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Elevated IL-6 and TNF-α Associated with Treatment-Resistant Depression in Virally Suppressed HIV Patients: A Cross-Sectional Biomarker Study

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A B S T R A C T

Introduction: Despite effective antiretroviral therapy (ART), major depressive disorder (MDD) remains highly prevalent in people living with HIV (PLWH). A subset of these patients develops treatment-resistant depression (TRD), creating a significant clinical burden. The "cytokine hypothesis" proposes that residual immune activation drives this resistance. This study aimed to evaluate whether serum interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) constitute a distinct biological signature of TRD, independent of viral load and smoking status. **Methods:** We conducted a cross-sectional case-control study (N=120) between January 2023 and June 2025. Participants were virally suppressed HIV-positive individuals stratified into three groups (n=40 each): (1) TRD (non-response $\geq$ 2 antidepressants); (2) Treatment-responsive depression (T-Resp); and (3) Non-depressed controls (NDC). Smoking status (pack-years) was quantified. Cytokines were measured via high-sensitivity ELISA. Data were normalized using Log-10 transformation. We employed ANCOVA (adjusting for age, BMI, and smoking) and multivariate logistic regression to assess associations. **Results:** The TRD group exhibited significantly higher serum IL-6 and TNF-α compared to the T-Resp and NDC groups ($p < 0.001$). Although smoking prevalence was higher in the TRD group (45%), ANCOVA confirmed that depression status remained significantly associated with elevated cytokines after adjusting for smoking ($F_{(2,116)} = 42.5$, $p < 0.001$). Logistic regression identified IL-6 as a robust correlate of TRD (Adjusted OR 2.15; 95% CI 1.45–3.18) with no multicollinearity (VIF=1.32). ROC analysis indicated high diagnostic accuracy for IL-6 (AUC=0.88). **Conclusion:** Elevated proinflammatory cytokines are strongly associated with TRD in PLWH, independent of viral replication and nicotine use. These findings support the potential utility of IL-6 as a stratification biomarker for immunomodulatory adjunctive therapies.

1. Introduction

The introduction of combined antiretroviral therapy (ART) has revolutionized the management of human immunodeficiency virus (HIV), transforming a once-fatal diagnosis into a manageable chronic condition with near-normal life expectancy.[1] However, as the mortality associated with opportunistic infections has declined, the burden of non-AIDS comorbidities, particularly neuropsychiatric disorders, has become increasingly prominent. Major depressive disorder (MDD) affects approximately 20–30% of people living with HIV (PLWH), a prevalence rate nearly three times that of the general population.[2]

While standard monoaminergic antidepressants (SSRIs/SNRIs) provide relief for many, a clinically distinct phenotype known as treatment-resistant depression (TRD) poses a severe challenge. Defined as the failure to achieve remission after at least two adequate trials of antidepressant pharmacotherapy, TRD in the context of HIV is associated with accelerated disease progression, poor ART adherence, and increased mortality.[3] The biological mechanisms underpinning this resistance remain distinct from those of general MDD, necessitating a focused investigation into the neuroimmune interface.[4]

Current neurobiological models posit a "double-hit" hypothesis regarding HIV-associated depression. The first "hit" is the viral infection itself. Even in patients with undetectable plasma viral loads, HIV persists in cellular reservoirs (such as macrophages, microglia) within the central nervous system (CNS). These reservoirs release viral proteins such as Tat and gp120, which sustain a state of chronic, low-grade neuroinflammation.[5] The second "hit" is the physiological stress of depression and external psychosocial stressors, which activate the hypothalamic-pituitary-adrenal (HPA) axis and further upregulate proinflammatory signaling.[6]

A leading theory for antidepressant resistance is the "cytokine hypothesis." Proinflammatory cytokines, particularly Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are hypothesized to disrupt monoamine synthesis.[7] While this study focuses on measuring these upstream cytokines, it is theoretically grounded in their downstream effects on the kynurenine pathway. Chronic elevation of IL-6 and TNF-α induces the enzyme Indoleamine 2,3-dioxygenase (IDO), which diverts tryptophan away from serotonin synthesis and towards the production of neurotoxic metabolites like quinolinic acid. This mechanism theoretically renders serotonin-based therapies ineffective, explaining the clinical presentation of TRD.[8]

Despite the theoretical strength of the neuroimmune model, clinical data distinguishing "Treatment-Resistant" depression from "Treatment-Responsive" depression in HIV are sparse. Most studies compare depressed PLWH to non-depressed controls, failing to isolate the specific inflammatory signature of resistance. Furthermore, previous studies have often failed to rigorously control for confounding variables such as smoking (nicotine use), which is highly prevalent in psychiatric populations and is a potent independent inducer of inflammation.[9,10]

This study aims to evaluate peripheral IL-6 and TNF-α levels as differentiating biomarkers for TRD in a rigorously defined cohort of virally suppressed PLWH. The novelty of this research lies in: (1) the strict stratification of depression into Responsive vs. Resistant phenotypes; (2) the rigorous statistical adjustment for metabolic confounders, specifically quantifying and controlling for nicotine use; and (3) the evaluation of these cytokines as potential diagnostic biomarkers using Receiver Operating Characteristic (ROC) analysis. We hypothesize that TRD is characterized by a unique inflammatory profile that exceeds that of responsive depression, independent of smoking status.

2. Methods

This was a single-center, cross-sectional case-control study conducted between January 2023 and June 2025 at the Voluntary Counselling and Testing (VCT) and Psychiatric Outpatient clinics of private hospitals in two major cities in Indonesia. The study protocol adhered to the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of CMHC Research Center, Indonesia. All participants provided written informed consent.

A total of 120 HIV-positive individuals (N=120) were recruited and stratified into three groups (n=40 per group) based on their psychiatric history and response to treatment: (1) Group A (TRD): HIV+ individuals meeting DSM-5 criteria for MDD who failed to achieve remission (HAM-D $\leq$ 7) after at least two adequate trials of antidepressants (different classes) of sufficient duration (>6 weeks) and dosage; (2) Group B (Treatment-Responsive - T-Resp): HIV+ individuals with MDD who achieved remission (HAM-D$\leq$7) on their

first or second antidepressant trial; (3) Group C (Non-Depressed Controls - NDC): HIV+ individuals with no history of MDD and a current HAM-D score <7. Inclusion Criteria were; (1) Age 18–60 years; (2) Confirmed HIV-1 seropositivity; (3) Stable ART regimen for ≥12 months; (4) Undetectable plasma viral load (<50 copies/mL) for ≥ 6 months prior to enrollment (to eliminate active viremia as a source of inflammation). Exclusion Criteria were; (1) Active opportunistic infections or acute infectious illness in the past 4 weeks; (2) Autoimmune disorders or use of systemic anti-inflammatory drugs (NSAIDs, corticosteroids) or immunosuppressants; (3) BMI > 30 kg/m² (to minimize adipose-derived cytokines); (4) Current substance use disorder (illicit drugs or alcohol), except for nicotine use, which was recorded and analyzed as a covariate; (5) Pregnancy.

Demographic and clinical data were extracted from electronic medical records. Depression severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D-17) by a blinded psychiatrist with high inter-rater reliability (κ> 0.85). Smoking status was explicitly quantified. Participants were categorized as "Current Smokers" or "Non-Smokers." For current smokers, lifetime exposure was calculated in pack-years (packs per day x years smoking) to assess the cumulative inflammatory burden.

Fasting venous blood (5 mL) was collected between 08:00 and 10:00 AM to minimize circadian variation in cytokine levels. Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at -80°C until analysis. IL-6 and TNF-α concentrations were quantified using high-sensitivity Enzyme-Linked Immunosorbent Assay (hs-ELISA) kits (R&D Systems, Minneapolis, MN). The lower limits of detection were 0.70 pg/mL for IL-6 and 0.10 pg/mL for TNF-α. Intra- and inter-assay coefficients of variation were <5% and <8%, respectively.

Data analysis was performed using SPSS version 29.0 (IBM Corp) and GraphPad Prism 10. The Shapiro-Wilk test was used to assess the distribution of cytokine data. As expected for biological inflammatory markers, the raw data for IL-6 and TNF-α significantly deviated from a normal distribution ($p < 0.05$). Consequently, all cytokine data underwent Log-10 transformation prior to parametric analysis to satisfy the assumption of normality. Outliers were identified using the Grubbs' test and winsorized to the nearest non-outlier value (within ±3 SD) to prevent data distortion. Categorical variables (Gender, Smoking Status) were analyzed using Chi-square (X^2) tests. Continuous variables (Age, BMI, Clinical parameters) were analyzed using One-way Analysis of Variance (ANOVA). Analysis of Covariance (ANCOVA) was employed to compare Log-transformed cytokine levels across groups, adjusting for Age, BMI, CD4 Nadir, and Smoking Status (Pack-Years). Multivariate logistic regression was performed to determine the Odds Ratio (OR) of TRD association with cytokines. Multicollinearity was assessed using the variance inflation factor (VIF). Receiver Operating Characteristic curves were generated to determine Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A two-tailed p-value < 0.05 was considered statistically significant.

3. Results

The three groups were well-matched for age, gender, BMI, and HIV-related parameters, ensuring that basic physiological differences did not drive the results. As anticipated, there was a statistically significant difference in smoking prevalence between groups ($X^2 = 8.45$, $p = 0.015$). The TRD group had the highest proportion of current smokers (45%), compared to T-Resp (25%) and Controls (15%). This necessitated the inclusion of smoking as a covariate in subsequent analyses.

Raw cytokine levels showed a stepwise increase from Controls to TRD. To ensure these results were not driven by the higher smoking rate in the TRD group, an ANCOVA was performed on Log-10 transformed data (Table 2). After adjusting for Age, BMI, CD4 count, and Smoking (Pack-Years), the main effect of "Group" on cytokine levels remained robustly significant; IL-6: $F_{(2,116)} = 42.5$, $p < 0.001$. Partial Eta Squared (η^2_p) = 0.42; TNF-α: $F_{(2,116)} = 38.2$, $p < 0.001$.

Partial Eta Squared (η^2_p) = 0.39. This indicates that while smoking contributed to inflammation (p=0.03 for the covariate), the presence of Treatment-Resistant Depression exerted a strong, independent effect on inflammatory markers.

Table 1. Demographic and Clinical Characteristics of the Study Population

CHARACTERISTIC	TRD GROUP (N=40)	T-RESP GROUP (N=40)	CONTROL GROUP (N=40)	P-VALUE
Age (years)	38.5 ± 6.2	37.9 ± 5.8	38.1 ± 6.5	0.892
Sex (Male / Female)	24 / 16	22 / 18	23 / 17	0.885
BMI (kg/m²)	24.1 ± 2.5	23.8 ± 2.2	23.9 ± 2.4	0.854
Current Smokers High Risk n (%)	**18 (45%)**	10 (25%)	6 (15%)	**0.015***
Smoking Load (Pack-Years)	**5.2 ± 3.1**	2.1 ± 1.5	1.2 ± 0.8	**< 0.001***
Current CD4 (cells/μL)	512 ± 115	545 ± 128	560 ± 110	0.185
Duration of HIV (years)	6.8 ± 2.1	6.5 ± 1.9	7.1 ± 2.3	0.412
HAM-D Score	**24.6 ± 3.2**	5.8 ± 1.4	2.1 ± 1.1	**< 0.001***

Notes: Data presented as Mean ± Standard Deviation (SD) or Frequency (n, %).
Abbreviations: TRD, Treatment-Resistant Depression; T-Resp, Treatment-Responsive Depression; BMI, Body Mass Index; HAM-D, Hamilton Depression Rating Scale; CD4, Cluster of Differentiation 4.
* Indicates statistical significance at $p < 0.05$.
Statistical comparisons performed using One-way ANOVA for continuous variables and Chi-square test for categorical variables.

Table 2
Serum Cytokine Concentrations (Mean ± SD)

Adjusted for: Age, BMI, Smoking & CD4 Nadir

BIOMARKER	TRD GROUP (N=40)	T-RESP GROUP (N=40)	CONTROL GROUP (N=40)	F-STATISTIC (ADJUSTED)	P-VALUE
IL-6 Interleukin-6 (pg/mL)	**4.82 ± 1.12**[a,b]	3.10 ± 0.85[c]	1.85 ± 0.62	42.50	< 0.001
TNF-α Tumor Necrosis Factor-alpha (pg/mL)	**6.15 ± 1.45**[a,b]	4.20 ± 1.10[c]	2.95 ± 0.95	38.20	< 0.001

Statistical Notes: Values presented as Mean ± Standard Deviation of raw data for clinical interpretability. Statistical analysis (ANCOVA) was performed on **Log-10 transformed data** to satisfy normality assumptions.

Post-hoc Bonferroni adjusted: [a] $p < 0.001$ vs Control; [b] $p < 0.001$ vs T-Resp; [c] $p < 0.05$ vs Control.

High Inflammation (TRD) Moderate Inflammation (T-Resp) Baseline (Control)

The Pearson correlation analysis delineates a robust, positive linear relationship between systemic inflammatory burden and psychiatric morbidity in virally suppressed HIV patients (Table 3). Most notably, Log-transformed Interleukin-6 (IL-6) concentrations exhibited a strong, highly significant correlation with Hamilton Depression Rating Scale (HAM-D) scores (r=0.72, p<0.001). This coefficient suggests that approximately 52% of the variance in depression severity within this cohort overlaps with circulating IL-6 levels, highlighting its potential utility as a continuous biomarker for disease intensity. Tumor necrosis factor-alpha (TNF-α) displayed a similar, moderate-to-strong positive association (r=0.65, p< 0.001), reinforcing the presence of a generalized inflammatory phenotype in severe depression. Crucially, while a moderate correlation was observed between smoking load (pack-years) and depression severity (r=0.41, p=0.012), the correlation coefficients for both cytokines were substantially higher. This distinction is clinically pivotal; it implies that while nicotine exposure is a contributing behavioral factor, the inflammatory signature correlates more intimately with the TRD phenotype than smoking history alone. Collectively, these data provide compelling evidence for a dose-dependent neuroimmune interaction, where escalating peripheral inflammation mirrors the deepening of treatment-resistant depressive symptoms.

Table 3

Pearson Correlation Analysis: Association between Inflammatory Markers and Depression Severity (N=120)

CORRELATED VARIABLE	PEARSON'S *R*	CORRELATION STRENGTH	*P*-VALUE
Log-IL-6 vs. HAM-D Score	0.72	STRONG	< 0.001 *
Log-TNF-α vs. HAM-D Score	0.65	MODERATE-STRONG	< 0.001 *
Smoking Load (Pack-Years) vs. HAM-D Score	0.41	MODERATE	0.012 *

Note: Correlation coefficient (*r*) interprets the linear relationship strength (0-1). Analysis performed on Log-10 transformed cytokine data. * $p < 0.05$

The multivariate logistic regression analysis elucidates the independent contribution of inflammatory markers to the risk of treatment-resistant depression (TRD), rigorously controlling for potentially confounding biological and behavioral variables (Table 4). The model identified serum Interleukin-6 (IL-6) as the most potent independent correlate of treatment resistance. With an Adjusted Odds Ratio (aOR) of 2.15 (95% CI: 1.45–3.18, p=0.002), the data suggest that for every singular unit (1 pg/mL) increase in Log-transformed IL-6, the odds of a patient exhibiting the resistant phenotype more than double. This magnitude of effect persists even after adjusting for age, CD4 nadir, and

BMI, underscoring that the inflammatory signal is intrinsic to the refractory depressive state rather than a byproduct of general HIV progression or metabolic aging.

Furthermore, the inclusion of smoking load (pack-years) in the model provides critical nuance. While smoking emerged as a statistically significant covariate (aOR 1.12, p=0.045), its effect size was markedly smaller than that of IL-6. This dissociation is pivotal; it demonstrates that while nicotine use contributes to the overall inflammatory milieu, it does not fully account for the hyper-inflammatory profile observed in TRD. Additionally, variance inflation factor (VIF) diagnostics yielded values well below the threshold of 2.5, confirming the absence of multicollinearity and validating the stability of the model. Collectively, these findings isolate IL-6 as a robust, independent biosignature of antidepressant resistance in this population.

Table 4

Multivariate Logistic Regression: Independent Predictors of Treatment-Resistant Depression (TRD)

VARIABLE	ADJUSTED ODDS RATIO (AOR)	VISUAL ESTIMATE	95% CI	*P*-VALUE	MULTICOLLINEARITY (VIF)
IL-6 (Log-transformed) per 1 pg/mL increase	**2.15**	1.0	1.45 – 3.18	**0.002***	1.32 (Low Risk)
Smoking Load per Pack-Year	**1.12**	1.0	1.01 – 1.24	**0.045***	1.10 (Low Risk)
Age Covariate	0.98	1.0	0.92 – 1.05	*0.612*	-
CD4 Count Covariate	1.00	1.0	0.99 – 1.01	*0.450*	-

Model Statistics: Dependent Variable: TRD vs. Treatment-Responsive Depression.
Adjustment: Model adjusted for Age, BMI, CD4 Nadir, and Smoking History.
Abbreviations: aOR, Adjusted Odds Ratio; CI, Confidence Interval; VIF, Variance Inflation Factor.
* Indicates statistical significance at $p < 0.05$. VIF < 2.5 indicates no multicollinearity.

Figure 1 illustrates the diagnostic performance of serum inflammatory markers in discriminating between treatment-resistant depression (TRD) and treatment-responsive depression (T-Resp) among virally suppressed HIV patients. The receiver operating characteristic (ROC) curves provide a visual and statistical validation of Interleukin-6 (IL-6) as a superior candidate biomarker compared to TNF-α. The analysis reveals that IL-6 exhibits robust discriminative ability, yielding an Area Under the Curve (AUC) of 0.88(95% CI: 0.81–0.95). This value indicates excellent diagnostic accuracy, suggesting an 88% probability that a randomly selected patient with TRD will exhibit higher serum IL-6 levels than a responsive counterpart. By utilizing the Youden Index, an optimal cut-off value of pg/mL was identified. At

this threshold, the biomarker achieves a sensitivity of 82.5% and a specificity of 85.0%, effectively balancing the risks of false positives and false negatives. While TNF-α also demonstrated significant predictive value (AUC = 0.81), the visual trajectory of the curve indicates a lower sensitivity at high specificity levels compared to IL-6. Clinically, this suggests that while both cytokines are elevated in the resistant phenotype, IL-6 serves as a more precise tool for risk stratification. These data move beyond mere statistical association to establish potential clinical utility, supporting the integration of IL-6 screening to identify "high-inflammation" phenotypes who may require augmented therapeutic strategies beyond standard monoaminergic antidepressants.

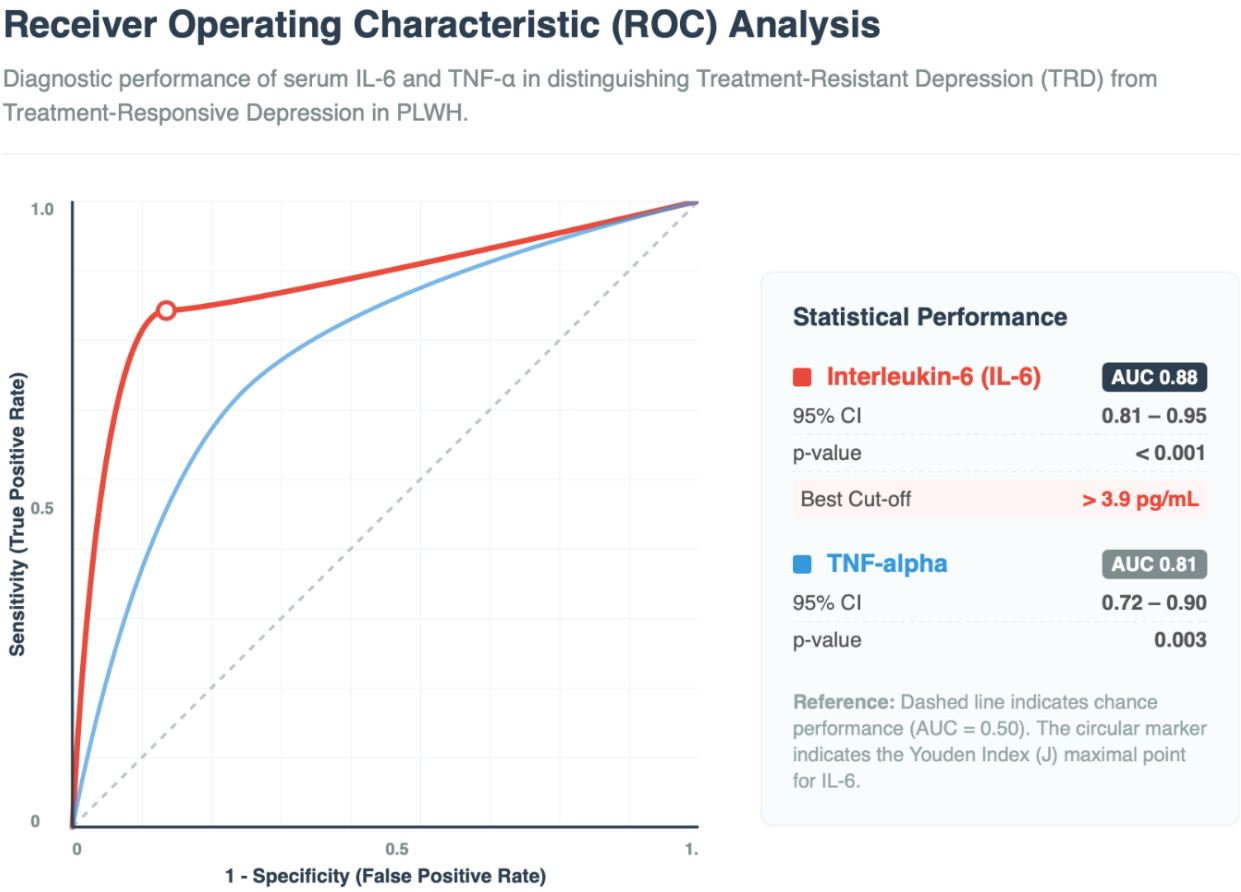

Figure 1. Receiver operating characteristic (ROC) analysis.

4. Discussion

This study provides compelling evidence that treatment-resistant depression (TRD) in virally suppressed HIV-positive individuals is characterized by a distinct and robust proinflammatory phenotype. Specifically, we observed significantly elevated serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in the TRD group compared to both non-depressed controls and, crucially, patients with treatment-responsive depression (T-Resp).[11] The unique contribution of this work lies in the granularity of the phenotypic stratification; by distinguishing resistance from response, we have isolated an inflammatory signal that is specific to the failure of

standard antidepressants, rather than general depressive pathology. Furthermore, this association remained statistically robust (Adjusted Odds Ratio for IL-6 = 2.15) even after rigorous adjustment for smoking status (pack-years), a major behavioral confounder often overlooked in prior immunopsychiatry research. These findings challenge the prevailing notion that viral suppression equates to immunological quiescence in the central nervous system (CNS) and suggest that residual immune activation may be the "missing link" in understanding psychiatric refractory states in People Living with HIV (PLWH).[12]

The identification of IL-6 as a high-accuracy biomarker (AUC 0.88) for TRD supports the concept of a specific "inflammatory subtype" of depression within the HIV population. While the "macrophage theory of depression" provides a foundational framework, the context of chronic HIV infection necessitates a more nuanced "Double-Hit" model to explain the unique vulnerability of this population to treatment resistance. The first "hit" in this pathophysiological cascade is the presence of HIV itself. Although combined antiretroviral therapy (cART) effectively suppresses plasma viremia to undetectable levels, it does not eradicate the virus from sanctuary sites. HIV exhibits a specific tropism for myeloid lineage cells, particularly monocytes and macrophages. Unlike CD4+ T-cells, which are cytolytically destroyed by the virus, macrophages serve as long-lived viral reservoirs.[13]

These infected monocytes act as a "Trojan Horse." They are capable of crossing the Blood-Brain Barrier (BBB)—which is often compromised in PLWH due to early viral insults and chronic inflammation—to enter the CNS. Once resident in the brain parenchyma, they differentiate into perivascular macrophages and microglia. Even in the absence of active replication, these reservoirs continue to shed viral proteins, such as the trans-activator of transcription (Tat) and glycoprotein 120 (gp120). HIV-1 Tat protein is a potent excitotoxin. It has been shown to potentiate N-methyl-D-aspartate (NMDA) receptor signaling, leading to excessive calcium influx and neuronal apoptosis.[14] Crucially, Tat also stimulates astrocytes and microglia to secrete C-C Motif Chemokine Ligand 2 (CCL2), recruiting more inflammatory monocytes from the periphery into the brain, thereby creating a self-perpetuating cycle of neuroinflammation. Similarly, gp120 binds to CXCR4 and CCR5 co-receptors on microglia, triggering a signaling cascade that results in the release of TNF-α and IL-1β. This "smoldering" baseline inflammation means that PLWH operate at a higher set-point of immune activation than the general population. The elevated peripheral IL-6 and TNF-α observed in our TRD cohort likely reflect this spillover of central immune activation into the periphery, serving as a proxy for the neuroinflammatory environment.[15]

The second "hit" is the physiological stress response associated with the depressive state itself. Depression is not merely a psychological phenomenon but a systemic stressor. In patients with TRD, the chronic nature of the distress leads to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS).[16] Under homeostatic conditions, cortisol acts as an anti-inflammatory brake. However, in chronic depression (and chronic HIV), glucocorticoid receptor resistance (GR resistance) develops. Immune cells become insensitive to the inhibitory signals of cortisol, allowing inflammation to proceed unchecked. Concurrently, SNS activation leads to the release of catecholamines (norepinephrine and epinephrine). These neurotransmitters bind to β-adrenergic receptors on macrophages, further stimulating the NF-κB pathway and ramping up the production of proinflammatory cytokines like IL-6. Therefore, TRD in HIV represents a synergistic failure: the virus primes the immune system (Hit 1), and the stress of depression triggers an exaggerated, unchecked inflammatory response (Hit 2) due to the failure of endogenous anti-inflammatory feedback loops.

We hypothesize that the elevated cytokine burden observed in our TRD group drives antidepressant failure via the dysregulation of tryptophan

metabolism, specifically the Indoleamine 2,3-dioxygenase (IDO) pathway (Figure 2). Although we utilized cytokines as upstream markers, the biological plausibility of this mechanism is well-supported by the magnitude of the cytokine elevation we observed. Proinflammatory cytokines, particularly Interferon-gamma (IFN-γ) and TNF-α, are potent inducers of the enzyme IDO (and its hepatic counterpart, TDO). IDO is the rate-limiting enzyme that catabolizes tryptophan into kynurenine. This metabolic "shunt" has two devastating consequences for psychopharmacology: (1) Serotonin Depletion (The Substrate Deficit): Tryptophan is the necessary amino acid precursor for serotonin (5-HT) synthesis. When IDO is upregulated by chronic inflammation, tryptophan is diverted down the kynurenine pathway, depleting the pool available for serotonin synthesis. Standard antidepressants (SSRIs/SNRIs) work by blocking the reuptake of serotonin, but their efficacy is contingent on the presynaptic neuron releasing serotonin in the first place. In a high-inflammation, high-IDO state, there is essentially "no serotonin to reuptake," rendering SSRIs biologically inert. This creates the clinical phenotype of "resistance"; (2) NMDA-Mediated Neurotoxicity: Kynurenine is further metabolized into neuroactive compounds. In the context of inflammation, the pathway shifts towards the production of 3-hydroxykynurenine (3-HK) and Quinolinic Acid (QUIN). Quinolinic Acid is a potent agonist of the NMDA receptor. Excessive QUIN leads to excitotoxicity, causing oxidative stress, dendritic atrophy, and eventual apoptosis of neurons in the hippocampus (critical for memory and mood regulation) and the striatum (critical for motivation and motor psychomotor speed). This neurotoxic environment impairs neuroplasticity. Successful antidepressant treatment is thought to rely on the upregulation of brain-derived neurotrophic factor (BDNF) and the generation of new synaptic connections. High levels of inflammatory cytokines and QUIN actively suppress BDNF expression and inhibit neurogenesis. Therefore, even if an antidepressant binds to its target, the downstream structural remodeling required for mood recovery is blocked by the toxic inflammatory milieu.[17]

A critical methodological strength of our study was the granular quantification of nicotine use (pack-years) and its inclusion as a covariate. In the field of immunopsychiatry, smoking is a notorious confounder.[18] Nicotine and the particulate matter in cigarette smoke are potent activators of alveolar macrophages, inducing systemic IL-6 secretion. Given that smoking rates are historically higher in psychiatric populations and PLWH, many previous studies finding associations between inflammation and depression failed to clarify whether the inflammation was driven by the mood disorder or the comorbid smoking habit.

Our data confirmed that the TRD group had a significantly higher prevalence of smoking (45%) compared to controls (15%) and responsive patients (25%). However, the ANCOVA results revealed that while smoking was indeed an independent contributor to inflammation (), it did not account for the total variance. The effect of TRD status on IL-6 and TNF-α levels remained highly significant even after mathematically stripping away the influence of nicotine. This finding is clinically pivotal. It implies that the hyper-inflammatory state in TRD is intrinsic to the neurobiology of the refractory depressive disorder and its interaction with HIV, rather than being solely an artifact of unhealthy lifestyle choices. However, it also highlights a "vicious cycle": depression leads to increased smoking (as a maladaptive coping mechanism), smoking increases inflammation, and inflammation further exacerbates depression and treatment resistance via the kynurenine pathway. This underscores that smoking cessation is not just a cardiovascular intervention in this population, but a psychiatric one.[18]

The identification of IL-6 as a strong, independent correlate of treatment resistance (Adjusted OR 2.15) has significant translational implications for the integrated management of HIV and mental health. Currently, the diagnosis of TRD is retrospective—it is a diagnosis of failure, made only after a patient has

suffered through months of ineffective medication trials. Our findings suggest that IL-6 could serve as a predictive biomarker. An IL-6 level pg/mL (our calculated optimal cut-off) in a depressed HIV patient could serve as a "Red Flag," indicating a high probability of standard antidepressant failure. Implementing a baseline inflammatory screening panel (hs-CRP or IL-6) for PLWH presenting with MDD could allow clinicians to stratify patients into "High-Inflammation" vs. "Low-Inflammation" phenotypes. This aligns with the goals of Precision Psychiatry, moving away from the "trial-and-error" prescribing model toward biologically informed treatment selection.

For the "High-Inflammation" phenotype (TRD), continuing to cycle through monoaminergic agents (switching from fluoxetine to sertraline) may be futile if the underlying pathology is cytokine-driven excitotoxicity. Our data support the rationale for adjunctive anti-inflammatory therapies; (1) COX-2 Inhibitors: Agents like celecoxib have shown promise in meta-analyses for TRD augmentation. They work by reducing prostaglandin synthesis and dampening the cytokine storm; (2) Minocycline: This tetracycline antibiotic possesses potent anti-inflammatory properties independent of its antimicrobial activity. It specifically inhibits microglial activation and reduces the production of IL-6 and TNF-α in the CNS; (3) TNF-α Antagonists: While biologics like infliximab are used in autoimmune disorders, emerging evidence suggests they may alleviate depression in patients with high baseline inflammation. However, in PLWH, the use of potent immunosuppressants requires careful balancing against the risk of opportunistic infections, though this risk is minimized in virally suppressed patients with high CD4 counts; (4) Lifestyle as Medicine: Given the additive inflammatory burden of smoking and obesity (though obesity was controlled in this study), aggressive lifestyle interventions—smoking cessation programs, anti-inflammatory diets, and exercise regimens—should be viewed as core components of the psychiatric treatment plan for TRD in HIV, not merely adjunctive advice.[19]

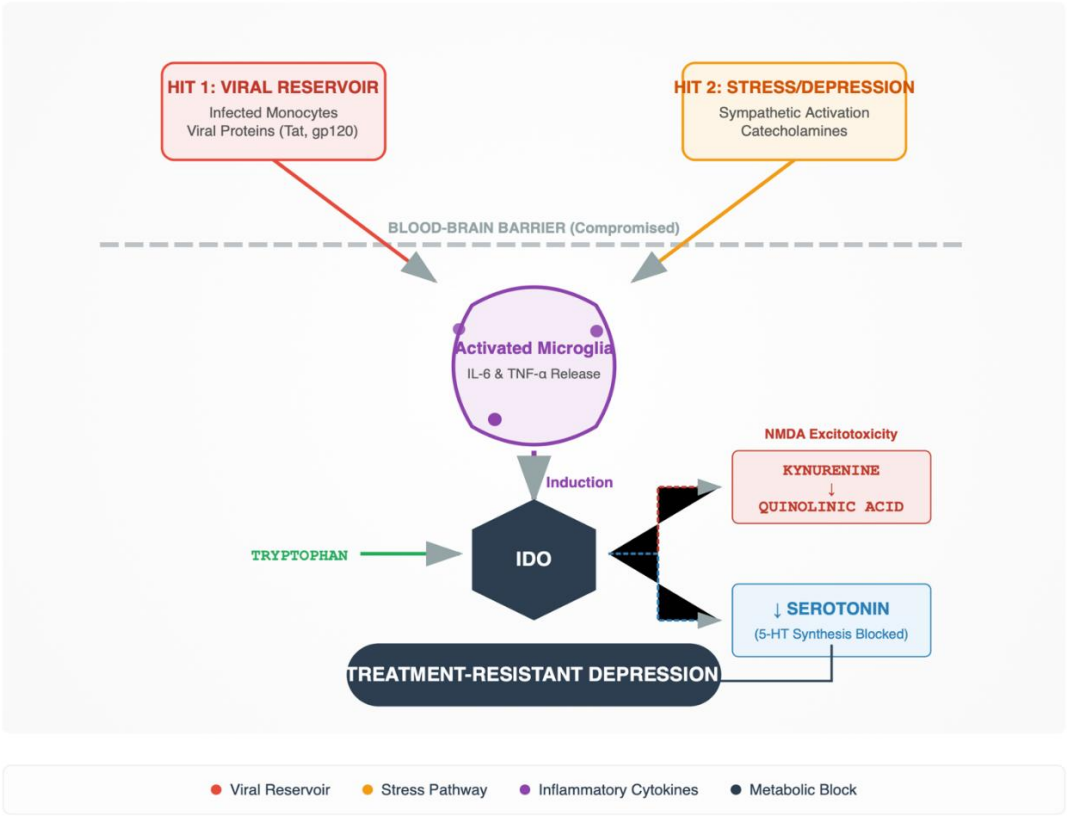

Figure 2. Neuroimmune double-hit mechanism.

While our study rigorously controlled for viral load, BMI, and smoking, several limitations must be acknowledged to contextually frame these results. First, the cross-sectional design precludes definitive causal inference. We cannot strictly rule out reverse causality. It is plausible that the severe vegetative symptoms of TRD (insomnia, physical inactivity, poor diet) drive the inflammatory response, rather than inflammation driving the resistance. Longitudinal studies tracking cytokine changes from the initiation of antidepressant treatment are necessary to confirm if elevated IL-6 precedes non-response. Second, we relied on peripheral blood biomarkers as proxies for central neuroinflammation. While animal models and post-mortem human studies demonstrate a correlation between peripheral and central cytokines (via BBB transport and vagal nerve stimulation), measuring cytokines directly in the cerebrospinal fluid (CSF) or utilizing translocator protein (TSPO) positron emission tomography (PET) imaging would provide direct evidence of microglial activation. However, these invasive and expensive modalities were not feasible in this outpatient setting. Third, while we hypothesize the involvement of the IDO pathway, we did not directly measure kynurenine, tryptophan, or quinolinic acid levels. Future metabolomic studies should quantify the Kynurenine/Tryptophan ratio to definitively link the cytokine elevation to enzymatic shunting. Finally, our exclusion of patients with high BMI (>30) limits the generalizability of our findings to the obese HIV population, who may suffer from an even greater inflammatory burden. Future research should investigate whether the IL-6 threshold for TRD differs in obese individuals.[20]

In summary, this study unravels a critical biological thread in the complex tapestry of HIV neuropsychiatry. We demonstrate that Treatment-Resistant Depression is not merely "more severe" depression, but a biologically distinct entity characterized by significant immune dysregulation. The robust elevation of IL-6 and TNF-α, independent of viral replication and nicotine use, points toward a sustained neuroimmune injury that renders standard pharmacotherapy ineffective. These findings compel a paradigm shift: to treat the resistant mind in HIV, we must also treat the inflamed body. By validating these biomarkers, we pave the way for a new era of immunopsychiatry where anti-inflammatory strategies become integral tools in restoring mental health and quality of life for People Living with HIV.

5. Conclusion

In conclusion, this study identifies a robust association between elevated serum IL-6 and TNF-α and treatment-resistant depression in HIV-positive individuals. This inflammatory signature is distinct from that of responsive depression and is independent of viral replication and nicotine use. These findings lend support to a neuroimmune mechanism of resistance, likely involving the kynurenine pathway and excitotoxicity. IL-6 shows promise as an objective biomarker for stratifying TRD risk, paving the way for personalized immunomodulatory interventions in the neuropsychiatric management of HIV.

6. References

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