International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
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ARTICLE TITLE	REACTIVATION OF HUMAN ENDOGENOUS RETROVIRUSES (HERV-W) AS A GENETIC-IMMUNOLOGICAL TRIGGER OF PSYCHOSIS: A REVIEW OF THE NEUROTOXIC MECHANISMS OF THE ENVELOPE PROTEIN (ENV)
DOI	https://doi.org/10.31435/ijitss.1(49).2026.5283
RECEIVED	07 February 2026
ACCEPTED	19 March 2026
PUBLISHED	30 March 2026
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REACTIVATION OF HUMAN ENDOGENOUS RETROVIRUSES (HERV-W) AS A GENETIC-IMMUNOLOGICAL TRIGGER OF PSYCHOSIS: A REVIEW OF THE NEUROTOXIC MECHANISMS OF THE ENVELOPE PROTEIN (ENV)

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ABSTRACT

Schizophrenia does not arise from a single genetic flaw or a solitary environmental insult; rather, it is born from the collision of both. In this review, we move beyond classical neurotransmitter theories to dissect the molecular pathogenicity of the Human Endogenous Retrovirus-W Envelope protein (HERV-W ENV). We trace the evolution of the historical "viral hypothesis" into the modern "two-hit" model, wherein environmental stressors literally awaken dormant retroviral elements within our own DNA. How does this intragenomic parasite damage the brain? We evaluate its neurotoxicity across three distinct pillars: structural, immunological, and signaling. Structurally, the protein's fusogenic properties induce severe membrane instability. Immunologically, it acts as a potent toxin, igniting the microglial TLR4 cascade and driving neurons into violent, inflammatory death via the NLRP3-Caspase-1-GSDMD pyroptosis pathway. Yet, the most profound damage occurs within intracellular signaling. HERV-W ENV actively sabotages the dopamine-glutamate axis. It forces NMDA receptors to escape the synapse laterally, starves the synaptic cleft by blocking ASCT1/2-mediated glutamine transport, and hijacks the AKT/GSK3β pathway to drive dopaminergic hyperactivity. These integrated mechanisms establish HERV-W ENV not just as a bystander, but as a direct causal bridge between immune dysregulation and synaptic failure. Recognizing this distinct "inflammatory biotype" of psychosis completely alters the therapeutic landscape. We conclude by exploring how neutralizing this viral protein with the monoclonal antibody Temelimab could move the field from symptomatic management toward true etiological intervention in precision psychiatry.

KEYWORDS

HERV-W; Schizophrenia, Neuroinflammation, Pyroptosis, Temelimab

CITATION

Jakub Robert Skalski, Łukasz Ćmok, Justyna Chudy, Julia Jadwiga Dobrowolska, Gabriela Daniel, Natalia Kaczmarczyk, Antoni Hajdas, Karolina Halat, Julia Szmuc, Iga Kałka. (2026) Reactivation of Human Endogenous Retroviruses (Herv-W) as a Genetic-Immunological Trigger of Psychosis: a Review of the Neurotoxic Mechanisms of the Envelope Protein (Env). *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.5283

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1. Introduction

We often think of the human genome as a pristine blueprint for life. In reality, nearly 8% of our DNA consists of the genetic fossils of ancient viral infections (Li & Karlsson, 2016; Wang et al., 2018). These Human Endogenous Retroviruses (HERVs) are the legacy of exogenous retroviruses that invaded the germline of our primate ancestors millions of years ago. For decades, the genomic era dismissed these sequences as mere "junk DNA"—evolutionary debris permanently silenced by mutations and epigenetic locks. That view is now obsolete. While most HERVs remain irreparably defective, specific families like HERV-W still harbor open reading frames (ORFs) capable of transcription and translation into functional proteins (Giménez-Orenga & Oltra, 2021; Tamouza et al., 2021; Yao et al., 2023; Simula et al., 2025).

True, some of these elements have been beautifully "domesticated" by evolution; the ERVWE1 locus, for instance, encodes Syncytin-1, a protein absolutely essential for placental development. But this domestication comes with a profound risk. When these same elements aberrantly reactivate in the central nervous system (CNS), they drive severe neurodegenerative and neuropsychiatric pathology (Wang et al., 2018; Balestrieri et al., 2019; Yao et al., 2023). This "resurrection" of dormant viral genes represents an entirely different category of disease: an intrinsic piece of our own DNA acting as an invading pathogen.

Schizophrenia has long been suspected to have an inflammatory or infectious origin, but the search for a single external pathogen repeatedly failed. The reactivation of HERV-W finally offers a molecular bridge between the classic "viral hypothesis" and the "genetic hypothesis." It suggests that psychosis is not simply a chemical imbalance of neurotransmitters, but a systemic condition triggered by an "intragenomic parasite" (Sighencea & Trifu, 2025). The HERV-W Envelope protein (ENV) is particularly toxic. Because its expression in the brain and blood correlates directly with symptom severity and inflammation, we can no longer view it as a mere bystander. It is an active driver of the disease process (Aftab et al., 2016; Wang et al., 2018; Tamouza et al., 2021).

In this review, we dissect the molecular pathogenicity of HERV-W ENV in psychosis. Moving beyond broad epidemiological associations, we map out the exact mechanistic pillars of its neurotoxicity. First, we examine the structural domains of the ENV protein that allow it to hijack neural and glial receptors (Giménez-Orenga & Oltra, 2021; Wang et al., 2018). Next, we trace the resulting immunological firestorm, which culminates in chronic neuroinflammation and neuronal pyroptosis (Jia et al., 2025; Li et al., 2023). Finally, we explore the signaling chaos it creates by fundamentally disrupting both dopaminergic and glutamatergic transmission (Johansson et al., 2020; Yan et al., 2022). By synthesizing these structural, immunological, and signaling perspectives, we aim to establish HERV-W ENV as a primary etiopathological trigger of psychosis.

2. Methodology

2.1. Study Design

To capture the full scope of a pathogen hidden within our own DNA, we chose an integrative review approach. This method allowed us to simultaneously weave together experimental, theoretical, and clinical data. Rather than looking at isolated symptoms, we structured our analysis around the HERV-W ENV protein itself, dividing its neurotoxicity into three distinct mechanistic pillars: immunological, signaling, and structural.

2.2. Search Strategy and Data Sources

We scoured major biomedical databases—primarily PubMed/MEDLINE, Web of Science, ScienceDirect, and Google Scholar. To trace the evolution of the field, we set our search window from 1984 (the year Crow first proposed the retroviral hypothesis of schizophrenia; Crow, 1984) up to March 2026. Our core search terms targeted the intersection of virology and psychiatry: HERV-W ENV, Schizophrenia, Neuroinflammation, Neuronal Pyroptosis, NMDAR Trafficking, Two-Hit Hypothesis, and Temelimab. We naturally employed standard Boolean operators (e.g., "HERV-W ENV AND Psychosis") to filter the noise and refine the results.

2.3. Inclusion and Exclusion Criteria

We maintained strict boundaries for what made it into the final manuscript. For inclusion, we required peer-reviewed primary research, systematic reviews, or meta-analyses dissecting the molecular mechanisms of HERV-W in neuropsychiatric disorders. We heavily prioritized recent, high-impact literature (2020–2025). This ensured maximum clinical relevance. Conversely, we excluded non-peer-reviewed content, articles published in languages other than English or Polish, and studies focusing solely on other endogenous retrovirus families (like HERV-K) unless they explicitly tied back to psychosis.

2.4. Data Analysis and Synthesis

We did not just summarize the literature; we used a thematic synthesis to rebuild the virus's pathway. We extracted hard data on the protein’s structural domains, mapped its physical interactions with glial and neuronal receptors, and traced the intracellular signaling chaos it creates. The ultimate goal was simple. We wanted to integrate these scattered findings into a single, cohesive etiological model—one that finally bridges the gap between genetic vulnerability and environmental triggers.

3. Historical Evolution: From the Viral Hypothesis to Endogenous Reactivation

For nearly four decades, the hunt for a viral cause of schizophrenia focused on external pathogens. We were looking in the wrong place. The conceptual framework eventually shifted to a startling realization: the pathogen was already encoded within the host's own DNA.

3.1. The Legacy of Timothy Crow and the Virogene Theory

Modern HERV research in psychiatry owes its intellectual lineage directly to Timothy J. Crow. In the mid-1980s, he articulated the "viral hypothesis" of schizophrenia, boldly challenging the dogma that the disorder was purely a dopaminergic dysfunction (Palaniyappan & Liddle, 2025). Crow noticed glaring epidemiological anomalies that classical genetics failed to explain. For instance, siblings typically developed the illness at a similar age of onset, but almost never at the same calendar time. This completely refuted a simple contagion effect (Palaniyappan & Liddle, 2025). Furthermore, the well-documented "season of birth" effect pointed toward a seasonally active environmental trigger (Slokar & Hasler, 2016). To reconcile these clues, Crow proposed that a "provirus"—a retroviral element integrated into the human genome—could be the underlying culprit (Crow, 1984; Palaniyappan & Liddle, 2025).

He posited a radical idea for the time: an exogenous pathogen might not be necessary at all if a dormant retroviral element could simply be reactivated. This "virogene" theory elegantly reconciled the genetic heritability of the disorder with environmental triggers (Palaniyappan & Liddle, 2025). Although Crow later shifted his own focus to cerebral asymmetry and the evolution of language, his early hypothesis laid the absolute foundation for the molecular hunt that would eventually identify HERV-W (Palaniyappan & Liddle, 2025).

3.2. The Discovery of Reverse Transcriptase and HERV-W

The virogene theory lacked hard biochemical proof until the late 1990s and early 2000s. The true turning point was the discovery of retroviral RNA and reverse transcriptase (RT) activity in the cerebrospinal fluid (CSF) and brains of patients with acute psychotic episodes (Karlsson et al., 2001; Yolken et al., 2000). Similar discoveries in patient serum soon followed (Huang et al., 2006). Crucially, healthy brains showed no such activity (Karlsson et al., 2001).

Where was this RT activity coming from? It was not an exogenous virus like HIV or HTLV. Sequence analysis traced it back to our own genome, specifically identifying elements of the HERV-W family (named for the tryptophan tRNA primer used for replication) (Leboyer et al., 2013). Researchers found that the ERVWE1 locus on chromosome 7q21.2 and other loci were transcriptionally active in these patients. The paradigm fundamentally shifted. The field moved away from horizontal transmission, focusing instead on vertical inheritance and subsequent reactivation—solidifying the role of endogenous elements in the disease (Yao et al., 2023).

3.3. The "Two-Hit" Hypothesis: Genetics Meets Environment

How do we bridge the gap between Crow's historical virogene concepts and modern clinical reality? The field currently frames HERV-W pathogenicity within the 'two-hit' hypothesis—a model where hereditary susceptibility violently collides with environmental stress (Feigenson et al., 2014). It does not happen overnight. First, there is the genetic or epigenetic vulnerability (the "First Hit"). A patient inherits specific HERV-W loci prone to reactivation, or perhaps carries a defect in the stochastic epigenetic machinery (such as DNA methylation or histone modification) that normally keeps these elements locked down. Indeed, studies confirm that HERV-W *env* gene copy numbers and sequence variations differ significantly between patients and controls, pointing to a baseline genetic predisposition to viral expression (Aftab et al., 2016; Slokar & Hasler, 2016).

But the virus remains silent without a trigger. The "Second Hit" comes from environmental stressors that dismantle this fragile epigenetic repression, leading to active transcription and protein synthesis. It effectively wakes the sleeping giant within the genome (Aftab et al., 2016; Giménez-Orenga & Oltra, 2021; Sighencea & Trifu, 2025). Epidemiologists have known for decades that prenatal and perinatal infections increase schizophrenia risk, but the two-hit model finally supplies the molecular mechanism. Common pathogens—like Influenza A, Toxoplasma gondii, Herpes Simplex Virus type 1 (HSV-1), and Epstein-Barr Virus (EBV)—do not just infect the host; they act as potent transactivators of HERV-W (Dou et al., 2025; Sighencea & Trifu, 2025). This beautifully explains why the disease is so episodic. When the organism's inflammatory state flares due to environmental exposures, HERV-W expression surges right alongside it.

4. Structural Pillars: The Molecular Architecture of Neurotoxicity

Before we can explore the damage HERV-W ENV inflicts on the brain, we must look at its physical blueprint. At its core, HERV-W ENV (Syncytin-1) is classified as an ancient, ubiquitous gamma-type envelope glycoprotein. These gamma-type Envs share a very specific molecular architecture, boasting highly conserved receptor-binding domains and fusion peptides that grant them extreme fusogenic capabilities (Hogan & Johnson, 2023). Evolution brilliantly co-opted this structure for mammalian placental fusion. In the brain, however, it is a disaster. When pathologically reactivated in the central nervous system, the preservation of this exact gamma-type structure allows the protein to exert profound, disruptive cellular effects (Hogan & Johnson, 2023).

As a class I viral fusion protein, it shares a core mechanistic profile in its fusion domains with lentiviruses like HIV-1. Yet, because it is specifically a gamma-type Env, it exhibits striking structural and functional homology to the envelope proteins of exogenous gammaretroviruses, such as the Murine Leukemia Virus (Gong et al., 2005; Hogan & Johnson, 2023). The cell synthesizes functional HERV-W ENV as a glycosylated precursor polyprotein (gPr73). A cellular furin cleavage site then splits this precursor into two distinct functional pieces: the surface (SU) domain and the transmembrane (TM) domain. They do not drift apart. Instead, these subunits remain tethered by a highly conserved, labile disulfide bond at a CXXC motif, assembling into a functional homotrimer (Durnaoglu et al., 2022; Hogan & Johnson, 2023; Wang et al., 2018). This seemingly simple bipartite architecture dictates everything—its binding partners, its fusogenic power, and its devastating neurotoxicity.

4.1. The Surface Subunit (SU/gp50) and Receptor Blockade

The surface subunit (SU/gp50) acts as the viral homing mechanism. It harbors the Receptor Binding Domain (RBD), which strictly dictates which cells the virus can target. In the brain, this tropism is disastrous. The SU domain specifically hunts down and binds to two sodium-dependent neutral amino acid transporters: ASCT1 (SLC1A4) and ASCT2 (SLC1A5) (Lavillette et al., 2002). ASCT2 serves as the primary target. Because it is highly expressed on astrocytes and neurons, it normally regulates the critical transport of glutamine, alanine, serine, and cysteine—the very foundation of the glutamate-glutamine cycle (Scalise et al., 2020). ASCT1 acts as a secondary target with a slightly different tissue footprint (Lavillette et al., 2002). The viral protein physically clamps onto the Extracellular Loop 2 (ECL2) of these transporters (Lavillette et al., 2002).

This is not just a docking event; it is a hostile takeover. By physically occupying these receptors, HERV-W ENV functionally sequesters them and creates a massive bottleneck in amino acid transport. This physical blockade cuts off the metabolic support of neurons. It offers a clear, mechanical explanation for the glutamatergic hypofunction we see in schizophrenia (Lavillette et al., 2002; Slokar & Hasler, 2016). While the highly divergent ECL2 region bears the scars of an ancient evolutionary "arms race" between retroviruses and mammalian hosts, HERV-W has retained a striking affinity for human ASCT receptors. Humans are uniquely vulnerable to this mechanism (Lavillette et al., 2002).

4.2. The Transmembrane Subunit (TM/gp24) and Membrane Instability

If the SU domain is the homing device, the transmembrane subunit (TM/gp24) is the weapon. This anchoring domain executes membrane fusion. It relies on a hydrophobic fusion peptide at its N-terminus, along with heptad repeats (HR1 and HR2) that collapse into a highly stable six-helix bundle (Gong et al., 2005). Once the SU binds its receptor and the CXXC motif undergoes disulfide bond isomerization, TM violently snaps into a new conformation. It stabs its fusion peptide directly into the target cell membrane, initiating the fusion process (Durnaoglu et al., 2022; Gong et al., 2005; Hogan & Johnson, 2023).

In a developing placenta, this exact fusogenic capability safely merges cytotrophoblasts into the syncytiotrophoblast. In the brain, it triggers chaos. While massive cell fusion (syncytia) is rare in neural tissue, the mere insertion of the fusion peptide perturbs the lipid bilayer enough to severely compromise neuronal integrity and synaptic function (Gong et al., 2005; Johansson et al., 2020). This structural assault also forces the stressed cell to leak cytotoxic redox reactants, driving myelin damage and broader neurodegenerative changes (Wang et al., 2018).

4.3. The Immunosuppressive Domain (ISD) and Molecular Mimicry

Deep within the TM subunit lies a highly conserved Immunosuppressive Domain (ISD). Exogenous retroviruses use this domain to hide from the host immune response. Even in human physiology, such as placental Syncytin-1, the ISD actively modulates cytokines and promotes maternal-fetal tolerance (Wang et al., 2018). But neuropathology tells a different story. Recent structural insights reveal that pathogenic variants of HERV-W ENV in the CNS often carry a single, charge-altering point mutation in this exact domain—a shift from glutamic acid to lysine. This tiny change severely diminishes its immunosuppressive power (Giménez-Orenga & Oltra, 2021; Meier et al., 2021).

Meanwhile, the highly glycosylated SU domain acts as a potent superantigen, triggering massive, uncontrolled polyclonal T-cell activation (Giménez-Orenga & Oltra, 2021; Perron et al., 2001). This clash between broken immunosuppressive traits and hyperactive superantigens traps the brain in a paradox. The host fails to clear the pathogenic protein, yet suffers from chronic immune dysregulation. We call this "smoldering" inflammation. It is a fundamental hallmark of the schizophrenic brain, entirely distinct from the raging, acute inflammation seen in classical viral encephalitis (Küry et al., 2018; Wang et al., 2018).

5. Immunological Pillars: The Neuroinflammatory Cascade

Forget the outdated dogma that the brain is an "immune privileged" sanctuary. In psychiatric disorders, neuroinflammation takes center stage. HERV-W ENV acts as a potent "immunotoxin," igniting a highly destructive inflammatory cascade directly within the CNS (Wang et al., 2018). It is not merely a byproduct of the disease. It is the definitive bridge connecting a silent genetic vulnerability to active, physical brain damage.

5.1. Microglial Activation via TLR4

When HERV-W ENV appears, microglia do not just observe it—they attack. The viral protein acts as a blatant Pathogen-Associated Molecular Pattern (PAMP), perfectly mimicking a live, exogenous viral infection. It binds with remarkable affinity to Toll-like Receptor 4 (TLR4), forming a tight complex with CD14 on the microglial surface (Rolland et al., 2006; Wang et al., 2018). This single physical interaction is the spark. We know this because when researchers pharmacologically or genetically block TLR4, the neurotoxic effects of HERV-W ENV completely vanish. The receptor serves as the absolute gatekeeper for HERV-mediated neuroinflammation (Wang et al., 2021).

Once TLR4 engages the viral protein, an aggressive signal transduction cascade takes over. The virus employs a brilliant, dual-pronged strategy. It forces the upregulation of the MyD88 adapter protein while simultaneously crushing the expression of its short splice variant, MyD88s—the cell's natural brake on inflammation (Wang et al., 2021). With the brakes gone, NF-κB floods the nucleus.

The resulting transcriptional storm forces microglia out of their neuroprotective (M2-like) state and traps them in a highly neurotoxic (M1-like) phenotype (Meier et al., 2021). These hijacked cells begin pumping out massive quantities of pro-inflammatory cytokines, specifically TNF-α, IL-6, and IL-1β. Each plays a distinct role in brain pathology. TNF-α drives local excitotoxicity (Wang et al., 2021), while IL-6 persistently alters synaptic plasticity and compromises the blood-brain barrier (Slokar & Hasler, 2016; Tamouza et al., 2021). Meanwhile, IL-1β sets the stage for a violent form of cell death (Jia et al., 2025). But the assault is not just cytokine-mediated. The activated microglia also churn out reactive oxygen species (ROS) and nitric oxide (NO) by massively inducing inducible nitric oxide synthase (iNOS) (Xiao et al., 2017). This severe oxidative and nitrosative stress directly kills neighboring neurons and oligodendrocytes, providing a clear molecular rationale for the gray matter loss and white matter abnormalities clinically observed in schizophrenia.

5.2. The Pyroptosis Pathway: NLRP3, Caspase-1, and GSDMD

How exactly do these neurons die? For years, apoptosis was the default assumption. We now know that HERV-W ENV triggers something far more destructive: pyroptosis. Apoptosis is a quiet, orderly, and non-inflammatory cellular suicide. Pyroptosis, by contrast, is an explosive, violent death that spills intracellular contents into the local environment, dramatically amplifying the immune response (Jia et al., 2025). This distinction changes everything. It finally provides a concrete mechanism for the chronic, self-sustaining inflammatory firestorm seen in psychosis. The execution of this cell death unfolds as follows:

This is not just a localized, isolated event. The explosive release of IL-1β creates a vicious feed-forward loop that rapidly activates neighboring microglia and astrocytes, propagating the neuroinflammatory firestorm. We see this exact molecular signature in the clinic. Blood samples from patients with recent-onset schizophrenia show remarkably strong positive correlations between HERV-W ENV expression and circulating levels of CASP1, GSDMD, and IL-1β (Jia et al., 2025). Can this cascade be stopped? Experimental data suggests it can. When researchers deployed specific pharmacological inhibitors targeting NLRP3 (CY-09), Caspase-1 (VX-765), and GSDMD (dimethyl fumarate, DMF), they successfully rescued neurons from ENV-induced death. This conclusively distinguishes the pathology from standard BID-mediated apoptosis and opens up multiple, highly specific targets for therapeutic intervention (Jia et al., 2025).

5.3. The cGAS-STING Axis and Innate Immunity

The damage, however, is not limited to surface receptor hijacking. HERV-W ENV also breaches the cell to directly engage intracellular DNA sensing machinery. In the schizophrenic brain, the viral protein physically interacts with cyclic GMP-AMP synthase (cGAS) (Li et al., 2023). Normally, the host cell keeps cGAS expression strictly suppressed using a specific long non-coding RNA, linc01930. But the virus removes this failsafe. By actively repressing the linc01930 promoter, HERV-W ENV unleashes the unrestricted upregulation of cGAS and its downstream effector, STING (Stimulator of Interferon Genes).

Once the cGAS-STING pathway is fully activated, it triggers the phosphorylation of Interferon Regulatory Factor 3 (IRF3). This factor then storms the nucleus and drives a massive production of Type I interferons, particularly IFN-β (Li et al., 2023). While interferons are typically protective during acute infections, chronically high levels of IFN-β in the CNS are deeply neurotoxic and pro-apoptotic. Ultimately, this reveals the truly multi-pronged nature of HERV-W immunotoxicity. By simultaneously triggering surface receptors (TLR4) and intracellular sensors (cGAS), the retroviral protein traps the neuron in a sustained, inescapable inflammatory state—attacking the cell from both the outside and the inside.

6. Signaling Pillars: Intracellular Pathways and Synaptic Dysfunction

Let's move beyond the physical damage. HERV-W ENV does not just poke holes in membranes or set off inflammatory alarms; it actively sabotages the very language of the brain. The protein acts as a molecular saboteur, fundamentally rewiring the intracellular pathways governing neurotransmission and driving a wedge into the delicate balance between the dopaminergic and glutamatergic systems.

6.1. Disruption of the Dopamine-Glutamate Axis

For decades, psychiatry has been split between two competing dogmas: the "Dopamine Hypothesis" (where striatal overdrive fuels positive symptoms) and the "Glutamate Hypothesis" (where NMDA receptor hypofunction drives cognitive and negative decline). What if they are both triggered by the exact same viral protein? HERV-W ENV offers a stunning, unifying molecular mechanism that bridges these seemingly disparate pathologies (Johansson et al., 2020; Yan et al., 2022). The profound impact of ENV on these signaling systems is summarized in Table 1.

6.1.1. The Glutamatergic System: NMDAR Trafficking and Astrocyte Failure

Consider the glutamatergic system. We know HERV-W ENV shuts down NMDA receptor function, but it does not act as a blunt, direct antagonist like ketamine or PCP (Johansson et al., 2020). Its method is much more insidious. Through single-molecule tracking, researchers discovered that the viral protein forces a physical displacement of the receptor. It drastically accelerates the surface diffusion of GluN2B-containing NMDARs, causing them to slide laterally right out of the postsynaptic density. This "lateral escape" changes everything. By pushing functional receptors away from the synaptic cleft, the virus engineers a profound hypofunction without ever blocking the channel pore (Johansson et al., 2020). Clinically, this destroys Long-Term Potentiation (LTP)—the cellular bedrock of learning and memory—and is fully sufficient to trigger psychotic-like behaviors in animal models. Crucially, this trafficking sabotage relies on TLR4-driven cytokine release from glia, perfectly intertwining the immunological and signaling pillars of the disease (Johansson et al., 2020).

The assault on glutamate does not stop at receptor displacement. Astrocytes normally clear glutamate from the synaptic cleft (via EAAT transporters), convert it to glutamine, and pump it back to neurons via ASCT2 to build fresh neurotransmitters. HERV-W ENV completely derails this recycling program. By physically binding and obstructing ASCT1 and ASCT2 receptors on astrocytes, the virus cuts off the glutamine supply line, depleting the essential precursor pools for both excitatory (glutamate) and inhibitory (GABA) signaling (Lavillette et al., 2002; Scalise et al., 2020; Slokar & Hasler, 2016). The synapse literally starves.

6.1.2. The Dopaminergic System: DRD2 Upregulation and AKT/GSK3β

While it starves the glutamatergic synapse, HERV-W ENV paradoxically sends the dopaminergic system into overdrive. It directly hunts down and interacts with the Dopamine D2 Receptor (DRD2), forcing its upregulation through direct promoter activation (Yan et al., 2022). This physical interaction sparks a multi-step signaling cascade that locks the neuron into a state of dopaminergic hyperactivity. First, the viral protein upregulates β-arrestin 2 (ARRB2), which subsequently recruits and activates Protein Phosphatase 2A (PP2A) via methylation at Leu309. What happens next is critical for neuronal function. The activated PP2A actively dephosphorylates AKT1 at specific residues (Ser473 and Thr308), effectively shutting down the kinase (Yan et al., 2022). Because AKT normally serves as the physiological brake on Glycogen Synthase Kinase 3β (GSK3β), shutting it down completely releases this inhibition. The result is unconstrained GSK3β overactivity.

This specific AKT/GSK3β axis forms a critical hub in schizophrenia pathology. We already know that baseline AKT1 deficiency acts as a genetic risk factor, and GSK3β overactivity directly drives dopaminergic hyperfunction and severe behavioral abnormalities (Emamian, 2012). By intentionally hijacking this exact pathway, the retrovirus engineers the dopaminergic excess so characteristic of clinical psychosis. But it does not stop at signaling. The viral protein also massively ramps up the expression of Tyrosine Hydroxylase (TH)—the rate-limiting enzyme for dopamine synthesis—along with the Dopamine Transporter (DAT) and presynaptic machinery like SNAP25 and VAMP1 (Yan et al., 2022). It turns the cell into a dopamine factory.

6.2. Dendritic Spine Pathology via miR-141-3p and Wnt/JNK

Beyond altering neurotransmitter release, we must consider the physical architecture of the neuron. A schizophrenic brain is famously characterized by a "disconnection syndrome"—a profound loss of dendritic spines and synaptic contacts. Recent data demonstrates that HERV-W ENV (ERVWE1) is a direct architect of this structural degradation in hippocampal neurons (Yao et al., 2023). Rather than relying on a simple toxic insult, the virus executes a highly specific epigenetic attack on the non-canonical Wnt signaling pathway.

The sabotage begins in the nucleus. HERV-W ENV binds to the host transcription factor Yin Yang 1 (YY1). This newly formed complex targets the promoter of miR-141-3p, drastically enhancing the transcription of this microRNA. Once unleashed, high levels of miR-141-3p post-transcriptionally hunt down and suppress Wnt5a mRNA. This bottleneck is fatal for the synapse. Stripped of Wnt5a, the downstream JNK signaling pathway crashes, ultimately leading to the severe downregulation of Arp2 (Actin-related protein 2), the master regulator of actin polymerization (Yao et al., 2023). Without Arp2, the dendritic cytoskeleton simply cannot hold its shape. The spines collapse. This cascading structural degradation provides a concrete, morphological basis for the cognitive deficits so frequently observed in the clinic, proving that this ancient viral protein can physically rewire the brain.

6.3. Serotonergic Neurotoxicity and ALKBH5

The destruction does not stop at dopamine and glutamate. HERV-W ENV also mounts a highly specific epigenetic attack on the serotonergic system. In 5-HT neurons, the viral protein actively upregulates ALKBH5, a critical m6A RNA demethylase (Wu et al., 2023). By stripping away global m6A modifications, the virus triggers a dangerous paradox: it artificially stabilizes the mRNA of the 5-HT1B receptor (HTR1B), forcing its massive overexpression.

Once upregulated, HTR1B aggressively drives the ERK-ELK1-Arc signaling cascade. The structural consequences are devastating. Serotonergic neurons rapidly lose their dendritic complexity, and their spine density simply plummets (Wu et al., 2023). This leaves us with a chilling realization. HERV-W ENV is not a localized toxin. It is a broad-spectrum molecular saboteur, simultaneously dismantling the dopamine, glutamate, and serotonin networks through entirely distinct, highly targeted mechanisms.

Table 1. Summary of HERV-W ENV Pathogenic Mechanisms in Psychosis

Pillar	Target Mechanism	Molecular Pathway	Physiological Consequence	References
Immunological	Microglia	TLR4/CD14 activation → NF-κB	Secretion of TNF-α, IL-6, IL-1β; iNOS induction (NO stress).	Rolland et al., 2006; Xiao et al., 2017
	Neurons	NLRP3 inflammasome → Caspase-1	Pyroptosis: GSDMD pore formation, cell lysis, IL-1β release.	Jia et al., 2025
	Intracellular	*linc01930* suppression → cGAS-STING	Induction of Type I Interferons (IFN-β); neurotoxicity.	Li et al., 2023
Signaling	Dopamine	DRD2 interaction → PP2A activation → AKT↓ → GSK3β activation	Increased TH, DAT, VMAT2; Dopaminergic hyperfunction.	Yan et al., 2022
	Glutamate	TLR4 → Cytokines → NMDAR	Lateral diffusion of GluN2B-NMDARs; Synaptic hypofunction; LTP deficits.	Johansson et al., 2020

	Structure *(Dendritic Spines)*	YY1 → miR-141-3p ↑ → Wnt5a ↓ → JNK pathway inhibition → Arp2 downregulation	Dendritic spine loss; Cytoskeletal collapse.	Yao et al., 2023
	Serotonin	ALKBH5 upregulation → decreased m6A methylation → Stabilization of HTR1B mRNA → ERK activation	Neuronal plasticity impairment; Reduced dendritic complexity.	Wu et al., 2023
Structural	Transporters	Binding to ASCT1 (SLC1A4) & ASCT2 (SLC1A5)	Blockade of glutamine transport; Disruption of Glutamate-Glutamine cycle.	Lavillette et al., 2002; Scalise et al., 2020
	Fusion	Fusion Peptide (TM domain)	Membrane instability; potential ectopic fusion; Cytotoxicity.	Gong et al., 2005; Hogan & Johnson, 2023

7. Epigenetic Landscapes and Environmental Derepression

Under normal conditions, the human genome acts as a strict warden. It keeps HERV-W tightly locked down using robust epigenetic mechanisms, primarily heavily methylating the viral Long Terminal Repeats (LTRs) (Giménez-Orenga & Oltra, 2021; Li & Karlsson, 2016). These LTRs essentially serve as control panels, harboring binding sites for key transcription factors like Sp1, Oct-1, and GCM1 (Hossain et al., 2024). But in schizophrenia, this epigenetic lockdown fails.

Global or locus-specific hypomethylation strips away the silencing marks. As framed by the "two-hit" model, environmental insults—such as severe prenatal infections or intense psychological stress—violently dismantle this repressive chromatin structure (Sighencea & Trifu, 2025). The locks are broken. The cell suffers a critical reduction in DNA methyltransferase activity or actively recruits demethylases directly to the HERV loci, allowing the dormant virus to awaken.

7.1. The "Collateral Damage" Hypothesis: GABBR1

The danger of these viral LTRs extends far beyond simple reactivation. Because these sequences are permanently integrated into our DNA, they often sit dangerously close to critical host genes, acting as rogue promoters or enhancers. GABBR1 (GABA B receptor 1) is a prime target. A HERV-W LTR sits directly inside the regulatory region of GABBR1 on chromosome 6p22.1—a genomic hotspot notoriously linked to schizophrenia susceptibility (Hegyi, 2013).

What happens next is a tragic epigenetic conflict. When an environmental trigger awakens the dormant HERV-W, the host cell panics. It immediately deploys its silencing machinery to suppress the viral LTR through targeted hypermethylation. But the defense is blind. Because the viral LTR is physically embedded within the GABBR1 regulatory region, the cell's desperate attempt to shut down the virus inadvertently shuts down its own GABA receptor. The host effectively damages itself just to suppress the viral threat.

By starving the brain of GABA B receptors, this collateral damage directly fuels the excitation-inhibition imbalance so characteristic of the schizophrenic brain. This is not a simple viral infection; it is a catastrophic friendly-fire event at the molecular level (Aftab et al., 2016; Slokar & Hasler, 2016). We see traces of this exact same dysregulation in other critical risk genes, such as PRODH and BDNF, where HERV elements originally acting as enhancers are caught in the crossfire of the disease course (Sighencea & Trifu, 2025; Slokar & Hasler, 2016).

8. Environmental Triggers and Transactivation Mechanisms

A dormant provirus remains harmless until provoked. But what exactly pulls the trigger? Over the past decade, several classic epidemiological risk factors for schizophrenia have been unexpectedly unmasked as potent HERV-W transactivators (Table 2) (Küry et al., 2018; Sighencea & Trifu, 2025). Take Influenza A, for instance. It does not merely coexist with the retrovirus; it actively remodels the host's chromatin. The flu virus strips away the repressive H3K9me3 histone mark from the ERVWE1 locus and simultaneously drives the expression of Glial Cells Missing 1 (GCM1)—a placenta-specific transcription factor that aggressively binds the newly exposed HERV-W LTR (Balestrieri et al., 2019; Giménez-Orenga & Oltra, 2021). The epigenetic lockdown is shattered.

Other neurotropic pathogens execute similar sabotage. *Toxoplasma gondii* infiltrates neurons and glial cells, completely altering the host cell's signaling environment. By establishing chronic NF-κB activation, the parasite drives a massive, synergistic upregulation of HERV-W elements, finally offering a molecular explanation for the long-debated epidemiological link between toxoplasmosis and psychosis (Sighencea & Trifu, 2025). Herpesviruses operate on a similar frequency. The Epstein-Barr Virus (EBV) uses its gp350 glycoprotein to bind receptors on astrocytes and B cells, violently triggering the NF-κB cascade to directly activate the HERV-W promoter (Meier et al., 2021; Wieland et al., 2022). Meanwhile, HHV-6A transactivates the retroviral envelope through a flood of inflammatory cytokines and direct cellular interactions within early-stage CNS lesions (Küry et al., 2018; Meier et al., 2021).

But pathogens are not the only triggers. Severe early life stress and childhood trauma can similarly dismantle the host's epigenetic landscape. Elevated cortisol and intense stress signaling systematically reduce methylation at HERV loci, effectively priming them for reactivation later in life. We now have hard clinical evidence for this mechanism. Recent unsupervised cluster analyses reveal a striking, direct correlation between childhood maltreatment and abuse scores and positive HERV-W ENV antigenemia in psychotic patients (Tamouza et al., 2021). The trauma literally leaves a viral scar.

Table 2. Environmental Triggers of HERV-W Reactivation

Trigger	Mechanism of Action	Link to Schizophrenia	References
Influenza A	Upregulation of GCM1 transcription factor; Removal of repressive histone H3K9me3.	Explains "Season of Birth" effect (Winter/Spring risk).	Balestrieri et al., 2019; Slokar & Hasler, 2016
Toxoplasma gondii	Infection of neurons/glia; Chronic NF-κB activation modulating host signaling to a permissive state.	Strong epidemiological link; Neurotropism of parasite.	Sighencea & Trifu, 2025
Epstein-Barr Virus	gp350 glycoprotein binds astrocyte receptors; Activates HERV-W promoter via NF-κB pathway.	Linked to immune dysregulation and autoimmune features.	Meier et al., 2021; Wieland et al., 2022
Early Life Stress	Cortisol-mediated epigenetic remodeling; Hypomethylation of HERV loci.	Direct correlation between childhood trauma scores (abuse/neglect) and HERV-W antigenemia.	Tamouza et al., 2021

9. Clinical Implications and Therapeutic Horizons

9.1. HERV-W as a Biomarker

The clinical reality of schizophrenia is notoriously heterogeneous. But the presence of the HERV-W ENV protein (often detected as "MSRV-Env" or "Syncytin-1" antigenemia) finally offers a tangible, biological coordinate. We are looking at a robust biomarker for a highly specific subtype of psychosis. When researchers analyze the serum and cerebrospinal fluid (CSF) of patients with acute schizophrenia and bipolar disorder, the viral antigen and its mRNA are consistently elevated, sharply distinguishing these patients from healthy controls (Slokar & Hasler, 2016). This is not just a passive echo of the disease. High antigenemia goes hand-in-hand with spiking C-reactive protein (CRP) and floods of pro-inflammatory cytokines. This molecular signature successfully identifies a distinct "inflammatory biotype" of psychosis—a subgroup that typically resists standard dopaminergic antipsychotics, yet stands to respond beautifully to targeted immunotherapies (Rangel et al., 2024; Tamouza et al., 2021; Wang et al., 2018).

9.2. Therapeutic Targeting: Temelimab

If HERV-W ENV acts as the pathogenic driver, the next logical step is clear: we must neutralize it (Giménez-Orenga & Oltra, 2021; Li et al., 2023). Enter Temelimab (GNbAC1). This humanized IgG4 monoclonal antibody was specifically engineered to hunt down the viral protein. By binding with extraordinarily high affinity directly to the Surface Unit (SU) domain, Temelimab physically blocks the virus from engaging TLR4. It stops the neuroinflammatory cascade before it can even start (Kornmann & Curtin, 2020).

The neurology field has already paved the way. Temelimab was primarily developed to treat Multiple Sclerosis, another devastating disease driven heavily by HERV-W. Rigorous clinical trials (such as CHANGE-MS and ANGEL-MS) have proven its safety. More importantly, they demonstrated its remarkable capacity to rescue the brain from neurodegeneration—measurably reducing brain atrophy and magnetization transfer ratio (MTR) loss, even in the absence of active, raging inflammation (Giménez-Orenga & Oltra, 2021; Mouliou & Dardiotis, 2022). Because MS and psychosis share the exact same TLR4-mediated neurotoxicity, Temelimab represents an exceptionally promising experimental therapeutic for HERV-positive schizophrenia. By disarming the circulating "immunotoxin," we could theoretically halt the glial firestorm, physically stabilize escaping synaptic receptors, and finally restore neurotransmitter balance (Johansson et al., 2020; Li et al., 2023).

We might not have to wait long for the next breakthrough. Current clinical trials are already deploying Temelimab against "Post-COVID" neuropsychiatric syndromes, driven by the recent realization that SARS-CoV-2 violently reactivates HERV-W. Official communications from mid-2024 confirmed that the final patient visits in these trials are complete. The results are imminent. If successful, these trials will provide the ultimate clinical rationale for testing Temelimab in schizophrenia. We are standing on the threshold of a new era. It is time to move the field past mere symptomatic management and deliver true, etiological interventions for psychotic disorders (Mouliou & Dardiotis, 2022).

9.3. Discussion and Implications for the Field

Schizophrenia research has been stalled for decades by an over-reliance on traditional neurotransmitter imbalance theories. The HERV-W ENV model breaks this deadlock. Based on the synthesized literature, we propose that this viral protein is not merely a passive marker of disease, but the central architect of the neurotoxic cascade in a significant subset of psychotic patients (Rangel et al., 2024; Tamouza et al., 2021). It finally provides the missing molecular link between transient environmental triggers (like a maternal viral infection) and permanent cellular pathologies (such as explosive pyroptosis and synaptic trafficking defects) (Jia et al., 2025; Johansson et al., 2020).

Redefining schizophrenia as a treatable neuroinflammatory condition is no longer just a theoretical exercise. However, identifying a distinct "inflammatory biotype" and deploying targeted therapies like Temelimab brings practical challenges (Giménez-Orenga & Oltra, 2021). Before such etiological interventions can be routinely deployed in psychiatric wards, the field urgently needs standardized, commercially viable ENV detection assays. We cannot treat what we cannot measure. Ultimately, shifting the focus from lifelong symptomatic management toward the neutralization of this "intragenomic parasite" requires a complete reimagining of psychiatric care (Leboyer et al., 2013).

10. Conclusions

The reactivation of HERV-W ENV in the human brain represents a profound failure of the genomic containment systems that have evolved over millions of years. It transforms a dormant genetic relic into an active agent of disease. The evidence reviewed here establishes HERV-W ENV not as a correlative byproduct of psychosis, but as its direct, causal trigger.

It attacks the brain on three interconnected fronts. Immunologically, it drives a chronic, sterile neuroinflammation by weaponizing TLR4 and triggering neuronal pyroptosis, creating a highly toxic microenvironment (Jia et al., 2025; Rolland et al., 2006). Structurally, it literally suffocates the synapse by physically obstructing critical amino acid transporters and destabilizing membranes with its viral fusion machinery (Lavillette et al., 2002; Scalise et al., 2020). Signaling-wise, the sabotage is equally severe: it forces NMDARs to escape the synapse laterally while pushing dopaminergic neurons into a state of hyperactive overdrive via the AKT/GSK3β pathway (Johansson et al., 2020; Yan et al., 2022).

This tripartite pathology is the "two-hit" hypothesis realized at the molecular level, placing HERV-W at the exact intersection of genetic vulnerability and environmental stress (Feigenson et al., 2014; Sighencea & Trifu, 2025). The 'enemy within' has finally been unmasked (Engel & Hiebert, 2010). As psychiatry moves toward precision medicine, the challenge for the next decade is no longer finding the culprit, but deploying the therapeutic arsenal to neutralize it. Future research must prioritize the validation of HERV-W ENV as a routine clinical biomarker for patient stratification, paving the way for large-scale clinical trials of neutralizing antibodies in early-onset psychosis.

Conflicts of Interest: No conflicts of interest to declare.

Ethical Approval: As an integrative review of published literature, this study did not require formal ethics committee approval.

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