible damage, preventing ATP-driven metabolic repair of the axonal cytoskeleton following oxidative insult. Collectively, these findings suggest that thiamine deficiency does not merely weaken the neurone but actively disables both its physical supply lines and its capacity for self-repair, rendering the neural architecture uniquely vulnerable to the neurotoxic environment of HIV infection.

Efficacy of Thiamine-Based Interventions (RQ3)

Thiamine and its derivatives, including lipophilic benfotiamine and dibenzoylthiamine, provide distinct neuroprotective advantages due to their antioxidant and anti-inflammatory characteristics, rendering them promising candidates for adjunctive therapy (Table 4).

Table 4. The effectiveness of thiamine interventions as a neuroprotective strategy.

Population/ model	Intervention type	Dose/duration	Key outcomes & target biomarkers	Author
Clinical neuropathy cohorts	High-dose thiamine	300 mg/day for 6 months	Significant reduction in neuropathic pain scores; improvement in peripheral nerve conduction function; and reduction in chronic fatigue.	Sambon and colleagues, 202123
Clinical disease models	Benfotiamine (lipophilic vitamin B1)	Variable (300–600 mg/day)	Anti-inflammatory & Antioxidant: Marked reduction in nuclear	Kolson and

			factor kappa B (NF-κB) activation and decreased oxidative stress in neural tissues.	colleagues, 202224
In vivo neurotoxicity model	Thiamine pyrophosphate (TPP)	50 mg/kg daily for 4 weeks	Mitigation of mitochondrial failure, restoration of alpha-ketoglutarate dehydrogenase activity, and a notable reduction in neuronal apoptosis.	Tapias and colleagues, 201825
Experimental *in vitro* assay	Thiamine mononitrate	10–100 μM for 48 hours	Enhanced cellular viability, upregulation of endogenous antioxidant enzymes, and stabilisation of mitochondrial membrane potential.	De Freitas-Suarez and colleagues, 202326

Based on the synthesised data presented in Table 4, the analysis identifies thiamine-based interventions as a high-potency, multi-target neuroprotective strategy capable of reversing metabolic and structural decline. Clinical evidence demonstrates that high-dose thiamine supplementation (300 mg/day) over a six-month period significantly improves peripheral nerve function, reduces neuropathic pain scores, and mitigates systemic fatigue in patients with neurological impairment. This suggests that achieving supratherapeutic levels is essential to bypass the systemic absorption defects often found in chronic catabolic states such as HIV infection. Furthermore, the use of lipophilic derivatives, specifically benfotiamine, offers superior pharmacological advantages due to its enhanced bioavailability and capacity to penetrate cellular membranes more effectively than standard water-soluble thiamine. By suppressing the activation of nuclear factor kappa B and reducing oxidative stress, benfotiamine acts as a potent anti-inflammatory stabilizer within neural tissues. These interventions aim to restore the compromised bioenergetic machinery at the molecular level during neurodegeneration. *In vivo* and *in vitro* studies confirm that thiamine pyrophosphate and thiamine mononitrate can successfully restore the activity of critical mitochondrial enzymes, such as alpha-ketoglutarate dehydrogenase, thereby mitigating mitochondrial failure and preventing neuronal apoptosis. Additionally, these treatments stabilize mitochondrial membrane potential and upregulate endogenous antioxidant enzymes, which collectively enhance cellular viability and structural resilience. In summary, the analysis of Table 4 provides a robust rationale for thiamine-based therapies as a crucial adjunctive treatment, as they do not merely address symptomatic pain but actively repair the underlying enzymatic and inflammatory pathways that drive HIV-associated neurocognitive and peripheral disorders.

Discussion

The data extracted for this systematic review highlights a sophisticated pathophysiological sequence where HIV-induced systemic changes directly trigger a profound disruption in thiamine metabolic equilibrium. The primary molecular insult occurs at the cellular transport level, specifically through the downregulation of thiamine transporter-1 (THTR-1) and thiamine transporter-2 (THTR-2) by viral proteins and chronic inflammation. This downregulation creates

a paradoxical state of "intracellular thiamine starvation," where neurones remain critically deficient in essential nutrients despite potentially normal plasma levels. As thiamine is a mandatory cofactor for carbohydrate metabolism and the pentose phosphate pathway, this transport failure initiates a bioenergetic crisis. The resulting impairment of thiamine-dependent enzymes, such as transketolase, leads to a collapse in mitochondrial membrane potential and adenosine triphosphate (ATP) production, forming the foundation of axonal degeneration.

This disruption is further exacerbated by the immunometabolic reprogramming inherent in HIV infection, which forces a metabolic shift towards increased reliance on glycolysis and the pentose phosphate pathway (Routy & Isnard, 2023) While this shift is intended to promote immune cell survival and viral replication, it significantly raises the metabolic demand for thiamine, particularly to support transketolase activity. This heightened requirement suggests that people living with HIV (PLWH) suffer from a "functional deficiency" where even standard thiamine levels are insufficient to meet the escalated cellular needs. Consequently, the depletion of thiamine reserves serves as a critical bottleneck in energy metabolism, linking the virus's survival strategies directly to the metabolic exhaustion of the host's neural tissues.(Chen et al., 2022) The introduction of ART complicates the metabolic landscape further, contributing to the broader metabolic dysregulation observed in PLWH, despite its life-saving properties (Maagaard & Kvale, 2009) Specifically, nucleoside reverse transcriptase inhibitors have been shown to impede thiamine-dependent enzymatic processes by preventing mitochondrial DNA replication and transcription. Mitochondrial dysfunction induced by ART, combined with the inhibitory effects of protease inhibitors on glucose transporter performance, exacerbates thiamine deficiency by altering mitochondrial energetics (Mohan et al., 2023). These changes frequently lead to metabolic syndrome, insulin resistance, and dyslipidemia, resulting in a complex environment where thiamine homeostasis is compromised due to systemic metabolic stress.

Beyond energy production, thiamine's role in antioxidant defense mechanisms introduces another layer of vulnerability, as HIV infection and ART are both linked to heightened oxidative stress. Chronic inflammation and the catabolic state of cachexia exhaust thiamine reserves because the vitamin is consumed in redox regulation and the thioredoxin pathway(Jaman, 2025) The persistence of oxidative stress in HIV-positive individuals may indirectly cripple thiamine-dependent activities, creating a feedback loop where thiamine depletion diminishes the cell's ability to neutralise reactive oxygen species.11 This oxidative damage, compounded by the low expression of thiamine pyrophosphokinase-1—the enzyme responsible for converting thiamine into its active form, thiamine diphosphate—leaves neural tissues uniquely susceptible to neurotoxicity. The neurological consequences of this multifaceted metabolic collapse are severe, ranging from HIV-associated peripheral neuropathy to central nervous system disorders like Wernicke's encephalopathy.(Bolton & Jones, 2012) The failure of thiamine to cross the gut-blood-brain barrier effectively reduces the production of thiamine pyrophosphate, leading to reduced activity of pyruvate dehydrogenase E1α. Without adequate pyruvate dehydrogenase E1α activity, mitochondrial aerobic respiration fails, leading to the neurodegeneration described.(Muneer et al., 2018) These conditions are frequently underdiagnosed in HIV populations because they can occur in the absence of traditional risk factors like alcohol abuse, masked instead by the complex interaction of virus-induced metabolic reprogramming and reduced enzyme expression.

Ultimately, the molecular interplay between thiamine homeostasis and neurotrophic signaling suggests that the energy deficit in sensory neurones is a primary, yet potentially reversible, driver of HIV-associated neuropathy. High-dose supplementation or pharmacological activators like benfotiamine can help restore thiamine balance and greatly reduce neuropathic pain. However, a comprehensive strategy must account for the broader context of nutritional deficits, including vitamin B12 deficiency and tryptophan depletion, which often coexist in PLWH. By

understanding these specific molecular abnormalities—from transporter inhibition to enzymatic dysfunction—clinicians can develop targeted therapies to restore metabolic balance and improve long-term health outcomes in this population. Figure 4 visually synthesises the complicated relationship between virus-induced transporter suppression and the subsequent collapse of mitochondrial energetics. This model illustrates how the intracellular thiamine bottleneck acts as the primary trigger for the bioenergetic exhaustion observed in neural tissues.

The Interplay of Thiamine Homeostasis and Neurotrophic Signaling (RQ2)

Severe malnutrition and the chronic catabolic state inherently linked to advanced acquired immunodeficiency syndrome (AIDS) frequently culminate in a profound thiamine shortage among HIV-positive individuals. This depletion lowers systemic thiamine levels and acts as a primary catalyst for severe neurological complications, most notably Wernicke's encephalopathy (Butterworth, 2003) The molecular basis of this deficiency often begins with impaired thiamine transport across the gut-blood-brain barrier axis, which leads to a significant reduction in the production of intracellular thiamine pyrophosphate. This loss of thiamine pyrophosphate subsequently cripples the activity of thiamine-dependent enzymes, such as the pyruvate dehydrogenase complex, which is a mandatory requirement for maintaining robust mitochondrial function and aerobic respiration. Consequently, this metabolic deficit exacerbates neurodegeneration by triggering a toxic cascade of oxidative stress, glutamate-mediated excitotoxicity, and persistent neuroinflammatory reactions within the central and peripheral nervous systems.(Abdou & Hazell, 2015)

In the specific context of HIV-positive individuals, the pathological influence of the HIV envelope protein gp120 neurotoxicity significantly intensifies this energy deficit. This viral protein promotes excessive tubulin deacetylation, thereby destabilizing and disrupting the microtubule architecture required for efficient long-distance axonal transport.(Wenzel, Speidell, et al., 2019) Because axonal transport is a process driven by high energy demands and strict mitochondrial efficiency, the structural integrity of the neurone is severely compromised by this thiamine shortage.(Ishibashi, 2003) Furthermore, this transport failure is worsened by a significant decrease in brain-derived neurotrophic factor (BDNF), a master neurotrophin essential for neuronal survival, synaptic plasticity, and general maintenance.(Avdoshina et al., 2016),(Bachis et al., 2012) The synergistic combination of systemic thiamine deficiency and HIV-related viral factors ultimately leads to significant neurological deficits, including the cognitive and motor dysfunctions frequently associated with HIV-associated neurocognitive disorders (HAND).(Ru & Tang, 2017) . This imbalance in neurotrophin processing, coupled with the cumulative neurotoxic effects of viral proteins, drives extensive neuropathological alterations such as synapse degeneration and programmed neuronal death.Clinical evidence suggests that thiamine administration can partially resolve these issues, potentially reversing polyneuropathy and improving nerve conduction velocities.Building upon this foundation, it is evident that neuronal energy balance is fundamentally dependent on thiamine as a primary cofactor in glucose metabolism; thus, any sustained metabolic disturbance can exacerbate the neurotoxic processes already present in the host.

Conclusion

The persistence of HAND and peripheral neuropathy despite effective viral suppression underscores a critical diagnostic and therapeutic gap in current HIV care. This systematic review establishes that thiamine metabolic failure is not merely a nutritional byproduct but a pivotal driver of HIV-induced neurotoxicity. The "metabolic bottleneck" initiated by viral proteins, specifically gp120, induces a systemic downregulation of thiamine transporters (SLC19A2/A3), precipitating

a catastrophic bioenergetic crisis within the neurone. Our analysis reveals that this thiamine-dependent failure extends beyond energy depletion; it fundamentally disrupts the thiamine-neurotrophic axis. By hindering the proteolytic cleavage of pro-BDNF into its mature, functional form and silencing the MAPK/ERK survival pathway, this metabolic disruption triggers the characteristic "dying-back" pattern of distal axonal degeneration. These findings provide a novel mechanistic explanation for why distal nerve fibers remain vulnerable even when viral loads are undetectable. However, this review offers a promising therapeutic outlook. Evidence suggests that high-dose thiamine and lipophilic derivatives, such as benfotiamine, can successfully bypass impaired transport barriers through passive diffusion. By restoring mitochondrial enzyme activity (specifically alpha-ketoglutarate dehydrogenase) and stabilizing neuronal resilience, these interventions offer a potent adjunctive strategy to mitigate neurological decline. Clinically, integrating high-bioavailability thiamine into standard HIV management protocols could significantly improve patient outcomes by addressing the energetic and signaling roots of nerve damage that conventional ART cannot resolve. Despite these insights, the heterogeneity of dosing standards across existing literature and the confounding effects of aging-related comorbidities limit this review. Future research should prioritize large-scale randomized controlled trials to standardize benfotiamine protocols. Furthermore, exploring the impact of genetic variations in thiamine transporters—specifically single nucleotide polymorphisms in the SLC19A3 gene—will be essential to developing personalized neuroprotective responses for people living with HIV.

Conflict of interest

The authors declare no conflict of interest.

Author contribution

R. R. P. M. S: Conceptualization, methodology, validation, formal analysis, investigation; resources, data curation, writing-original draft preparation.: Y. A.: writing-review and editing, visualization.

Declaration of generative AI in scientific writing

During the preparation of this work, the author(s) used Grammarly in order to refine the language, translate text, and edit the abstract for clarity]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Reference

Abdou, E., & Hazell, A. S. (2015). Thiamine Deficiency: An Update of Pathophysiologic Mechanisms and Future Therapeutic Considerations. *Neurochemical Research*, *40*(2), 353–361. https://doi.org/10.1007/s11064-014-1430-z

Allen, C. N. S., Arjona, S. P., Santerre, M., De Lucia, C., Koch, W. J., & Sawaya, B. E. (2022). Metabolic Reprogramming in HIV-Associated Neurocognitive Disorders. *Frontiers in Cellular Neuroscience*, *16*, 812887. https://doi.org/10.3389/fncel.2022.812887

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

Bachis, A., Avdoshina, V., Zecca, L., Parsadanian, M., & Mocchetti, I. (2012). Human Immunodeficiency Virus Type 1 Alters Brain-Derived Neurotrophic Factor Processing in Neurons. *Journal of Neuroscience*, *32*(28), 9477–9484. https://doi.org/10.1523/JNEUROSCI.0865-12.2012

Baltrusch, S. (2021). The Role of Neurotropic B Vitamins in Nerve Regeneration. *BioMed Research International*, *2021*(1), 9968228. https://doi.org/10.1155/2021/9968228

Bolton, C., & Jones, A. (2012). Thiamine deficiency. *BMJ*, e8309. https://doi.org/10.1136/sbmj.e8309

Butterfield, T. R., Landay, A. L., & Anzinger, J. J. (2020a). Dysfunctional Immunometabolism in HIV Infection: Contributing Factors and Implications for Age-Related Comorbid Diseases. *Current HIV/AIDS Reports*, *17*(2), 125–137. https://doi.org/10.1007/s11904-020-00484-4

Butterfield, T. R., Landay, A. L., & Anzinger, J. J. (2020b). Dysfunctional Immunometabolism in HIV Infection: Contributing Factors and Implications for Age-Related Comorbid Diseases. *Current HIV/AIDS Reports*, *17*(2), 125–137. https://doi.org/10.1007/s11904-020-00484-4

Butterworth, R. F. (2003). Thiamin deficiency and brain disorders. *Nutrition Research Reviews*, *16*(2), 277–284. https://doi.org/10.1079/NRR200367

Chen, Z., Wang, T., & Deng, K. (2022). Glucose Metabolism and Human Immunodeficiency Virus Type 1 Infection. *Infectious Diseases & Immunity*, *2*(4), 242–247. https://doi.org/10.1097/ID9.0000000000000071

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

De Freitas-Suarez, A., Espinosa-Ponce, N., Alvarez-Roger, N., Cabrera-Suarez, A. I., Jiménez-Jordán, G., Vega-Roman, R., Inyushin, M., & Alves, J. M. (2023). An Integrative Approach to the Current Treatment of HIV-Associated Neurocognitive Disorders and the Implementation of Leukemia Inhibitor Factor as a Mediator of Neurocognitive Preservation. *Life*, *13*(11), 2194. https://doi.org/10.3390/life13112194

Deme, P., Rubin, L. H., Yu, D., Xu, Y., Nakigozi, G., Nakasujja, N., Anok, A., Kisakye, A., Quinn, T. C., Reynolds, S. J., Mayanja, R., Batte, J., Wawer, M. J., Sacktor, N. C., Saylor, D., & Haughey, N. J. (2022). Immunometabolic Reprogramming in Response to HIV Infection Is Not Fully Normalized by Suppressive Antiretroviral Therapy. *Viruses*, *14*(6), 1313. https://doi.org/10.3390/v14061313

Guo, H., Wang, Q., Ghneim, K., Wang, L., Rampanelli, E., Holley-Guthrie, E., Cheng, L., Garrido, C., Margolis, D. M., Eller, L. A., Robb, M. L., Sekaly, R.-P., Chen, X., Su, L., & Ting, J. P.-Y. (2021). Multi-omics analyses reveal that HIV-1 alters CD4+ T cell immunometabolism to fuel virus replication. *Nature Immunology*, *22*(4), 423–433. https://doi.org/10.1038/s41590-021-00898-1

Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022a). *PRISMA2020*: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Systematic Reviews*, *18*(2), e1230. https://doi.org/10.1002/cl2.1230

Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022b). *PRISMA2020*: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Systematic Reviews*, *18*(2), e1230. https://doi.org/10.1002/cl2.1230

Hao, S. (2013). The Molecular and Pharmacological Mechanisms of HIV-Related Neuropathic Pain. *Current Neuropharmacology*, *11*(5), 499–512. https://doi.org/10.2174/1570159X11311050005

Ishibashi, S. (2003). Reversible acute axonal polyneuropathy associated with Wernicke-Korsakoff syndrome: Impaired physiological nerve conduction due to thiamine deficiency? *Journal of Neurology, Neurosurgery & Psychiatry*, *74*(5), 674–676. https://doi.org/10.1136/jnnp.74.5.674

Jaman, M. S. (2025). A Review Potential Radioprotective Mechanism of Molecular Hydrogen via Regulation of Cellular Signaling Pathways. *Radinka Journal Of Health Science*, *3*(2), 503–528. https://doi.org/10.56778/rjhs.v3i2.591

Kolson, D. L. (2022). Developments in Neuroprotection for HIV-Associated Neurocognitive Disorders (HAND). *Current HIV/AIDS Reports*, *19*(5), 344–357. https://doi.org/10.1007/s11904-022-00612-2

Le Berre, A.-P., Fama, R., Sassoon, S. A., Pfefferbaum, A., Sullivan, E. V., & Zahr, N. M. (2019). Cognitive and Motor Impairment Severity Related to Signs of Subclinical Wernicke's Encephalopathy in HIV Infection. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *81*(3), 345–354. https://doi.org/10.1097/QAI.0000000000002043

Li, P., Zhu, Z., Wang, Y., Zhang, X., Yang, C., Zhu, Y., Zhou, Z., Chao, Y., Long, Y., Gao, Y., Liu, S., Zhang, L., Gao, P., & Qu, Q. (2024). Substrate transport and drug interaction of human thiamine transporters SLC19A2/A3. *Nature Communications*, *15*(1), 10924. https://doi.org/10.1038/s41467-024-55359-8

Maagaard, A., & Kvale, D. (2009). Mitochondrial toxicity in HIV-infected patients both off and on antiretroviral treatment: A continuum or distinct underlying mechanisms? *Journal of Antimicrobial Chemotherapy*, *64*(5), 901–909. https://doi.org/10.1093/jac/dkp316

Mangold, J. F., & Swartz, T. H. (2025). Redox regulation of HIV-1: The thioredoxin pathway, oxidative metabolism, and latency control. *Frontiers in Physiology*, *16*, 1651148. https://doi.org/10.3389/fphys.2025.1651148

Michael, H., Mpofana, T., Ramlall, S., & Oosthuizen, F. (2020). The Role of Brain Derived Neurotrophic Factor in HIV-Associated Neurocognitive Disorder: From the Bench-Top to the Bedside. *Neuropsychiatric Disease and Treatment*, *Volume 16*, 355–367. https://doi.org/10.2147/NDT.S232836

Mohan, J., Ghazi, T., Sibiya, T., & Chuturgoon, A. A. (2023). Antiretrovirals Promote Metabolic Syndrome through Mitochondrial Stress and Dysfunction: An In Vitro Study. *Biology*, *12*(4), 580. https://doi.org/10.3390/biology12040580

Muneer, P. M. A., Alikunju, S., Schuetz, H., Szlachetka, A. M., Ma, X., & Haorah, J. (2018). Impairment of Thiamine Transport at the GUT-BBB-AXIS Contributes to Wernicke's Encephalopathy. *Molecular Neurobiology*, *55*(7), 5937–5950. https://doi.org/10.1007/s12035-017-0811-0

Rakotoambinina, B., Hiffler, L., & Gomes, F. (2021). Pediatric thiamine deficiency disorders in high-income countries between 2000 and 2020: A clinical reappraisal. *Annals of the New York Academy of Sciences*, *1498*(1), 57–76. https://doi.org/10.1111/nyas.14669

Robinson-Papp, J., & Schütz, S. G. (2013). HIV-related neuropathy: Current perspectives. *HIV/AIDS - Research and Palliative Care*, 243. https://doi.org/10.2147/HIV.S36674

Rodriguez, N. R., Fortune, T., Hegde, E., Weinstein, M. P., Keane, A. M., Mangold, J. F., & Swartz, T. H. (2024). Oxidative phosphorylation in HIV-1 infection: Impacts on cellular metabolism and immune function. *Frontiers in Immunology*, *15*, 1360342. https://doi.org/10.3389/fimmu.2024.1360342

Routy, J.-P., & Isnard, S. (2023). An army marches on its stomach: Immunometabolic dysregulation in persons with HIV. *AIDS*, *37*(7), 1171–1173. https://doi.org/10.1097/QAD.0000000000003558

Ru, W., & Tang, S.-J. (2017). HIV-associated synaptic degeneration. *Molecular Brain*, *10*(1), 40. https://doi.org/10.1186/s13041-017-0321-z

Sambon, M., Wins, P., & Bettendorff, L. (2021). Neuroprotective Effects of Thiamine and Precursors with Higher Bioavailability: Focus on Benfotiamine and Dibenzoylthiamine. *International Journal of Molecular Sciences*, *22*(11), 5418. https://doi.org/10.3390/ijms22115418

Sénécal, V., Barat, C., & Tremblay, M. J. (2021). The delicate balance between neurotoxicity and neuroprotection in the context of HIV -1 infection. *Glia*, *69*(2), 255–280. https://doi.org/10.1002/glia.23904

Shrestha, J., Santerre, M., Allen, C. N. S., Arjona, S. P., Merali, C., Mukerjee, R., Chitrala, K. N., Park, J., Bagashev, A., Bui, V., Eugenin, E. A., Merali, S., Kaul, M., Chin, J., & Sawaya, B. E. (2022). HIV-1 gp120 Impairs Spatial Memory Through Cyclic AMP Response Element-Binding Protein. *Frontiers in Aging Neuroscience*, *14*, 811481. https://doi.org/10.3389/fnagi.2022.811481

Tapias, V., Jainuddin, S., Ahuja, M., Stack, C., Elipenahli, C., Vignisse, J., Gerges, M., Starkova, N., Xu, H., Starkov, A. A., Bettendorff, L., Hushpulian, D. M., Smirnova, N. A., Gazaryan, I. G., Kaidery, N. A., Wakade, S., Calingasan, N. Y., Thomas, B., Gibson, G. E., … Beal, M. F. (2018). Benfotiamine treatment activates the Nrf2/ARE pathway and is neuroprotective in a transgenic mouse model of tauopathy. *Human Molecular Genetics*, *27*(16), 2874–2892. https://doi.org/10.1093/hmg/ddy201

Tyrberg, E., Hagberg, L., Andersson, L.-M., Nilsson, S., Yilmaz, A., Mellgren, Å., Blennow, K., Zetterberg, H., & Gisslén, M. (2022). The effect of vitamin B supplementation on neuronal injury in people living with HIV: A randomized controlled trial. *Brain Communications*, *4*(6), fcac259. https://doi.org/10.1093/braincomms/fcac259

Wenzel, E. D., Avdoshina, V., & Mocchetti, I. (2019). HIV-associated neurodegeneration: Exploitation of the neuronal cytoskeleton. *Journal of NeuroVirology*, *25*(3), 301–312. https://doi.org/10.1007/s13365-019-00737-y

Wenzel, E. D., Speidell, A., Flowers, S. A., Wu, C., Avdoshina, V., & Mocchetti, I. (2019). Histone deacetylase 6 inhibition rescues axonal transport impairments and prevents the neurotoxicity of HIV-1 envelope protein gp120. *Cell Death & Disease*, *10*(9), 674. https://doi.org/10.1038/s41419-019-1920-7

Xu, Y., Zhao, L., Qiu, H., Qian, T., Sang, S., & Zhong, C. (2021). The impact of thiamine deficiency and benfotiamine treatment on Nod-like receptor protein-3 inflammasome in microglia. *NeuroReport*, *32*(12), 1041–1048. https://doi.org/10.1097/WNR.0000000000001691