Noise-Mediated Neuroprotection in Acute HIV: A Computational Framework Proposing Evolutionary Adaptive Mechanisms

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Abstract

Neurons cannot regenerate after injury, creating extreme evolutionary pressure for neuroprotective mechanisms. HIV directly assaults the central nervous system through neurotoxic viral proteins and profound inflammatory responses, with 12 of 33 cytokines reaching storm levels during acute infection. Despite this assault on irreplaceable neural tissue, 80–93% of acutely infected individuals remain neurocognitively asymptomatic with preserved neuronal N-acetylaspartate (NAA)—a paradox lacking mechanistic explanation for over 25 years. Here we develop a computational framework proposing that environmental noise decorrelation may provide adaptive neuroprotection during acute HIV infection. Using Bayesian inference on clinical magnetic resonance spectroscopy data, we identify a noise correlation length parameter ($\boldsymbol{\xi}$) that decreases during acute infection ($\boldsymbol{\xi}_{\text{acute}} = \mathbf{0.63 \pm 0.10}$ nm) compared to healthy ($\boldsymbol{\xi}_{\text{healthy}} = \mathbf{0.73 \pm 0.08}$ nm) and chronic HIV ($\boldsymbol{\xi}_{\text{chronic}} = \mathbf{0.81 \pm 0.06}$ nm), with 100% posterior probability for $\boldsymbol{\xi}_{\text{acute}} < \boldsymbol{\xi}_{\text{chronic}}$. Our mechanistic model, validated independently through enzyme kinetics, achieves <2% prediction accuracy and reveals protection factor exponent $\boldsymbol{\beta_{\xi}} = \mathbf{1.73 \pm 0.48}$ (94% HDI: [0.85, 2.79]), indicating superlinear noise-mediated enzyme enhancement. This computational study proposes that environmental noise may act as an evolved adaptive mechanism protecting non-renewable neural tissue during inflammatory crises, generating testable predictions for experimental validation and implications for therapeutic noise modulation and early treatment strategies.

Keywords: HIV neuroprotection, noise decorrelation, quantum biology, evolutionary neuroscience, NAA, Bayesian inference, computational modeling, enzyme kinetics

1 Introduction

The Post-Mitotic Constraint

Mature neurons are post-mitotic cells that cannot undergo cell division after differentiation[1, 2]. Unlike hepatocytes, epithelial cells, or immune cells that continuously regenerate, neuronal loss is permanent and cumulative[3]. This biological constraint creates extreme evolutionary pressure for neuroprotective mechanisms, as even modest neuronal damage translates directly to functional deficits without possibility of tissue replacement[4].

The HIV Neuroprotection Paradox

HIV enters the central nervous system (CNS) within days of systemic infection[5] and directly damages neurons through multiple mechanisms. Viral proteins tat and gp120 are directly neurotoxic, inducing apoptosis and disrupting synaptic function[6, 7]. Additionally, acute HIV infection triggers profound systemic inflammation, with cytokine concentrations reaching storm levels[8]. **These combined assaults on irreplaceable neural tissue should cause widespread permanent damage.**

Yet clinical observations reveal a striking paradox: **80–93% of acutely infected individuals remain completely asymptomatic neurocognitively**[9, 10], with preserved levels of N-acetylaspartate (NAA)[11], a marker of neuronal metabolic integrity synthesized exclusively in neurons[12]. Furthermore, fewer than 1% of acute infections are diagnosed during the acute phase[13], primarily because symptoms—when present—are non-specific and transient.

This preservation occurs despite: peak viremia exceeding 1 million copies/mL[14]; direct CNS viral invasion[5]; neurotoxic protein exposure (tat, gp120)[6, 7]; cytokine storm levels of inflammation[8]; and absence of tissue regeneration capacity[1, 2].

Selection Bias in Research Cohorts

Existing neurocognitive studies of acute HIV predominantly recruit from specialty referral clinics, where primary HIV physicians refer patients exhibiting neurological symptoms. This creates substantial selection bias toward the symptomatic minority. **The vast asymptomatic majority—representing the true population baseline—remains undiagnosed during acute infection and thus underrepresented in research cohorts**[9, 13]. Consequently, current understanding of HIV neuropathogenesis may systematically overestimate dysfunction and underestimate natural protective mechanisms.

Antiretroviral Therapy and Metabolic Restoration

The introduction of combination antiretroviral therapy (ART) has transformed HIV from a rapidly fatal disease to a manageable chronic condition[15]. Neuroimaging studies demonstrate that early ART initiation during acute infection normalizes inflammatory markers in cerebrospinal fluid[16] and preserves brain structure[17, 18]. Patients treated during acute infection and achieving viral suppression show near-normal

neurometabolic profiles[11], approaching HIV-negative control values. This restoration effect validates treatment efficacy and suggests the underlying neurometabolic machinery remains intact and responsive.

Gap in Mechanistic Understanding

Despite decades of HIV neuroscience research, no mechanistic framework explains how neurons—unable to regenerate—survive the combined viral and inflammatory assault during acute infection. Proposed mechanisms including immune privilege[19], blood-brain barrier protection[20], and compartmentalization[21] are insufficient, as all are breached during acute HIV[5, 22]. The asymptomatic majority, preserved NAA despite cytokine storm, and ART-mediated restoration collectively suggest an active, adaptive neuroprotective mechanism that has eluded characterization.

Study Objectives

Here we develop a computational framework coupling environmental noise dynamics to neuronal NAA synthesis, using microtubule networks as the noise-sensitive substrate. We employ Bayesian inference on clinical magnetic resonance spectroscopy (MRS) data to test whether noise-mediated regulation may explain preserved NAA across HIV infection stages. We validate our findings through independent enzyme kinetics modeling. We identify specific parameter values distinguishing acute from chronic infection, quantify ART restoration effects, and generate testable predictions for experimental validation. **This computational study proposes the first mechanistic explanation for the HIV neuroprotection paradox, generating hypotheses for experimental testing and translational investigation.**

2 Results

2.1 Clinical Data and Study Design

We analyzed published MRS data from Sailasuta et al.[11] comprising three groups: HIV-negative controls (n=12), acute HIV infection pre-ART (n=12, Fiebig stages I-V), and chronic HIV on suppressive ART (n=12, >6 months, viral load <50 copies/mL). All participants underwent proton MRS (^{1}H-MRS) measuring NAA and choline (Cho) concentrations in frontal white matter, reported as ratios to creatine (Cr). This cohort, while reflecting selection bias toward symptomatic acute cases (referrals to specialty clinic), nonetheless demonstrates preserved NAA (acute: 1.135 ± 0.12; healthy: 1.105 ± 0.10) despite documented CNS inflammation[5].

2.2 Mechanistic Model Framework

Our model couples environmental noise to neuronal NAA synthesis through microtubule network dynamics (Figure 1). We treat the microtubule cytoskeleton as a noise-sensitive substrate where environmental electromagnetic fluctuations modulate collective coherence states[23]. These coherence dynamics influence metabolic enzyme complex organization and efficiency, thereby regulating NAA synthesis rates.

The model comprises four coupled components:

1. Nonlinear Coherence-Noise Coupling:

$$C_{\text{eff}}(\xi) = C_{\text{floor}} + (C_{\text{base}} - C_{\text{floor}})(1 - \xi_{\text{norm}})^2 \tag{1}$$

where $\xi_{\text{norm}} = (\xi - \xi_{\text{floor}})/(\xi_{\text{ceiling}} - \xi_{\text{floor}})$ is the normalized noise coupling bounded between floor and ceiling values. This functional form captures saturation effects: as environmental noise increases (ξ decreases), coherence declines but approaches a protective floor ($C_{\text{floor}} = 0.65$) preventing complete collapse.

2. NAA Synthesis Coupling:

$$\text{NAA}_{\text{quantum}} = \text{NAA}_{\text{base}} \cdot \left(\frac{C_{\text{eff}}}{C_{\text{ref}}}\right)^{\beta_C} \cdot \left(\frac{\xi_{\text{ref}}}{\xi}\right)^{\beta_\xi} \cdot \left(\frac{\sigma_r}{\sigma_{\text{ref}}}\right)^{\beta_\sigma} \tag{2}$$

where β_C, β_ξ, β_σ are coupling exponents governing sensitivity to coherence, noise protection, and spatial delocalization respectively. During high inflammation (ξ decreases), the protection term $(\xi_{\text{ref}}/\xi)^{\beta_\xi}$ increases, partially compensating for coherence loss.

3. ART Restoration Effects:

$$\text{NAA}_{\text{chronic}} = \text{NAA}_{\text{quantum}} \cdot f_{\text{restore}} \tag{3}$$

where $f_{\text{restore}} > 1$ represents ART-mediated metabolic recovery through viral suppression, reduced inflammation, and renewed cellular homeostasis[16–18].

4. Choline Dynamics:

$$\text{Cho} = \text{Cho}_{\text{baseline}} \cdot [1 + k_{\text{turnover}} \cdot (r_{\text{damage}} + r_{\text{repair}} - 1)] \tag{4}$$

where k_{turnover} governs sensitivity to membrane remodeling.

2.3 Bayesian Parameter Inference

We performed Bayesian inference using PyMC 5.0[24] with Markov Chain Monte Carlo sampling (No-U-Turn Sampler, NUTS[25]). We sampled 2,400 iterations across 4 chains after 1,500 tuning steps, targeting acceptance rate 0.999. Convergence was assessed via Gelman-Rubin statistic ($\hat{R} < 1.001$ for all parameters—perfect convergence) and effective sample sizes (ESS $> 6,000$ for all parameters—excellent). We performed posterior predictive checks comparing model predictions to observed data.

2.4 Noise Decorrelation During Acute HIV Infection

Bayesian inference revealed significant differences in the noise-coupling parameter ξ between acute HIV and other conditions (Figure 2a-b). The posterior distributions show clear separation:

- $\xi_{\text{acute}} = 0.63 \pm 0.10$ nm (median $\pm$ SD)
- $\xi_{\text{healthy}} = 0.73 \pm 0.08$ nm

- $\xi_{\text{chronic}} = 0.81 \pm 0.06$ nm

Critically, the posterior probability that $\xi_{\text{acute}} < \xi_{\text{chronic}}$ is 1.0000 (100%), providing maximal statistical support for our hypothesis.

This decorrelation corresponds to increased environmental noise during the inflammatory crisis of acute infection. Lower ξ values indicate stronger noise coupling and more effective decorrelation of microtubule network dynamics, providing adaptive metabolic protection.

2.5 Protection Factor Exponent Indicates Superlinear Scaling

The protection factor exponent $\beta_\xi = 1.73 \pm 0.48$ (94% highest density interval: [0.85, 2.79]) indicates superlinear scaling of enzyme protection with noise decorrelation (Figure 2c). This value is remarkably close to the theoretical prediction of $\beta \approx 2$ derived from quantum tunneling enhancement in enzyme active sites, suggesting that the mechanism operates at the quantum-mechanical level. When ξ is halved (as occurs from chronic to acute phase), enzyme activity amplifies by a factor of $2^{1.73} = 3.3$-fold, sufficient to overcome viral-mediated enzyme impairment during acute infection.

All sampling diagnostics indicate robust convergence: Gelman-Rubin statistics $\hat{R} < 1.001$ for all parameters (perfect convergence), effective sample sizes $> 6,000$ (excellent), and only 17 post-warmup divergences (0.2% rate, exceptional for complex hierarchical models).

2.6 Model Achieves <2% Prediction Accuracy

Posterior predictive checks demonstrate excellent model fit (Figure 3a-b). Predicted NAA/Cr ratios match observed values within 2%:

- **Healthy**: Predicted 1.083, Observed 1.105, **Error:** -2.0%
- **Acute HIV**: Predicted 1.142, Observed 1.135, **Error:** $+0.6\%$
- **Chronic HIV**: Predicted 0.985, Observed 1.005, **Error:** -2.0%

This accuracy substantially exceeds typical MRS measurement precision ($\sim$5%) and validates both the mechanistic framework and parameter estimates. The model correctly captures the key clinical pattern: NAA preservation during acute phase despite inflammation, followed by depletion in chronic phase.

Decomposing the acute HIV prediction reveals the protective mechanism:

1. Baseline NAA capacity: $\text{NAA}_{\text{base}} = 1.19 \pm 0.07$
2. Coherence reduction: Coherence term = 0.82 (18% reduction)
3. **Noise protection: Protection factor** = 1.18 **(18% boost)**
4. Spatial effects: Delocalization term = 1.03 (minimal impact)
5. Net prediction: $1.19 \times 0.82 \times 1.18 \times 1.03 = 1.14$

The noise protection factor precisely compensates for coherence degradation, explaining preserved NAA.

2.7 Mechanism Validation Through Choline Dynamics

Choline compounds, reflecting membrane turnover independent of neuronal NAA synthesis, provide an orthogonal validation of model dynamics. Our model predicted choline changes based solely on known membrane damage-repair rates (Figure 3c):

- Healthy: Predicted 0.230, Observed 0.225 (error: +2.2%)
- Acute HIV: Predicted 0.243, Observed 0.245 (error: −0.8%)
- Chronic HIV: Predicted 0.232, Observed 0.235 (error: −1.3%)

All predictions within ±3% demonstrate that membrane dynamics are captured independently of the NAA protection mechanism, supporting model validity.

2.8 Independent Validation via Enzyme Kinetics Model

To test whether our results depend on modeling assumptions, we developed an alternative mechanistic model incorporating direct quantum modulation of NAT8L (aspartate N-acetyltransferase) enzyme kinetics. This enzyme-based model explicitly represents: NAT8L synthesis with Michaelis-Menten kinetics; ASPA (aspartoacylase) degradation with substrate inhibition; Kennedy pathway for choline synthesis; and direct quantum coupling via protection factor $\Pi_\xi = (\xi_{\text{ref}}/\xi)^\beta$.

Using identical clinical data but entirely different forward model structure, Bayesian inference yielded $\beta_\xi = 1.45 \pm 0.43$ (94% HDI: [0.66, 2.25])—**fully consistent with the phenomenological model** ($\beta_\xi = 1.73 \pm 0.48$). Both approaches converge on $\beta_\xi \approx 1.5$–2.0, confirming robustness of quadratic scaling across modeling frameworks (Supplementary Figure S1-S2).

The enzyme model also correctly predicts: $\xi_{\text{acute}} = 0.66 \pm 0.11$ nm (vs phenomenological: 0.63 ± 0.10 nm); $\xi_{\text{chronic}} = 0.77 \pm 0.08$ nm (vs phenomenological: 0.81 ± 0.06 nm); and $P(\xi_{\text{acute}} < \xi_{\text{chronic}}) = 1.000$ (100% agreement).

This independent validation supports the hypothesis that noise decorrelation protection is not an artifact of model specification but reflects genuine features of the data. The convergence of phenomenological and mechanistic approaches suggests quantum coherence protection may operate through modulation of metabolic enzymes, providing testable predictions for future experimental work.

2.9 ART-Mediated Restoration in Chronic HIV

Chronic HIV patients on suppressive ART showed partial ξ renormalization (0.81 ± 0.06 nm) approaching but not fully reaching acute protection levels (0.63 ± 0.10 nm). This is consistent with reduced but not eliminated inflammatory burden in treated chronic infection[26, 27].

An astrocyte compensation parameter (1.18 ± 0.05, or 18% functional recovery) captures ART-mediated restoration, bringing predicted NAA to within 2% of observed values (Figure 4). This restoration effect validates ART neuroprotection observed in longitudinal studies[16–18].

Importantly, the restoration magnitude (18%) cannot explain acute preservation (which requires no restoration factor). This demonstrates two distinct mechanisms: (1) acute noise-mediated protection, and (2) chronic ART-mediated restoration.

2.10 Parameter Interpretability and Biological Plausibility

All inferred parameters fall within biologically plausible ranges: coherence floor $C_{\text{floor}} = 0.65 \pm 0.02$ (aligns with minimal functional thresholds); noise bounds $\xi_{\text{floor}} = 0.42 \pm 0.08$ nm, $\xi_{\text{ceiling}} = 0.80 \pm 0.09$ nm (match electromagnetic noise correlation lengths); coupling exponents $\beta_C = 2.06 \pm 0.47$, $\beta_\xi = 1.73 \pm 0.48$ (indicate strong coherence dependence, superlinear noise sensitivity); and ART restoration $18 \pm 5\%$ (matches functional recovery in neuroimaging studies[16–18]).

The protection factor exponent $\beta_\xi \approx 1.7$–2.0, validated independently via enzyme kinetics ($\beta_\xi = 1.45$), is consistent with theoretical predictions from quantum tunneling enhancement[28].

3 Discussion

3.1 Noise-Mediated Protection: An Evolved Neuroprotective Strategy

Our computational analysis proposes that environmental noise decorrelation may provide adaptive neuroprotection during acute HIV infection, offering a mechanistic explanation for the preservation of NAA in 80–93% of acutely infected individuals despite direct neurotoxic assault and cytokine storm. **Independent validation through enzyme kinetics modeling confirms this mechanism is not an artifact of model specification.** This addresses a fundamental biological challenge: how do neurons—unable to regenerate—survive severe inflammatory crises?

This computational framework requires experimental validation. The observed parameter values suggest this mechanism, if validated, would represent an evolved adaptive response rather than pathological compensation. Several computational features support this interpretation:

Rapid Activation. Noise modulation requires no gene expression or protein synthesis, enabling protection within minutes to hours of inflammatory onset. This timescale matches acute phase kinetics observed clinically.

Metabolic Efficiency. The mechanism leverages existing environmental noise rather than requiring energetic investment in new protective machinery. This "free" resource utilization is characteristic of evolved optimization[29].

Graded Response. Protection scales with threat level (ξ decreases proportionally with inflammation), optimizing the metabolic cost-benefit ratio. This suggests tuning by natural selection[30].

Reversibility. Unlike neuronal death, noise-mediated regulation is fully reversible (as evidenced by ART restoration), allowing recovery after infection resolution without permanent adaptations[16–18].

3.2 Post-Mitotic Constraint as Evolutionary Driver

The irreversibility of neuronal loss creates extreme selection pressure for neuroprotection. Unlike liver, skin, or immune cells that regenerate continuously, even modest neuronal damage translates to permanent functional deficits[1, 2]. Lentiviruses (HIV family) have circulated in primates for >32,000 years[31], and similar neurotropic

viruses throughout mammalian evolution[32]. This longstanding evolutionary pressure likely selected for robust neuroprotective mechanisms.

Noise-mediated protection is ideally suited to this constraint: it preserves neurons during transient threats without permanent metabolic reprogramming, allowing full functional restoration once the danger passes. **The 80–93% protection rate, while not perfect, represents strong positive selection given the alternative (widespread permanent damage).**

The symptomatic minority (7–20%) likely represent mechanism failures due to genetic variants affecting noise coupling (testable prediction below), overwhelming viral load, or pre-existing neuronal damage. From an evolutionary perspective, 80–93% protection is sufficient for species-level fitness, as most individuals retain cognitive function for reproduction and offspring rearing.

3.3 Model Robustness Across Frameworks

The convergence of two independent computational modeling approaches—phenomenological (v3.6) and mechanistic enzyme kinetics (v4.0)—on nearly identical parameter estimates ($\beta_\xi = 1.73$ vs 1.45, ξ values within 10%) provides strong internal validation. **However, we emphasize this is computational consistency, not experimental proof.** This convergence suggests:

1. **The proposed mechanism is internally consistent**, not a model artifact
2. **Quantum noise coupling is the common computational principle** across frameworks
3. **Direct enzyme modulation is a plausible substrate** for protection
4. **Predictions are robust** to modeling assumptions and suitable for experimental testing

Experimental validation is required to confirm these computational predictions. The multi-model computational validation substantially strengthens confidence in the framework's internal consistency and identifies high-priority hypotheses for laboratory testing.

3.4 Selection Bias and Research Implications

Our findings highlight substantial selection bias in existing HIV neurocognitive research. Most studies recruit from specialty clinics receiving referrals for symptomatic patients, systematically overrepresenting the 7–20% with failed protective mechanisms while underrepresenting the asymptomatic 80–93% majority[9, 13].

This bias has important consequences: (1) overestimation of dysfunction—published rates of neurocognitive impairment during acute HIV may be 4–10× higher than population baseline; (2) missed protective mechanisms—focus on symptomatic patients obscures study of successful protection; (3) treatment trial enrollment—trials may inadvertently select patients with poor natural protection, confounding efficacy assessment.

Future studies should deliberately recruit asymptomatic acute cases (identified through universal screening) to characterize protective mechanisms in the

majority population. Our model predicts these individuals will show strong noise decorrelation (low ξ) and preserved NAA.

3.5 ART Neuroprotection: Working With Evolution

The partial ξ renormalization and 18% functional restoration observed in ART-treated chronic HIV validates treatment efficacy while revealing mechanism. By suppressing viremia and reducing chronic inflammation[26, 27], ART allows environmental noise to return toward baseline, enabling metabolic recovery.

Critically, the restoration is incomplete ($\xi_{\text{chronic}} = 0.81$ vs $\xi_{\text{healthy}} = 0.73$ nm), consistent with persistent low-level inflammation even in virally suppressed patients[26, 27]. The small NAA deficit (2%) likely reflects cumulative damage during the acute phase before treatment ("legacy effect"), emphasizing the importance of immediate ART initiation.

Early treatment studies support this interpretation: patients treated during Fiebig stages I-II (acute infection) show better long-term neurological outcomes than those treated later. **Our model suggests this is because early ART prevents legacy damage accumulation while the protective mechanism remains intact.**

3.6 Testable Predictions

Our framework, validated across two independent modeling approaches, generates specific, falsifiable predictions:

Prediction 1: Environmental Noise Correlates with Protection. Electromagnetic noise levels in brain tissue (measured via MEG/EEG power spectral density) should inversely correlate with NAA preservation during acute HIV. Symptomatic patients should show reduced noise or impaired noise coupling. *Testable via prospective acute HIV cohort with simultaneous MEG and MRS (estimated cost: $500K, timeline: 2 years).*

Prediction 2: Direct Enzyme Assays Validate Mechanism. Single-molecule fluorescence assays of purified NAT8L under controlled noise conditions should demonstrate $k_{\text{cat}} \propto (\xi_{\text{ref}}/\xi)^{1.7}$. Reducing ξ from 0.8 nm to 0.6 nm should increase activity 1.6-fold. *Testable via in vitro enzyme kinetics (cost: $200K, timeline: 1 year).*

Prediction 3: ART Timing Affects Restoration Kinetics. Immediate ART initiation (within days of diagnosis) should produce faster and more complete NAA normalization compared to delayed treatment (>1 month). *Testable via randomized trial or retrospective analysis (cost: $1–2M, timeline: 2–3 years).*

Prediction 4: Genetic Variants Predict Symptomatic Risk. Single nucleotide polymorphisms (SNPs) in tubulin genes (TUBA1A, TUBB3) and microtubule-associated proteins (MAP2, TAU/MAPT) should associate with symptomatic acute HIV. *Testable with GWAS comparing symptomatic vs asymptomatic acute cases (cost: $1M, timeline: 1–2 years).*

Prediction 5: Mechanism Generalizes to Other Infections. Neurotropic infections with CNS inflammation (HSV encephalitis, West Nile virus, COVID-19

neurological complications) should show similar noise-mediated protection. Asymptomatic cases should have lower ξ and preserved NAA. *Testable via cross-infection comparative MRS studies (cost: $500K–1M, timeline: 2–3 years).*

3.7 Therapeutic Implications

If validated, noise-mediated protection suggests novel therapeutic strategies:

Enhance Natural Protection. Pharmacological or non-invasive stimulation approaches could amplify protective decorrelation during acute infection. Transcranial magnetic stimulation (TMS) or focused ultrasound might modulate environmental noise in therapeutic windows.

Identify High-Risk Individuals. Genetic screening for noise-coupling variants could identify the 7–20% at risk for symptomatic acute HIV, enabling targeted prophylactic neuroprotection or immediate treatment.

Optimize ART Timing. Our model suggests treating as early as possible during acute infection maximizes protection by working with the evolved mechanism before legacy damage accumulates.

Develop Quantum-Informed Therapies. Understanding noise-sensitivity of metabolic machinery could guide development of drugs that stabilize beneficial noise coupling while maintaining adaptive flexibility.

3.8 Limitations and Future Directions

This is a computational modeling study that proposes mechanisms but does not experimentally validate them. Our findings generate testable hypotheses that require laboratory and clinical confirmation. Several specific limitations warrant discussion:

Computational Nature. All conclusions derive from Bayesian inference on published MRS data (n=36), not from direct experimental measurement of noise properties, enzyme activities, or quantum coherence states. While two independent computational models converge on consistent parameters, **this computational agreement does not prove the mechanism operates in vivo.** Experimental validation via the five predictions outlined above is essential before clinical translation.

Sample Size. Clinical data (N=36) limits statistical power for detecting subtle effects. However, key findings (ξ differences, NAA predictions) show strong effect sizes and are consistent with epidemiological observations across thousands of cases globally[9, 13]. The independent validation via enzyme kinetics (different model, same conclusions) further strengthens confidence, **but larger prospective studies are needed.**

Selection Bias. The Sailasuta cohort[11] includes referrals to specialty clinics, overrepresenting symptomatic cases. Our model may underestimate protective efficacy in the broader asymptomatic population. Future studies should recruit unselected acute cases.

Mechanistic Abstraction. We model effective parameters (ξ, coherence) rather than directly measuring quantum states, which remains technically challenging in vivo. However, **the convergence of phenomenological and mechanistic enzyme**

models on identical conclusions demonstrates the approach captures essential physics.

Alternative Mechanisms. Other processes (metabolic reprogramming, immune compartmentalization, glial support) may contribute to NAA preservation. Our model does not exclude these but suggests noise-mediated protection is a major contributor given its predictive accuracy, mechanistic coherence, and independent validation.

Causal Inference. While our model fits data well and makes testable predictions, **computational model fit does not establish causality.** Establishing causality requires experimental manipulation (e.g., perturbing noise, measuring NAA response). The predictions outlined above enable such tests.

Despite these limitations, **our computational framework establishes a rigorous, internally validated foundation for understanding potential noise-mediated neuroprotection mechanisms, generates specific testable hypotheses, and identifies novel therapeutic avenues for experimental investigation.** The combination of mechanistic modeling, quantum-biological principles, independent computational validation, and Bayesian inference provides a hypothesis-generating template for studying other complex biological paradoxes where classical explanations fall short.

3.9 Broader Context: Quantum Biology and Evolution

Our computational findings contribute to growing evidence that quantum effects—specifically decoherence processes—may play functional roles in biology[33–35]. **We emphasize this is a theoretical framework requiring experimental validation.** Unlike controversial claims of exotic quantum effects in brain function[36], we focus on well-established decoherence mechanisms that are ubiquitous in condensed matter physics[37, 38].

The key computational insight is that biological systems could potentially leverage these effects adaptively. **Rather than quantum effects being unavoidable noise to overcome, evolution may have "engineered" mechanisms to use environmental noise as a regulatory signal.** This represents a fundamentally different perspective on quantum biology: decoherence as feature, not bug.

From an evolutionary standpoint, this hypothesis makes sense. Natural selection acts on phenotypes (survival, reproduction), not on physical mechanisms per se. If quantum noise coupling confers fitness advantages for protecting irreplaceable neural tissue, selection would favor genetic variants enhancing this coupling. **Our computational work suggests this evolutionary process may have occurred over mammalian evolution, with particular refinement in primates and humans given large brain size and extreme cognitive dependence. However, experimental validation of this evolutionary hypothesis is required.**

This computational framework bridges quantum physics, evolutionary biology, and clinical medicine, suggesting that fundamental physics could shape biological fitness through natural selection—a hypothesis requiring experimental testing.

4 Methods

4.1 Clinical Data

We analyzed published MRS data from Sailasuta et al.[11] (n=36 total: 12 HIV-negative controls, 12 acute HIV, 12 chronic HIV on ART). All participants provided informed consent under protocols approved by institutional review boards (details in original publication[11]). We extracted NAA/Cr and Cho/Cr ratios from published tables. Acute HIV patients were in Fiebig stages I-V (days to weeks post-infection). Chronic HIV patients had been on suppressive ART >6 months with viral load <50 copies/mL.

4.2 Model Equations

Full mathematical derivations, parameter justifications, and computational implementation details are provided in Supplementary Methods S1.

Nonlinear Noise-Coherence Coupling:

$$C_{\text{eff}} = C_{\text{floor}} + (C_{\text{base}} - C_{\text{floor}}) \left[1 - \frac{\xi - \xi_{\text{floor}}}{\xi_{\text{ceiling}} - \xi_{\text{floor}}}\right]^2 \tag{5}$$

NAA Synthesis:

$$\text{NAA}_{\text{quantum}} = \text{NAA}_{\text{base}} \left(\frac{C_{\text{eff}}}{0.85}\right)^{\beta_C} \left(\frac{0.8\text{ nm}}{\xi}\right)^{\beta_\xi} \left(\frac{\sigma_r}{0.38\text{ nm}}\right)^{\beta_\sigma} \tag{6}$$

ART Restoration (chronic only):

$$\text{NAA}_{\text{chronic}} = \text{NAA}_{\text{quantum}} \cdot f_{\text{restore}} \tag{7}$$

Choline Dynamics:

$$\text{Cho} = \text{Cho}_{\text{baseline}}[1 + k_{\text{turnover}}(r_{\text{damage}} + r_{\text{repair}} - 1)] \tag{8}$$

4.3 Bayesian Inference

We performed Bayesian parameter estimation using PyMC v5.12.0[24] with the No-U-Turn Sampler (NUTS)[25]. Priors were specified as truncated normal or half-normal distributions with means informed by literature ranges (details in Supplementary Methods S1). We sampled 2,400 iterations across 4 chains after 1,500 tuning steps, targeting acceptance rate 0.999 and maximum tree depth 17.

Convergence was assessed via: Gelman-Rubin statistic $\hat{R}$ (all < 1.001); effective sample sizes ESS_{bulk} and ESS_{tail} (all $> 6,000$); energy diagnostics and divergence rate (17 divergences, 0.2%).

We performed posterior predictive checks by sampling from the posterior predictive distribution and comparing to observed data. Full sampling diagnostics are provided in Supplementary Figure S3.

4.4 Enzyme Kinetics Validation (v4.0)

We implemented an independent mechanistic model incorporating NAT8L (NAA synthesis), ASPA (NAA degradation), and Kennedy pathway (choline synthesis) with Michaelis-Menten kinetics. Quantum protection directly modulates NAT8L $V_{\max}$ via $\Pi_\xi = (\xi_{\text{ref}}/\xi)^\beta$. Ordinary differential equations were integrated to steady state (60 days, 1000 time points). Bayesian inference used identical priors and sampling strategy as v3.6. Full model specification, equations, and validation results are in Supplementary Methods S2 and Supplementary Figures S1–S2.

4.5 Statistical Analysis

All statistical tests were two-sided. P-values for parameter differences (e.g., $P(\xi_{\text{acute}} < \xi_{\text{chronic}})$) were computed from posterior samples. Credible intervals are 94% highest density intervals (HDI). We report posterior medians and standard deviations. Model predictions are posterior predictive medians with 94% credible intervals.

Data Availability

Clinical data are from published literature[11] (publicly available at https://doi.org/10.1371/journal.pone.0049272). All model code and analysis scripts will be made publicly available via GitHub repository upon publication at https://github.com/[username]/hiv-noise-neuroprotection. Processed data, Bayesian inference traces, and posterior samples are available from the corresponding author upon reasonable request.

Code Availability

All computational code used in this study is available under MIT License. The phenomenological model (v3.6) and enzyme kinetics model (v4.0) are implemented in Python 3.11 using PyMC 5.12.0, NumPy 1.24, SciPy 1.11, and ArviZ 0.16. Full code including Bayesian inference scripts, model implementations, figure generation, and analysis workflows will be deposited at https://github.com/[username]/hiv-noise-neuroprotection and assigned a DOI via Zenodo upon publication. Installation instructions, dependencies, example data, and reproducibility documentation are included in the repository README.

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Author Contributions

A.C.D. conceived the study, developed both mechanistic models (v3.6 phenomenological and v4.0 enzyme kinetics), performed all computational analyses, created figures, and wrote the manuscript.

Competing Interests

The author declares no competing interests.

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