The Viral Trajectory

Pathogen Reactivation Across the Three Temporal Phases of Alzheimer's Disease

Latent and Reactivating Herpesviruses, the Antimicrobial Aβ Response, Microglial Priming, and Immunosenescence as a Temporal Driver of the Collapse Trajectory

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience. Fifth in the Collapse trilogy series, companion volume to Convergent Synaptic Collapse, Homeostatic Microglial Collapse, Bioenergetic Collapse, and The Tryptophan Partition.

“The glial reaction surrounding the miliary necroses cannot be interpreted as a passive accompaniment of the deposition; it is the active response of an organism to a chronic stimulus whose nature remains to be characterized.”

— Oskar Fischer, 1907 (paraphrased)

For Ruth Itzhaki and Robert Moir, who carried Fischer's intuition across the molecular century and made the viral hypothesis a tractable scientific question; and for the patients in the Welsh and Australian cohorts whose date of birth, by accident of policy, supplied the field's first quasi-experimental evidence.

THE COLLAPSE TRILOGY — COMPANION VOLUME

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

IV. The Tryptophan Partition

V. The Viral Trajectory ☐ this volume

The trilogy's three principal volumes address distinct substrate axes of neurodegenerative collapse — synaptic circuit, microglial state, and bioenergetic substrate. The Tryptophan Partition companion identifies a shared metabolic substrate that couples the three axes through a single amino acid's allocation. The present companion volume identifies a shared *temporal driver* that runs the system through its three phases — latent and reactivating herpesviruses whose interaction with the host changes mechanism, anatomy, and consequence at each phase. It is situated in the microglial section because the homeostatic microglial transition under chronic type-I interferon signaling is the load-bearing immunological lynchpin of the integrated framework, but the argument extends across the trilogy.

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Abstract

The Collapse trilogy organizes Alzheimer's disease into three temporal phases, each anatomically and mechanistically distinct: a Phase I bioenergetic prodrome (approximately ages 20–50) centered on the locus coeruleus and the brainstem monoaminergic nuclei, in which PARP-1 hyperactivation and NAD+ erosion produce a slow cell-autonomous attrition; a Phase II microglial inflection (ages 50–70) centered on the hippocampal formation and the oligodendrocyte–microglia axis, in which the homeostatic microglial identity collapses into a damage-associated state and the disease-associated transcriptional program becomes self-sustaining; and a Phase III synaptic decompensation (ages 70+) centered on the perineuronal-net–protected parvalbumin interneurons and the complement-mediated pruning of corticohippocampal synapses, in which the cognitive deficits that define the clinical syndrome appear. This dissertation advances the thesis that viral pathogens — principally the herpesviridae (HSV-1, HHV-6A/B, VZV, EBV, CMV) and, in the modern era, SARS-CoV-2 — are not merely correlated with Alzheimer's disease but are best understood as a *temporal driver* whose interaction with the host changes mechanism, anatomy, and consequence at each of the three phases. The framework treats viruses neither as the unique cause of Alzheimer's disease (which they are not) nor as incidental passengers (which the convergence of cohort, vaccine, and autopsy evidence increasingly forecloses) but as a coupling variable that runs the disease through its three phases by exploiting the phase-specific weaknesses of the host: latency and the antimicrobial Aβ response in Phase I; reactivation and microglial priming in Phase II; immunosenescence and unchecked viral reactivation in Phase III.

The thesis is organized in eight analytical chapters. Chapter I recapitulates the three-phase temporal architecture of Alzheimer's disease and motivates the phase-coupled framing. Chapter II analyzes Phase I, in which HSV-1 establishes lifelong latency in the trigeminal ganglion, periodic reactivation seeds the brainstem through retrograde trigeminal projection, and the Aβ antimicrobial response — characterized in the work of Soscia, Kumar, and Eimer — deposits amyloid as the

innate-immune cost of repeated subclinical reactivation. Chapter III analyzes Phase II, in which the frequency of reactivation rises with HPA-axis aging, chronic IDO induction shifts the tryptophan partition toward the kynurenine branch, and the microglial homeostatic state collapses under sustained type-I interferon signaling into the DAM/MGnD trajectory. Chapter IV analyzes Phase III, in which T-cell exhaustion, NK senescence, and the clonal expansion of CD8+ T cells identified by Gate and colleagues unleash a final wave of viral reactivation in a brain whose synaptic infrastructure has been progressively undermined; SARS-CoV-2 is treated here as an acute Phase-III accelerator. Chapter V surveys the viral cast — HSV-1, HHV-6, VZV, EBV, CMV, and SARS-CoV-2 — and develops the case for cumulative pathogen load rather than single-virus etiology. Chapter VI develops the integrated framework: the three phases are not three independent insults but three temporal expressions of a single iterative cycle in which each reactivation seeds the next phase. Chapter VII conducts a critical reassessment, addressing the seroprevalence problem, the failed and equivocal antiviral trials, the Allnutt critique of Readhead, the limits of the Tanzi–Moir antimicrobial Aβ hypothesis, and the strongest contemporary causal evidence: the regression-discontinuity natural experiments around zoster vaccination in Wales and Australia (Eyting et al., 2025; Liu et al., 2025). Chapter VIII develops therapeutic implications and six falsifiable predictions.

The dissertation concludes that the viral hypothesis of Alzheimer's disease, properly understood, is not a competitor to the amyloid-cascade or the tau-propagation hypotheses but a *temporal scaffolding* for them: Aβ and tau are the host's responses to chronic viral antigenic load distributed across decades, and the apparent failure of pure anti-amyloid and anti-tau therapeutics to halt disease progression in late-phase patients reflects the fact that these therapies address the host's response rather than the antigenic drive that triggers it. The viral trajectory framework is testable, falsifiable, and — as the zoster-vaccine natural experiments suggest — already partially confirmed.

Keywords: herpes simplex virus, HSV-1, HHV-6, varicella zoster virus, Epstein–Barr virus, cytomegalovirus, SARS-CoV-2, antimicrobial Aβ, locus coeruleus, microglial priming, immunosenescence, zoster vaccination, regression discontinuity, Alzheimer's disease

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1. Introduction

1.1 The Research Problem

The viral hypothesis of Alzheimer's disease is one of the oldest mechanistic conjectures in the field. Oskar Fischer, in his 1907 paper on "miliary necrosis" in senile dementia, observed not only the plaques that would later carry Alois Alzheimer's name but also a characteristic glial response surrounding them — a response Fischer interpreted as evidence of an active, ongoing inflammatory process rather than a passive bystander to deposition. The interpretation was forgotten through most of the twentieth century as the amyloid cascade hypothesis consolidated the field around a model in which Aβ deposition was the proximate cause and inflammation a downstream consequence. Melvyn Ball revived the viral conjecture in 1982, observing that the regions of the brain most affected in Alzheimer's disease overlapped with the trigeminal projection fields through which herpes simplex virus type 1 (HSV-1) is known to traffic during reactivation. Ruth Itzhaki and colleagues, beginning in the early 1990s, supplied molecular evidence: HSV-1 DNA was detectable in the brains of elderly subjects with and without Alzheimer's disease, but the presence of HSV-1 DNA *in combination with* the APOE ε4 allele conferred a markedly elevated risk of disease (Itzhaki et al., 1997). The Itzhaki–Wozniak group then demonstrated colocalization of HSV-1 antigen with amyloid plaques in human brain (Wozniak et al., 2009) and, with the Tanzi laboratory, established that Aβ has direct antimicrobial activity against HSV-1 in vitro and in vivo (Soscia et al., 2010; Kumar et al., 2016; Eimer et al., 2018).

For the better part of three decades, this body of evidence sat in an awkward position relative to the mainstream amyloid-cascade and tau-propagation frameworks. The viral evidence was suggestive but not yet causal; the in vitro antimicrobial Aβ literature was striking but limited to a small set of laboratories; the antiviral trials in symptomatic patients (Devanand et al., 2020) were small, underpowered, and equivocal; and the most ambitious population-level claim — that subclinical herpes reactivation over decades was the proximate driver of amyloid deposition — could not be tested directly. The mainstream response was to treat the viral evidence as interesting but unproven, and the textbooks have largely continued to characterize Alzheimer's disease as a proteinopathy with secondary inflammation.

Two developments in the past five years have shifted the evidentiary landscape. First, the COVID-19 pandemic supplied a natural experiment in acute viral neurotropism on a scale not previously available: hundreds of millions of patients exposed to a single novel pathogen with detectable neurological and cognitive consequences (Taquet et al., 2021, 2022; Crunfli et al., 2022), and a measurable association between SARS-CoV-2 infection and accelerated dementia incidence in the cohorts old enough to have entered the prodromal window (Wang et al., 2022). Second, the zoster vaccination programs in Wales (which used a sharp birth-date eligibility cutoff that permitted regression-discontinuity inference) and in Australia (Eyting et al., 2025; Liu et al., 2025) supplied something the viral hypothesis had never previously had: quasi-experimental evidence, with effect sizes substantially larger than any pharmacological intervention to date and with a credible identification strategy that approaches randomized control. These two developments do not prove that viruses cause Alzheimer's disease, but they have substantially raised the prior on a model in which viral exposure is a load-bearing mechanistic input.

This dissertation addresses the question: **What role do viral pathogens play across the three temporal phases of Alzheimer's disease, and how does the host–virus interaction differ at each phase?** The thesis advanced is that viruses are best understood not as an alternative etiology to amyloid and tau but as a *temporal coupling variable* that runs the disease through its three phases — Phase I bioenergetic prodrome, Phase II microglial inflection, Phase III synaptic decompensation — by exploiting phase-specific weaknesses of the host immune and metabolic systems. The framework retains the amyloid and tau pathologies as central to the disease but reinterprets them as the host's responses to a chronic antigenic drive distributed across decades, rather than as autonomous proteinopathies that happen to occur in the same brain.

1.2 Significance

The significance of the viral trajectory framework is fivefold. First, it supplies a *temporal* organization of the viral evidence that the existing literature lacks. The Itzhaki and Tanzi literatures have largely been static — describing what HSV-1 does to neurons in cell culture, or what Aβ does to HSV-1 in a Petri dish — and the cohort literature has largely been outcome-based, reporting hazard ratios for dementia conditional on viral exposure or antiviral use. Neither literature has explicitly mapped the viral effects onto the three temporal phases through which the disease actually progresses. The framework supplied here does so, with distinct mechanistic claims at each phase.

Second, the framework reconciles two findings that have been mutually puzzling: that HSV-1 seroprevalence in adults exceeds 70 percent in most populations (which would predict an enormous and implausible population-attributable fraction if HSV-1 were a sufficient cause) and that anti-HSV antiviral use is associated with a substantial reduction in subsequent dementia incidence in Taiwanese, Swedish, French, and Korean cohorts (Tzeng et al., 2018; Lopatko Lindman et al., 2019, 2021; Linard et al., 2020, 2022; Bae et al., 2022). The framework resolves the puzzle by locating viral pathogenicity not in the binary fact of infection but in the *frequency and intensity of reactivation* over decades, which is modifiable by APOE genotype, immune competence, HPA-axis activity, stress, sleep, and — pharmacologically — by antiviral suppression.

Third, the framework supplies a mechanistic interpretation of the zoster-vaccination natural experiments. The Wales regression-discontinuity result (Eyting et al., 2025) showed that birth-date eligibility for zoster vaccination produced a substantial reduction in dementia incidence — substantially larger than the effect sizes seen with any pharmacological intervention. The Australian replication (Liu et al., 2025) confirmed the direction and order of magnitude. The framework explains this by noting that the zoster vaccine reduces the reactivation rate of VZV, which has been shown to transactivate latent HSV-1 in 3D neural tissue models (Cairns et al., 2022), and that reduced cumulative reactivation across decades is the operative mechanism through which the vaccine reduces Phase II microglial priming and Phase III decompensation.

Fourth, the framework reorganizes the therapeutic landscape. Where the amyloid-cascade framework generates monoclonal anti-Aβ antibodies (aducanumab,

lecanemab, donanemab) whose clinical effects have been modest and whose pharmacoeconomics are unattractive, the viral trajectory framework supplies a different therapeutic surface: prophylactic antiviral suppression in APOE ε4 carriers from middle age forward; targeted vaccination programs to suppress reactivation of the highest-impact pathogens; and combination therapy in which antiviral suppression is paired with anti-Aβ, anti-tau, anti-CD38, anti-C1q, and tryptophan-partition rebalancing interventions appropriate to the patient's phase. The framework also makes a clear prediction about why pure anti-amyloid monotherapy underperforms: it addresses the host response without addressing the antigenic drive that triggers it.

Fifth, the framework integrates with the other cross-cutting companion volumes of the Collapse trilogy. The Tryptophan Partition companion (Gustafsson, 2026) identifies tryptophan allocation across the kynurenine, NAD+, serotonergic, and tryptamine branches as a coupling variable between the three Collapse axes; the present viral-trajectory companion identifies chronic viral antigenic load as the upstream driver of the IDO induction that biases the tryptophan partition. The two companions are therefore not parallel claims but a coupled pair: viruses drive IDO induction, IDO induction reshapes the tryptophan partition, and the tryptophan-partition reshaping is one of the principal molecular substrates through which viral pathogenicity is translated into the three-phase collapse trajectory.

1.3 Scope and Limitations

This dissertation is a synthetic review, not a report of original experimental data. Its contribution lies in the integration of literatures from herpesvirus biology, neuroimmunology, the antimicrobial-peptide framing of innate immunity, epidemiology of dementia and antiviral exposure, the regression-discontinuity literature on vaccine effects, and the three-phase temporal model of Alzheimer's disease developed in the Collapse trilogy. The work draws principally on Alzheimer's disease because the trilogy is organized around AD, but the viral mechanisms generalize naturally to Parkinson's disease (where Bjornevik-style EBV evidence is beginning to emerge in cognate ways) and to multiple sclerosis (where the Bjornevik et al. 2022 *Science* paper has already established EBV as a causal antecedent).

The thesis cannot resolve whether viruses are *the* upstream cause of Alzheimer's disease — a question the available evidence does not yet answer with the precision

needed for a categorical claim — and it does not attempt to. The framework asserts the weaker but more defensible claim that viruses are a *load-bearing* input across all three phases, that the phase-specific mechanisms are distinct enough to repay separate analysis, and that the most important therapeutic implication is not the displacement of amyloid- and tau-targeting therapeutics but their combination with antiviral and vaccine-based interventions in phase-appropriate windows. The thesis also does not resolve whether the antimicrobial Aβ hypothesis of Soscia, Kumar, and Eimer is correct in its strongest form (that Aβ deposition is *strictly* an antimicrobial response and would not occur in the absence of pathogen exposure) — Chapter VII treats this ambiguity directly.

A particular limitation worth flagging at the outset is that the viral literature has historically been dominated by a small set of laboratories — Itzhaki and Wozniak at Manchester; Tanzi, Moir, Kumar, and Eimer at Massachusetts General; Readhead and Dudley at Mount Sinai; Cairns at Tufts; Gate at Stanford and later Northwestern — and replication across independent groups has been uneven. The present synthesis treats laboratory provenance as a piece of evidence to be weighed, not a disqualification, but the reader should be aware that several of the key findings discussed below come from a small number of groups and would benefit from broader replication.

1.4 A Brief Recapitulation of the Three-Phase Model

The Collapse trilogy organizes Alzheimer's disease into three temporal phases, each anatomically and mechanistically distinct, with approximate age windows that should be read as central tendencies rather than hard boundaries.

Phase I (approximately ages 20–50): The Bioenergetic Prodrome. The locus coeruleus and the dorsal raphe nucleus — the brainstem monoaminergic nuclei whose long, thin, unmyelinated axons distribute noradrenaline and serotonin across the entire forebrain — accumulate hyperphosphorylated tau and exhibit early signs of bioenergetic stress. PARP-1 hyperactivation on oxidatively damaged DNA depletes NAD+ at rates that exceed salvage; sirtuin signaling fails; the integrated stress response is engaged; and a small fraction of LC neurons enter a state of slow attrition. The phase is clinically silent or expressed as nonspecific symptoms (sleep dysregulation, depression, autonomic dysfunction) that do not yet trigger clinical attention. The Braak staging of tau pathology places the LC at Stage 0/I, before any

cortical involvement.

Phase II (approximately ages 50–70): The Microglial Inflection. Microglial cells in the hippocampal formation and the entorhinal cortex lose their TGF-β/SMAD-maintained homeostatic identity and transition through the disease-associated microglial (DAM) trajectory characterized by Keren-Shaul, Schwartz, Amit, and Deczkowska. The transition is initially adaptive — DAM microglia respond to amyloid and to damaged neurons — but becomes maladaptive when sustained because the disease-associated transcriptional program suppresses homeostatic functions including synaptic surveillance, neurotrophic support, and the clearance of pre-aggregates. Oligodendrocyte ferroptosis and the loss of myelin sheath integrity follow, and the hippocampal pathology that defines mild cognitive impairment becomes detectable on MRI. The phase is clinically expressed as subjective cognitive decline progressing to MCI.

Phase III (approximately ages 70+): The Synaptic Decompensation. The parvalbumin-positive (PV+) interneurons in cortex and hippocampus — whose perineuronal nets (PNNs) had previously protected them from oxidative and proteolytic damage — undergo PNN digestion by MMP-9 and complement-mediated synaptic pruning by C1q/C3/CR3. The loss of fast-spiking inhibitory tone disrupts gamma-frequency oscillations, which in turn disrupt the hippocampal–neocortical communication on which memory consolidation depends. Excitatory synapses are pruned in a complement-mediated process re-activated from a developmental program. The phase is clinically expressed as dementia.

The three phases are not independent: each one feeds the next. Phase I LC degeneration removes noradrenergic anti-inflammatory tone from the brain, which biases microglia toward the activated state that Phase II requires. Phase II microglial activation produces complement components and cytokines that prime the Phase III synaptic pruning. Phase III synaptic loss produces the cognitive deficits that define clinical Alzheimer's disease. The trilogy treats these couplings as the substrate-level architecture; the present dissertation argues that viral reactivation across decades is an upstream temporal driver that runs the system through this architecture.

2. Literature Review

2.1 Historical Foundations: Fischer, Ball, Itzhaki

Oskar Fischer (1907) described "miliary necrosis" — what would later be called amyloid plaques — in the brains of patients with senile dementia, and he characterized the glial response surrounding the plaques as an active inflammatory reaction. Fischer's interpretation was that the dementia was a consequence of a chronic infectious or inflammatory process rather than a primary neuronal degeneration. The interpretation was contested at the time and largely forgotten during the consolidation of the amyloid-cascade framework in the late twentieth century, but it has been revived in the context of the antimicrobial Aβ hypothesis and the immunometabolic reframing of neurodegeneration.

Melvyn Ball (1982, 1986) noted that the regions of the brain most consistently affected in Alzheimer's disease — the entorhinal cortex, the hippocampal formation, the temporal neocortex, and the basal forebrain — overlap with the projection fields of the trigeminal and olfactory nerves through which HSV-1 traffics during reactivation. Ball proposed that subclinical HSV-1 reactivation across decades could deposit antigenic material in these regions and trigger the chronic inflammation that Fischer had described. The proposal was met with skepticism at the time because direct molecular evidence for HSV-1 in human brain tissue was lacking.

The evidentiary picture changed when Ruth Itzhaki and colleagues (Jamieson et al., 1991; Itzhaki et al., 1997) used polymerase chain reaction amplification to detect HSV-1 DNA in postmortem human brain tissue from both Alzheimer's disease patients and controls. The detection rates were similar between the two groups — HSV-1 DNA was present in roughly half of all brains tested — but the *combination* of HSV-1 DNA positivity with the APOE ε4 allele was strongly associated with Alzheimer's disease. The interaction effect was the critical finding: neither HSV-1 alone nor APOE ε4 alone conferred the elevated risk that the combination did. The result implicated APOE ε4 as a modifier of HSV-1 pathogenicity — a finding that has been replicated in multiple cohorts and that anchors the contemporary HSV-1 hypothesis (Tsai et al., 2011; Linard et al., 2020).

The Itzhaki–Wozniak group subsequently demonstrated colocalization of HSV-1 antigen with amyloid plaques in human Alzheimer's disease brain (Wozniak et al.,

2009), and the Tanzi laboratory began publishing the antimicrobial-peptide interpretation of Aβ that would become the second pillar of the contemporary viral hypothesis (Soscia et al., 2010; Kumar et al., 2016; Eimer et al., 2018).

2.2 The Aβ Antimicrobial Hypothesis: Soscia, Kumar, Eimer, Moir

The antimicrobial Aβ hypothesis advanced principally by Robert Moir, Rudolph Tanzi, Deepak Kumar Vijaya Kumar, and William Eimer reframes amyloid deposition as the host's innate-immune response to microbial challenge. Soscia et al. (2010, *PLoS ONE*) demonstrated that Aβ peptides — both Aβ40 and Aβ42 — exhibit antimicrobial activity against a panel of bacterial and fungal pathogens at concentrations comparable to those of LL-37 and other canonical antimicrobial peptides. The paper proposed that Aβ should be classified as an antimicrobial peptide of the innate immune system, with the implication that its deposition in brain might reflect an antimicrobial response rather than a passive protein-folding failure.

Kumar et al. (2016, *Science Translational Medicine*) extended the framework to HSV-1, showing that Aβ oligomers and fibrils protected mice from systemic Salmonella infection and that 5XFAD mice expressing human Aβ were protected against herpes simplex encephalitis. The mechanism involved Aβ oligomerization triggered by microbial surfaces — Aβ binds heparan sulfate proteoglycans on microbial cell walls, oligomerizes locally, and entraps the microbe within an amyloid mesh. The paper provided the first in vivo demonstration that Aβ deposition was protective against a viral infection in a relevant model system.

Eimer et al. (2018, *Neuron*) extended the framework further, demonstrating that HSV-1 and HHV-6 infection of 5XFAD mouse brains accelerated amyloid deposition, and that the deposition trapped viral particles within the amyloid mesh. The paper proposed that the canonical Alzheimer's amyloid plaque is best understood as the residue of a chronic antimicrobial response distributed across decades — a model that explicitly recasts amyloid as a defense, not as a primary pathology.

The Moir, Lathe, and Tanzi (2018) review consolidated the framework into a unified statement: amyloid is an effector arm of innate immunity in the brain; chronic pathogen exposure drives chronic amyloid deposition; the apparent disease character of Alzheimer's amyloid is the consequence of an antimicrobial response that has been sustained beyond its useful duration. The framework predicts that

anti-amyloid therapeutics that remove Aβ without addressing the underlying antigenic drive should produce limited clinical benefit — a prediction that the modest effects of aducanumab, lecanemab, and donanemab in late-stage trials have been broadly consistent with.

The antimicrobial Aβ hypothesis is not without its critics. The principal objection is that the in vivo concentrations of Aβ required to demonstrate antimicrobial activity in cell-culture assays are substantially higher than those measured in plasma or CSF under physiological conditions; the response is that the relevant concentrations are those achieved *locally*, in tissue compartments and in proximity to microbial surfaces, not those measured in fluid compartments. A second objection is that the antimicrobial framing does not explain the specific spatial distribution of plaques (cortex and hippocampus rather than the regions of highest pathogen exposure); the response is that the spatial distribution reflects the connectomic geography of viral reactivation rather than the geography of initial infection. The framework is best treated as strongly suggestive — and increasingly well-supported in vivo — but not yet definitively established as the unique interpretation of amyloid biology.

2.3 The Herpesviridae: HSV-1, HHV-6, VZV, CMV

The herpesviridae are a family of large double-stranded DNA viruses with the defining property of establishing lifelong latency in host neurons or lymphocytes after primary infection. The latent state is characterized by viral genome persistence without active replication; periodic reactivation produces short bursts of replication that the immune system normally controls but that can produce clinical disease (cold sores, shingles, mononucleosis-like syndromes) under conditions of immune suppression, stress, or systemic illness. Three of the eight human herpesviridae are of particular relevance to Alzheimer's disease: HSV-1, HHV-6A/B, and VZV. CMV, EBV, and HSV-2 are also relevant in smaller proportions.

HSV-1 establishes latency in the trigeminal ganglion and in other peripheral sensory ganglia after primary oral infection; periodic reactivation produces orolabial herpes (cold sores) and, in a small fraction of cases, herpes encephalitis when reactivation traffics centrally rather than peripherally. The seroprevalence of HSV-1 in adults exceeds 70 percent in most populations and approaches 95 percent in some. The combination of HSV-1 seropositivity and the APOE ε4 allele is associated with elevated dementia risk (Itzhaki et al., 1997; Lövheim et al., 2015; Linard et al., 2020).

The Lövheim et al. (2015) Swedish cohort study — based on the Betula sample with 11 years of follow-up — showed that anti-HSV IgG titer combined with APOE ε4 carrier status conferred a hazard ratio of approximately 2 for incident Alzheimer's disease relative to either factor alone.

HHV-6 establishes latency in T cells and in the CNS itself; HHV-6A appears to be more neurotropic than HHV-6B and has been implicated in multiple sclerosis as well as Alzheimer's disease. Readhead et al. (2018, *Neuron*) reported substantially elevated HHV-6A and HHV-7 transcript abundance in the brains of Alzheimer's disease patients in the Mount Sinai Brain Bank cohort and proposed that HHV-6A was a load-bearing driver of disease. The paper was widely cited and substantially influenced the field's renewed interest in viral hypotheses. The Readhead findings were subsequently challenged by Allnutt et al. (2020), who reanalyzed the same and other RNA-seq datasets with stricter pathogen-detection methodology and found that HHV-6 transcripts were detectable in fewer brains than the original report had suggested, and that the disease-control differences were not statistically robust. The Readhead group has defended its original findings; the field's consensus is that HHV-6 likely contributes in a smaller fraction of cases than the 2018 paper suggested but is not refuted entirely.

VZV establishes latency in dorsal root and cranial nerve ganglia after primary chickenpox infection in childhood; reactivation in later life produces shingles (herpes zoster), which affects approximately one-third of adults over a lifetime and which carries a postherpetic neuralgia complication in 10–15 percent of cases. The zoster vaccine has been the source of the strongest contemporary causal evidence for viral involvement in Alzheimer's disease, through the Wales and Australia natural experiments discussed below. VZV is mechanistically interesting because of the Cairns et al. (2022) finding that VZV infection of 3D neural tissue models triggers reactivation of latent HSV-1 in the same tissue — a "transactivation" effect that supplies a mechanistic substrate for the broader claim that suppression of one herpesvirus reduces reactivation of others.

CMV establishes latency in monocytes and lymphoid cells; reactivation is normally subclinical in immunocompetent hosts but is a major cause of disease in immunocompromised patients. CMV is principally relevant to Alzheimer's disease through its effect on the adaptive immune system: CMV seropositivity drives lifelong clonal expansion of CMV-specific CD8+ T cells, accelerates T-cell exhaustion, and is

the principal driver of the immunosenescence phenotype that characterizes Phase III. The Gate et al. (2020, *Nature*) finding that clonally expanded CD8+ T cells in AD CSF recognize EBV antigens — and the broader literature on antigen-experienced T-cell expansions in aging — places CMV alongside EBV as a driver of the T-cell repertoire that determines whether late-life viral reactivation can be controlled or not.

2.4 EBV and the MS Lesson: Bjornevik 2022

Epstein–Barr virus establishes latency in B lymphocytes after primary infection (mononucleosis, when symptomatic) and is the canonical example of an oncogenic herpesvirus. EBV has been suspected of involvement in multiple sclerosis for decades, but the strongest causal evidence emerged with Bjornevik et al. (2022, *Science*), who analyzed serial serum samples from 10 million U.S. military personnel and showed that EBV seroconversion preceded clinical MS onset by a median of five years and that EBV-negative individuals essentially did not develop MS. The hazard ratio for MS following EBV seroconversion was 32. The paper has been widely accepted as definitive evidence that EBV is a necessary (though not sufficient) cause of multiple sclerosis.

The EBV–MS finding is methodologically important for the Alzheimer's question because it demonstrates that herpesvirus involvement in chronic neurological disease can be established with prospective cohort data when the relevant exposure window is captured. The Alzheimer's question is more difficult because the relevant exposure (HSV-1 reactivation) is high-prevalence and intermittent rather than a discrete seroconversion event, but the EBV–MS result establishes that the methodology can yield definitive results when the exposure is appropriately characterized.

The Gate et al. (2020) finding of EBV-specific clonally expanded CD8+ T cells in Alzheimer's CSF connects the EBV–MS literature directly to Alzheimer's disease. The expansion is consistent with chronic EBV antigenic exposure that the host's adaptive immune system has been responding to over time, and the presence of EBV-specific T cells in CSF suggests CNS antigenic load rather than purely peripheral antigen presentation. Whether this represents EBV reactivation in CNS lymphocytes, EBV-driven peripheral immune activity that traffics centrally, or some other mechanism remains to be clarified.

2.5 SARS-CoV-2 and Accelerated Cognitive Decline

The COVID-19 pandemic supplied an unprecedented natural experiment in acute viral neurotropism. SARS-CoV-2 infects the brain through multiple routes: direct neuroinvasion through the olfactory epithelium and trigeminal nerve, hematogenous spread through endothelial cells expressing ACE2, and indirect effects through systemic cytokine elevation and microvascular thrombosis. The neurological consequences range from acute encephalopathy (in severe disease) through persistent cognitive symptoms ("brain fog") that resemble the prodromal phase of dementia (de Erausquin et al., 2021; Taquet et al., 2021, 2022).

The cohort evidence that emerged through 2022–2024 documented an elevated incidence of dementia diagnosis in the months and years following SARS-CoV-2 infection, with the effect concentrated in older adults and in those with pre-existing cognitive symptoms (Wang et al., 2022). The interpretation has been contested: is SARS-CoV-2 producing new dementia, or is it accelerating dementia in patients already in the prodromal window? The framework advanced in this dissertation treats the latter as more likely — SARS-CoV-2 is a Phase III accelerator that decompensates patients already in Phase II — but the data do not yet definitively distinguish these interpretations.

Crunfli et al. (2022, *PNAS*) demonstrated direct SARS-CoV-2 infection of human astrocytes in postmortem brain tissue from COVID-19 patients, accompanied by metabolic dysfunction and impaired support of neurons in culture. The finding establishes that SARS-CoV-2 neurotropism is not limited to neurons but extends to the glial compartment, with implications for the kind of chronic neuroinflammation that the viral trajectory framework treats as the central mechanism. Charnley et al. (2022) reported that fragments of the SARS-CoV-2 spike protein can self-assemble into amyloid-like aggregates, raising the possibility that SARS-CoV-2 exposure could contribute directly to amyloid pathology beyond the indirect inflammatory route.

2.6 Antiviral Therapy and Dementia Risk: Taiwan, Sweden, France, Korea

A series of cohort studies in Taiwan, Sweden, France, and Korea has examined whether prescription of anti-HSV antiviral medications (principally acyclovir, valacyclovir, and famciclovir) is associated with reduced subsequent dementia incidence. The results have been broadly concordant in direction, with effect sizes that are clinically meaningful but smaller than the zoster-vaccine effects discussed below.

Tzeng et al. (2018, *Neurotherapeutics*) analyzed the Taiwan National Health Insurance Research Database and found that patients with HSV infections who received antiviral therapy had a substantially lower risk of subsequent dementia diagnosis than those who did not. The hazard ratio was approximately 0.1 — a 90 percent reduction — though the absolute number of events was small and the confidence interval wide. Subsequent analyses have suggested that the effect size is closer to a 30–50 percent reduction in more carefully matched analyses.

Lopatko Lindman et al. (2019, 2021) analyzed Swedish national registry data and found a similar protective effect of anti-HSV antivirals, with the effect concentrated in long-term users and in patients with a history of clinically symptomatic herpes. Linard et al. (2020, 2022) analyzed French claims data with similar findings. Bae et al. (2022) analyzed Korean data and reported concordant results. The consistency across four independent national systems is the principal strength of this evidence, but all four studies are observational and subject to confounding by indication, healthy-user bias, and informative censoring.

Devanand et al. (2020) reported the VALAD trial, a randomized double-blind placebo-controlled study of high-dose valacyclovir versus placebo in patients with mild Alzheimer's disease and HSV-1 or HSV-2 seropositivity. The trial enrolled 130 patients and was underpowered to detect modest clinical effects. The primary outcomes were equivocal, with non-significant trends favoring valacyclovir on some measures and not others. The VALAD trial is the only randomized trial of antiviral therapy in symptomatic Alzheimer's patients to date; its result is consistent with a modest effect that the trial was not powered to detect, but it cannot be cited as positive evidence for antiviral benefit.

2.7 The Zoster Vaccination Natural Experiments: Wales and Australia

The strongest contemporary causal evidence for viral involvement in Alzheimer's disease comes from two regression-discontinuity natural experiments around zoster vaccination programs in Wales (Eyting et al., 2025, *Nature*) and in Australia (Liu et al., 2025). The Welsh program, initiated in 2013, used a sharp birth-date eligibility cutoff: individuals born on or after a specific date were eligible for the zoster vaccine, and those born before were not. The cutoff produced two demographically nearly-identical groups of individuals — separated only by a few days of birth — with markedly different vaccine exposure. Eyting and colleagues analyzed dementia incidence in the two groups over the subsequent decade and found a substantial reduction in dementia among the vaccinated group: approximately 20 percent reduction over 7 years of follow-up. The effect size is substantially larger than any pharmacological intervention to date.

The regression-discontinuity design is methodologically powerful because it approximates randomization in a way that observational cohort studies cannot. Individuals born just before and just after the cutoff are essentially identical in observable and unobservable characteristics; the only difference between them is the policy-induced vaccine exposure. The design therefore provides identification of a causal effect rather than an association, and the magnitude of the effect — 20 percent over 7 years — is large enough to be highly clinically meaningful.

Liu et al. (2025) replicated the design in Australian data with a similar identification strategy and reported concordant results. Schnier et al. (2024) reported related findings for the older Zostavax vaccine. The convergence of three independent national-level natural experiments on a substantial reduction in dementia incidence following zoster vaccination is the strongest piece of evidence in the contemporary viral-hypothesis literature. The mechanistic interpretation is the central question: how does vaccination against VZV reduce dementia incidence?

Several mechanisms have been proposed. First, the vaccine reduces VZV reactivation directly, removing one source of CNS antigenic load. Second, VZV reactivation can transactivate latent HSV-1 (Cairns et al., 2022), so suppression of VZV reactivation indirectly suppresses HSV-1 reactivation as well. Third, the vaccine may have nonspecific (trained immunity) effects that reduce the inflammatory tone of the host over time, with knock-on effects on microglial state and CNS inflammation. The framework developed in this dissertation treats all three

mechanisms as likely contributory and predicts that the Phase II microglial inflection is the principal mechanistic locus through which zoster vaccination produces its anti-dementia effect.

2.8 Gaps in the Literature

Six significant gaps in the existing literature motivate the present synthesis. First, the viral evidence has been organized by virus (the HSV-1 literature, the HHV-6 literature, the EBV literature, the VZV literature, the SARS-CoV-2 literature) rather than by host phase, and the question of how viruses interact with the three temporal phases of Alzheimer's disease has not been systematically addressed. Second, the antimicrobial Aβ hypothesis has been treated as a separate framework from the cohort and vaccine evidence, and the question of how they fit together as a single mechanistic story has been underdeveloped. Third, the immunosenescence and clonal T-cell expansion literatures (Gate, CMV, EBV) have not been integrated with the antiviral-cohort literature in a unified account of Phase III. Fourth, the regression-discontinuity zoster-vaccine evidence is recent enough that its mechanistic interpretation has not yet been worked through in detail. Fifth, the relationship between viral antigenic load and the tryptophan partition — the immunometabolic substrate that the Tryptophan Partition companion volume develops — has not been articulated. Sixth, the failure of pure anti-amyloid monotherapy in late-stage Alzheimer's trials has been interpreted as a problem for the amyloid-cascade hypothesis, but it could equally be interpreted as confirmation of a viral-trajectory model in which Aβ is downstream of antigenic drive that must itself be addressed; this reinterpretation has not been systematically developed. This dissertation addresses all six gaps.

3. Methodology

3.1 Disciplinary Approach

This dissertation adopts a systems-level integrative review methodology, synthesizing primary experimental literature, clinical trial data, epidemiologic cohort data, regression-discontinuity natural experiments, and theoretical frameworks across herpesvirus biology, neuroimmunology, antimicrobial peptide biology, the three-phase temporal model of Alzheimer's disease, and the Collapse trilogy's substrate-level architecture. The approach is consistent with the integrative dissertation tradition established for the Collapse trilogy: the contribution lies in the construction of a unifying mechanistic framework that maps existing evidence onto a temporal scaffold, rather than in the report of original experimental data.

3.2 Source Selection Criteria

Primary sources were selected for publication in peer-reviewed journals indexed in PubMed/MEDLINE or Web of Science; for experimental methodology adequate to support cited claims; for relevance to one or more of the three phases or the principal viral pathogens; and for recency, with preference for publications after 2010 except for foundational work (Fischer 1907; Ball 1982; Itzhaki et al. 1997; Soscia et al. 2010). Review articles are cited for historiographical positioning but are not used as primary evidence for mechanistic claims. Where competing interpretations exist — most prominently for the Readhead 2018 / Allnutt 2020 dispute about HHV-6 in AD brain — both sides are cited and the unresolved character of the dispute is characterized.

3.3 Analytical Framework: Three-Phase Temporal Mapping

The analysis proceeds through four levels of integration. At the **virus level**, the biology of each principal pathogen is traced from primary infection through latency through reactivation, with attention to the neuronal compartments in which latency is established, the triggers of reactivation, and the host immune response to reactivation. At the **phase level**, each of the three temporal phases of Alzheimer's disease is treated as a substrate that the host–virus interaction reshapes in distinctive ways — Phase I as the substrate for the antimicrobial Aβ response, Phase II as the substrate for microglial priming, Phase III as the substrate for immunosenescence-driven decompensation. At the **systems level**, the partition between phases is examined as a coupled control system in which each phase feeds the next and in which the viral input is reshaped by the host response at each transition. At the **clinical level**, the framework is evaluated against the cohort, trial, and natural-experiment evidence available.

3.4 Citation Protocol

Citations follow APA 7th edition. Primary experimental claims are cited to originating papers rather than to reviews. Where conflicting evidence exists, both sides are cited and the conflict is characterized.

4. Chapter I — The Temporal Architecture of Alzheimer's Disease

4.1 The Biomarker Timeline and the Clinical Timeline

The contemporary biomarker model of Alzheimer's disease, developed principally by Clifford Jack and colleagues (Jack et al., 2010, 2013, 2018) and instantiated in the NIA-AA research framework, organizes the disease around a sequence of biomarker changes whose temporal ordering is approximately invariant across patients: cerebrospinal Aβ42 declines first (corresponding to amyloid deposition in brain), followed by elevations in cerebrospinal phospho-tau and total tau (corresponding to tau pathology), followed by structural neurodegeneration on MRI, followed by cognitive symptoms. The biomarker timeline is the source of the now-canonical observation that Alzheimer's disease is detectable in CSF and PET markers fifteen to twenty years before the appearance of clinical symptoms. Symptoms are the late expression of a slow underlying process.

The biomarker timeline is informative but incomplete. It captures the deposition and the structural-degeneration phases of the disease but does not resolve the earlier prodromal phase in which Aβ deposition begins, and it does not capture the anatomical priority of the brainstem monoaminergic nuclei whose involvement begins decades before cortical amyloid is detectable. Heiko Braak's neuropathological staging of tau pathology (Braak and Braak, 1991; Braak et al., 2011) supplies the brainstem-priority correction: tau pathology is detectable in the locus coeruleus by Stage 0/I, well before the entorhinal cortex (Stage I/II), the hippocampus (Stage III), and the neocortex (Stage IV–VI). The LC tau is the earliest neuropathologically detectable change in Alzheimer's disease, and it appears in autopsy samples from individuals in their twenties and thirties — decades before clinical symptoms.

The Collapse trilogy's three-phase model integrates the biomarker timeline with the Braak staging and adds a substrate-level interpretation of the transitions between phases. Phase I (approximately ages 20–50) corresponds to Braak Stages 0/I — LC and brainstem tau pathology without cortical involvement — and to the bioenergetic-collapse substrate (PARP-1 hyperactivation, NAD+ erosion, ISR engagement). Phase II (approximately ages 50–70) corresponds to Braak Stages II–IV — entorhinal and hippocampal involvement — and to the microglial-collapse

substrate (loss of homeostatic identity, DAM transition, complement priming). Phase III (approximately ages 70+) corresponds to Braak Stages V–VI — neocortical involvement — and to the synaptic-collapse substrate (PV+ interneuron loss, PNN digestion, complement-mediated pruning). The three phases are anatomically distinct, temporally ordered, and mechanistically coupled.

4.2 Phase I (Ages 20–50): The Brainstem Prodrome

Phase I begins in the brainstem monoaminergic nuclei — principally the locus coeruleus and the dorsal raphe — and is characterized by a slow, cell-autonomous bioenergetic attrition. The locus coeruleus is the central anchor: it is the principal source of noradrenaline for the forebrain, its neurons have unusually long, thin, unmyelinated axons that distribute noradrenaline across the entire cortex, and its biochemistry generates substantial reactive oxygen species through monoamine oxidase activity on noradrenaline metabolism. The LC is therefore both anatomically and biochemically vulnerable in a way that few other brain regions are. The PARP*Locus*Coeruleus*Phase*I working paper (Gustafsson, 2026) develops a model in which LC neurons fail through PARP-1 hyperactivation on oxidatively damaged DNA, NAD+ depletion below the threshold required to maintain sirtuin signaling and mitochondrial function, integrated stress response engagement that becomes maladaptive when sustained, and slow attrition of LC neuron count across decades.

The LC is also the anatomical entry point for retrograde viral access to the brainstem. The trigeminal nerve sends sensory afferents to the brainstem nuclei in the pons, including direct and indirect connections to the LC; HSV-1 latency in the trigeminal ganglion can, in principle, traffic to the LC during reactivation. The anatomical possibility has been demonstrated in animal models (Lewandowski et al., 2002) and is consistent with the LC-priority pattern of tau pathology that Braak documented. The Phase I interpretation advanced in this dissertation is that the LC is the principal target of subclinical HSV-1 reactivation across decades, and that the cumulative effect of repeated retrograde viral seeding events on LC neurons — combined with the cell-autonomous bioenergetic vulnerabilities the trilogy characterizes — is what produces the LC tau pathology that Braak identified as Stage 0/I.

The clinical expression of Phase I is silent or subclinical. The symptoms that can be attributed to LC dysfunction — sleep dysregulation (REM sleep abnormalities,

fragmented sleep), autonomic dysfunction (orthostatic intolerance, abnormal heart-rate variability), and depression — are nonspecific and rarely trigger clinical attention. The biomarker expression of Phase I is similarly limited: standard CSF biomarkers are normal, PET imaging is unrevealing, and the only currently available imaging modality with sensitivity to LC pathology is neuromelanin-sensitive MRI, which is not in routine clinical use. The result is that Phase I is essentially undetected in clinical practice and is identified only retrospectively, in autopsy series and in research cohorts with neuromelanin MRI protocols.

4.3 Phase II (Ages 50–70): The Hippocampal–Microglial Inflection

Phase II marks the transition from a brainstem-confined process to a forebrain-engaging one. The pathological signature is the entry of microglia in the hippocampus and entorhinal cortex into the DAM/MGnD trajectory: the homeostatic transcriptional program maintained by TGF-β/SMAD signaling and characterized by Butovsky and colleagues (Butovsky et al., 2014) collapses, and the cells adopt a disease-associated state characterized by TREM2-dependent lipid metabolism, complement component upregulation, lysosomal expansion, and the loss of homeostatic synaptic surveillance. The transition is initially adaptive — DAM microglia respond to amyloid plaques and to damaged neurons in ways that should be protective — but becomes maladaptive when sustained, because the transcriptional program suppresses the very homeostatic functions that maintain healthy brain.

The microglial inflection has several upstream drivers. Amyloid deposition itself, accumulating in cortex through Phase I, is one. The accumulation of damage-associated molecular patterns from senescent neurons is another. But the framework advanced in this dissertation identifies a third driver that the conventional account has underweighted: chronic viral antigenic exposure, particularly from HSV-1 and HHV-6 reactivation, which produces sustained type-I interferon signaling, sustained IDO induction, and sustained recruitment of monocyte-derived macrophages into the CNS. The Phase II microglial transition is, on this account, an *immune* transition first and a metabolic transition second; the immune transition is driven by the cumulative antigenic load that decades of subclinical viral reactivation have deposited.

The clinical expression of Phase II is subjective cognitive decline progressing to mild cognitive impairment. The biomarker expression includes the standard CSF and PET amyloid biomarkers (which become positive in this window for many patients), the standard tau biomarkers (which lag amyloid by several years), and — increasingly — peripheral and central inflammatory biomarkers (kynurenine-to-tryptophan ratio, glial fibrillary acidic protein, sTREM2). The Phase II window is the principal target of contemporary disease-modifying therapeutics: lecanemab and donanemab are approved for use in MCI and mild AD, which corresponds to late Phase II in this framework.

4.4 Phase III (Ages 70+): The Synaptic Decompensation

Phase III marks the transition from a process whose pathology is detectable but whose cognitive consequences are limited to one in which cognitive function fails. The pathological signature is the loss of parvalbumin-positive interneurons and the digestion of perineuronal nets in cortex and hippocampus. The PV+ interneurons are the fast-spiking inhibitory cells that generate gamma-frequency oscillations and that support the precise temporal coordination of cortical and hippocampal activity required for memory consolidation. Their loss disrupts gamma oscillations (the Tsai lab's principal finding) and disinhibits cortical excitatory activity, producing both seizure susceptibility (a known accompaniment of late AD) and a breakdown of the temporal coding on which cognitive function depends.

The PV+ interneurons are protected, in young brains, by perineuronal nets — dense extracellular matrix structures composed of chondroitin sulfate proteoglycans, hyaluronan, tenascin-R, and link proteins — that physically protect the cells from oxidative damage and from extracellular proteolytic activity. PNN digestion by matrix metalloproteinase 9 (MMP-9) removes the protection, exposing the PV+ cells to the inflammatory milieu that has been accumulating through Phase II. The result is selective vulnerability of the PV+ interneurons in a brain whose extracellular environment has become hostile.

Phase III is also characterized by complement-mediated synaptic pruning. C1q, C3, and CR3 are re-activated from a developmental program — in which they marked weak synapses for microglial pruning during postnatal circuit refinement — to a pathological program in which they tag synapses for pruning in the adult brain. The Stevens laboratory's work (Hong et al., 2016; Lui et al., 2016) established that

complement knockout rescues synaptic loss in AD mouse models *independent of amyloid burden*, demonstrating that the synaptic loss is causally downstream of complement activity rather than of amyloid deposition per se. The Phase III interpretation advanced here is that the complement priming is the consequence of Phase II microglial activation, which is in turn the consequence of chronic viral antigenic load.

The clinical expression of Phase III is dementia. The patient cannot perform activities of daily living without assistance, memory is severely impaired, and the disease progresses inexorably toward death. The biomarker expression is full positivity across the standard panel: low Aβ42 and Aβ42/40 ratio in CSF, high phospho-tau and total tau in CSF, structural atrophy on MRI, and reduced FDG uptake on PET. Phase III is the target of symptomatic therapy (cholinesterase inhibitors, memantine) and increasingly of disease-modifying therapy in early-Phase III patients.

4.5 Why a Phase Model? Methodological Notes

Two methodological notes on the three-phase model are worth making explicit. First, the phase boundaries are central tendencies rather than hard cutoffs. A patient may enter Phase II in their forties (if APOE ε4 homozygous and with a high cumulative viral antigenic load), or may not enter it until their sixties (if APOE ε2 homozygous and with low antigenic load). The phase model is best understood as a description of the temporal architecture of the disease in the population, not as a deterministic prediction of any individual patient's trajectory. Individual trajectories are shaped by genotype, by lifetime viral exposure, by lifestyle and immune competence, and by stochastic factors that the population-level model does not capture.

Second, the phase model is *anatomical and substrate-level* before it is temporal. The three phases correspond to three anatomically distinct loci (LC and brainstem; hippocampus and microglia; PV+ interneurons and PNNs) and three substrate-level collapses (bioenergetic; microglial; synaptic). The temporal ordering follows from the anatomical and substrate-level architecture: the LC fails first because of its biochemistry, microglia fail next because they accumulate the consequences of cumulative pathology, and synapses fail last because the complement and PNN-digestion processes that prune them are themselves consequences of microglial activation. The temporal ordering is not arbitrary; it follows from the architecture.

The viral trajectory framework developed in the present dissertation maps onto this architecture: viruses interact with each phase through phase-specific mechanisms that exploit phase-specific vulnerabilities. Chapter II develops the Phase I interaction; Chapter III the Phase II interaction; Chapter IV the Phase III interaction; Chapter V the survey of viral pathogens; Chapter VI the integrated framework; Chapter VII the critical reassessment; Chapter VIII the therapeutic and predictive implications.

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5. Chapter II — Phase I: Latency, Periodic Reactivation, and the Aβ Antimicrobial Response

5.1 The Biology of HSV-1 Latency

Herpes simplex virus type 1 establishes lifelong latency in sensory neurons of the trigeminal ganglion and, in a smaller fraction of cases, in the olfactory bulb and the autonomic ganglia of the head and neck (Roizman and Whitley, 2013). Primary infection — typically in early childhood through oral contact — is followed by an acute lytic phase in mucosal epithelium and by retrograde axonal transport of viral particles to the cell bodies of the trigeminal sensory neurons that innervate the affected epithelium. Within the neuronal nucleus, the viral genome circularizes and adopts the latent configuration: the lytic genes are silenced by host heterochromatinization, a small set of latency-associated transcripts (the LATs) accumulate, and the virus enters a quiescent state from which it can be reactivated by a range of physiological stimuli.

The latent state is not a steady state. Mathematical and experimental analyses of HSV-1 reactivation suggest that the latent genome is subject to periodic stochastic excursions toward the lytic program, most of which are suppressed by host immune surveillance before they produce productive replication (Bloom, 2016). Successful reactivation — defined as completed lytic replication followed by anterograde axonal transport of newly synthesized virions to the periphery — occurs at rates that vary widely across individuals and across life stages. In immunocompetent adults, symptomatic recurrence (cold sores) typically occurs zero to several times per year; subclinical shedding without symptomatic lesion is substantially more frequent and is detectable in saliva samples from a substantial fraction of HSV-1-seropositive

individuals on any given week (Wald et al., 2002). The total number of reactivation events over a lifetime — counting both symptomatic and subclinical — is potentially in the thousands.

The triggers of reactivation include emotional and physical stress (mediated through HPA-axis activation and cortisol elevation), febrile illness, ultraviolet radiation, hormonal cycling, immune suppression (iatrogenic or otherwise), and certain dietary perturbations. The shared feature across triggers is some form of suppression of host immune surveillance: cortisol elevation suppresses T-cell function; febrile illness diverts immune resources to the febrile pathogen; immunosuppressive medication acts directly on the surveillance machinery. The frequency of reactivation is therefore a function of the integrated burden of stressors and of the integrity of the host's immune system, both of which change systematically across the lifespan.

5.2 The Trigeminal–Brainstem Axis: Anatomical Priority of the Locus Coeruleus

The trigeminal nerve is the principal route by which HSV-1 traffics during reactivation. Anterograde transport from the trigeminal ganglion delivers virions to the orofacial periphery (producing cold sores); retrograde transport from the trigeminal ganglion into the central nervous system is anatomically possible and, in animal models, has been demonstrated to occur (Lewandowski et al., 2002; Esiri, 1982). The retrograde route is normally suppressed by the immune surveillance that operates at the level of the trigeminal nerve root entry zone, but a small fraction of reactivation events propagate centrally, and the cumulative consequence of repeated central propagation across decades is a steady deposition of viral antigen and viral DNA into the brainstem nuclei that the trigeminal nerve directly or indirectly accesses.

The locus coeruleus receives indirect input from the trigeminal nerve through the principal sensory nucleus of the trigeminal nerve and through the spinal trigeminal nucleus, both of which project to the LC. The LC also receives direct input from the trigeminal mesencephalic nucleus, which is itself anatomically continuous with the trigeminal sensory pathway. The trigeminal–LC axis is therefore a plausible anatomical route by which HSV-1 reactivation in the trigeminal ganglion can produce repeated antigen deposition in the LC across a lifetime. The framework advanced in

this dissertation is that this is the principal mechanism by which Phase I is initiated and sustained.

The Braak observation that tau pathology appears first in the LC, well before any cortical involvement, is consistent with this anatomical interpretation. The LC is the brain region with the most consistent and earliest accumulation of hyperphosphorylated tau in autopsy samples from young and middle-aged adults — including from individuals who never developed clinical Alzheimer's disease (Braak et al., 2011). The Braak interpretation has been that the LC is intrinsically vulnerable to tau pathology because of its biochemistry; the viral interpretation advanced here is complementary rather than competing: the LC is intrinsically vulnerable *and* receives the trigeminal antigenic load that drives the chronic inflammation under which the intrinsic vulnerability is realized.

The relationship between LC tau pathology and HSV-1 reactivation has been directly tested in animal models. De Chiara et al. (2019, *PLoS Pathogens*) developed a model in which recurrent HSV-1 reactivation was induced in mice by repeated thermal stress, and they demonstrated that the cumulative effect of multiple reactivation events was the development of AD-like tau pathology and cognitive deficits — a finding that the conventional amyloid-cascade framework could not easily account for. The De Chiara findings have been criticized for the artificial nature of the reactivation paradigm, but they supply direct in vivo evidence that the link between HSV-1 reactivation and AD-like pathology is mechanistic rather than merely correlational.

5.3 Aβ as Antimicrobial Peptide: The Soscia–Kumar–Eimer Triad

The antimicrobial Aβ hypothesis advanced by Soscia, Kumar, Eimer, Moir, and Tanzi (Soscia et al., 2010; Kumar et al., 2016; Eimer et al., 2018) provides the mechanistic interpretation of Phase I that this dissertation adopts. Aβ — the proteolytic fragment of the amyloid precursor protein produced by sequential β-secretase and γ-secretase cleavage — is, on this account, an antimicrobial peptide of the innate immune system. The principal lines of evidence are:

First, Aβ peptides have direct antimicrobial activity against a wide panel of bacteria, fungi, and viruses in cell-free assays at concentrations comparable to those of LL-37 and other canonical antimicrobial peptides (Soscia et al., 2010). The activity is mediated by direct binding to microbial cell wall components — heparan sulfate

proteoglycans, lipopolysaccharide, peptidoglycan — and by Aβ oligomerization on the microbial surface to entrap the pathogen within an amyloid mesh. The mechanism is conserved across the broad range of pathogens tested and is consistent with the general biology of antimicrobial peptides.

Second, Aβ protects against systemic Salmonella infection and against herpes simplex encephalitis in mouse models (Kumar et al., 2016). 5XFAD mice expressing human Aβ have substantially better survival after intracranial HSV-1 inoculation than non-transgenic controls. The protection is dose-dependent and is abolished by pharmacological inhibition of Aβ oligomerization. The result is the strongest in vivo demonstration of Aβ's antimicrobial function and is the most direct evidence that Aβ is not merely an incidental toxin but an active immune effector.

Third, HSV-1 and HHV-6 infection of 5XFAD mouse brains accelerates amyloid deposition, and the deposition entraps the viral particles within the amyloid mesh (Eimer et al., 2018). The finding establishes that the brain's response to viral neuroinvasion is to deposit amyloid as a containment mechanism — a finding consistent with the broader claim that the AD amyloid plaque is the residue of a chronic antimicrobial response.

The implications for Phase I are direct. If the LC and surrounding brainstem are receiving repeated subclinical HSV-1 reactivation across decades, and if Aβ is an antimicrobial peptide deposited in response to viral neuroinvasion, then the slow accumulation of Aβ in brain across decades is best understood as the cumulative residue of decades of subclinical viral reactivation. The amyloid deposition is not a primary pathology; it is the residue of a successful (or partially successful) antimicrobial response. The deposition becomes pathological only when it is sustained beyond its useful duration, and when it begins to seed the tau pathology and the microglial activation that drives Phase II.

5.4 The Reactivation–Deposition Cycle: An Iterative Model

The Phase I dynamic that the framework predicts is iterative. A typical cycle proceeds as follows: a stress event triggers HSV-1 reactivation in the trigeminal ganglion; the reactivation propagates retrogradely to the LC through the trigeminal–LC anatomical axis; viral antigens are deposited in LC neurons; the local innate immune response includes microglial activation and Aβ deposition as an antimicrobial response; the antigenic load is partially cleared, but a residue of Aβ remains; and the cycle resets, awaiting the next reactivation event.

Over decades, the cumulative effect of this iterative cycle is:

- **Slow Aβ accumulation in the LC and adjacent brainstem regions**, as the residue of successive antimicrobial responses. This accumulation is initially below the detection threshold of current biomarker methods and is not captured by amyloid PET protocols optimized for cortical deposition.
- **Cumulative LC neuronal damage** from the combination of viral cytotoxicity (low-level, since most reactivation events are subclinical), oxidative stress from microglial activation, and the cell-autonomous PARP-1/NAD+ vulnerabilities that the Bioenergetic Collapse thesis characterizes. The damage is initially compensated by spare capacity, but a fraction of LC neurons fails permanently with each cycle.
- **Microglial priming in the brainstem**, as the local microglia accumulate the transcriptional changes associated with repeated antigen exposure. The priming does not yet produce the full DAM/MGnD transition — that is a Phase II event — but it establishes the substrate from which Phase II will emerge.
- **Tau hyperphosphorylation in surviving LC neurons**, mediated by HSV-1 itself (Piacentini et al., 2014, *Journal of Alzheimer's Disease*, demonstrated that HSV-1 infection activates GSK-3β and increases tau phosphorylation in neuronal models) and by the inflammatory milieu. The hyperphosphorylated tau is the substrate from which the Braak Stage I/II pathology will emerge.

The iterative model makes several testable predictions. First, the rate of Phase I progression should correlate with the rate of HSV-1 reactivation across decades, which is itself a function of cortisol load, sleep quality, immune competence, and APOE genotype. Second, individuals on chronic antiviral suppression should show slower Phase I progression than matched controls. Third, the LC tau load should correlate with cumulative HSV-1 antigen exposure in cohorts where both can be

measured. Fourth, APOE ε4 carriers should show accelerated Phase I because APOE ε4 modifies HSV-1 latency and reactivation in a pro-reactivation direction.

5.5 APOE as a Modifier of HSV-1 Latency and Reactivation

The APOE ε4 allele is the strongest non-Mendelian genetic risk factor for late-onset Alzheimer's disease, conferring approximately a threefold increased risk in heterozygotes and a tenfold to fifteenfold increased risk in homozygotes. The conventional explanation has been that APOE ε4 modifies amyloid clearance and aggregation. The viral hypothesis offers a complementary explanation: APOE ε4 modifies the HSV-1 latency/reactivation dynamics in ways that increase cumulative viral antigenic load on the brain across decades.

Burgos et al. (2002, 2003) demonstrated that APOE ε4 carriers have increased HSV-1 load in brain tissue compared to APOE ε3 or ε2 carriers, and that APOE genotype affects HSV-1 reactivation in mouse models (Itzhaki et al., 1997 cited Burgos in support of the original APOE-HSV interaction hypothesis). The mechanism appears to involve APOE-mediated regulation of HSV-1 entry, latency establishment, and reactivation efficiency, though the molecular details remain incompletely understood. The Linard et al. (2020) French cohort study confirmed the APOE ε4–HSV interaction at the epidemiological level: anti-HSV antiviral use was associated with reduced dementia risk specifically in APOE ε4 carriers.

The viral interpretation of APOE ε4 does not displace the amyloid-clearance interpretation; the two are likely complementary. APOE ε4 carriers may accumulate more amyloid both because they reactivate HSV-1 more frequently (producing more antigenic drive for antimicrobial Aβ deposition) and because they clear deposited Aβ less efficiently (producing more accumulation per deposition event). The combined effect is the substantial elevated risk that the epidemiology has documented.

5.6 Direct Evidence: Bourgade, Civitelli, De Chiara

Three lines of direct experimental evidence support the Phase I framework. First, Bourgade et al. (2015, 2016) demonstrated that HSV-1 infection of human neuronal cultures induces Aβ40 and Aβ42 production within hours, mediated by upregulation of APP processing. The induction is dose-dependent and is specific to HSV-1; controls with heat-inactivated virus or with unrelated viruses produce smaller or no effect. The finding establishes that the Aβ deposition in response to HSV-1 is not merely a passive accumulation but an active cellular response — consistent with the antimicrobial Aβ hypothesis.

Second, Civitelli et al. (2015) demonstrated that HSV-1 infection of neuronal cultures activates GSK-3β and produces tau hyperphosphorylation at AD-relevant epitopes within 48–72 hours. The hyperphosphorylation is independent of the Aβ response and represents a separate mechanism by which HSV-1 contributes to AD-like pathology. The finding bridges the viral and tau-pathology literatures.

Third, De Chiara et al. (2019, *PLoS Pathogens*) demonstrated that recurrent HSV-1 reactivation in mice — induced by repeated thermal stress over months — produces cumulative neuropathology that resembles human AD: amyloid deposition, tau hyperphosphorylation, neuroinflammation, and cognitive deficits in behavioral assays. The result is the strongest in vivo evidence that the iterative reactivation cycle proposed in §5.4 produces the predicted pathology when sufficient cycles are accumulated. The model has been criticized for the artificial nature of the thermal-stress reactivation protocol, but the cumulative pathology produced is qualitatively similar to spontaneous AD pathology and constitutes important mechanistic evidence.

5.7 What Phase I Looks Like in a 30-, 40-, or 50-Year-Old

The clinical and biomarker presentation of Phase I in a middle-aged individual is largely silent. The standard CSF biomarkers (Aβ42, p-tau, total tau) are within the normal range in most Phase I patients, though the most sensitive contemporary assays may detect early Aβ42 decline in individuals in their forties. Standard MRI and amyloid PET are typically negative. The only markers with sensitivity to Phase I are research-grade: neuromelanin-sensitive MRI of the locus coeruleus, which can detect early LC pigment loss; and high-sensitivity plasma p-tau217 assays, which have begun to show elevations in cognitively normal middle-aged adults with subsequent disease progression.

The framework advanced in this dissertation predicts that Phase I is detectable in young and middle-aged adults if one measures the right variables: plasma kynurenine-to-tryptophan ratio (reflecting cumulative IDO induction from chronic viral antigenic load); plasma anti-HSV IgG titers and avidity (reflecting cumulative reactivation history); neuromelanin-sensitive LC MRI (reflecting cumulative LC neuronal loss); and serial cortisol and HPA-axis measurements (reflecting the stress load that modulates reactivation rate). None of these measures is currently in routine clinical use for early AD screening, but the framework predicts that they would, in combination, detect Phase I in individuals decades before standard biomarkers do.

The clinical implications of Phase I detection are substantial. If Phase I is detected at age 40, the patient has potentially 30+ years of accumulating pathology to attenuate before clinical disease emerges. The therapeutic implications — discussed in Chapter VIII — include prophylactic antiviral suppression, stress management interventions to reduce reactivation frequency, and combination therapy with NAD+ precursors and other Phase I–targeted interventions.

6. Chapter III — Phase II: Reactivation Frequency, Microglial Priming, and the Prodromal Inflammation

6.1 The Reactivation Frequency Curve and HPA-Axis Aging

The transition from Phase I to Phase II is driven, on the framework advanced here, by a steady increase in the frequency and intensity of HSV-1 reactivation events as the host enters middle age. Several aging-related changes contribute to this increase. HPA-axis dysregulation produces sustained cortisol elevation that suppresses T-cell function; thymic involution reduces the naive T-cell pool; sleep architecture deteriorates, removing the slow-wave sleep periods during which immune surveillance is most effective; and the cumulative effect of decades of low-grade systemic inflammation produces "inflammaging" — the chronic low-grade inflammatory state characteristic of aging humans (Franceschi et al., 2000, 2018).

Each of these changes biases the host–virus equilibrium toward more frequent reactivation. The latent HSV-1 genome is not directly destabilized by aging, but the host's capacity to suppress the stochastic excursions toward the lytic program is reduced, and the rate at which excursions complete to productive replication increases. The cumulative effect is a substantial rise in reactivation frequency from young adulthood through middle age, with corresponding rises in cumulative viral antigenic load on brain tissue.

The Phase II inflection — the transition from silent Phase I to symptomatic Phase II — corresponds, in the framework, to the point at which cumulative antigenic load on brain microglia exceeds the threshold required to drive the homeostatic-to-DAM transition. The exact threshold is patient-specific and depends on APOE genotype, microglial transcriptional landscape, and the existing burden of Phase I pathology in the brainstem (which itself contributes inflammatory drive to forebrain microglia through descending noradrenergic and serotonergic projections that are progressively impaired).

6.2 Chronic IDO Induction and the Kynurenine Shift

Sustained viral antigenic exposure produces sustained type-I interferon signaling, which in turn drives chronic induction of indoleamine 2,3-dioxygenase (IDO) in microglia, monocytes, and infiltrating macrophages. The Tryptophan Partition companion volume (Gustafsson, 2026) develops the consequences of chronic IDO induction in detail; the present section summarizes them in the context of Phase II.

Chronic IDO induction does three things to the tryptophan partition. First, it shunts tryptophan from protein synthesis and from the serotonergic branch into the kynurenine branch. The serotonergic withdrawal is the molecular basis of the inflammation hypothesis of depression and explains the strong epidemiological association between late-life depression and subsequent dementia: depression is, in this reading, a marker of the chronic inflammatory IDO induction that will subsequently manifest as cognitive decline. Second, IDO induction biases the kynurenine partition toward the quinolinic-acid terminus, which is excitotoxic at the NMDA receptor and which exacerbates the calcium-dysregulation pathology that the Bioenergetic Collapse thesis identifies. Third, IDO induction couples to the integrated stress response through GCN2 sensing of tryptophan-codon stalling, producing ATF4 activation that further commits substrate to the kynurenine branch.

The net effect of chronic IDO induction across Phase II is a sustained inflammatory metabolic state characterized by elevated kynurenine, depressed serotonin, and a metabolic profile that the Maes et al. (2011) "new 5-HT" hypothesis of depression captures and that the present framework extends to AD. The plasma kynurenine-to-tryptophan ratio rises in this window and is detectable as an early biomarker of disease progression, decades before standard AD biomarkers turn positive.

6.3 The Microglial Homeostatic Collapse: DAM/MGnD Under Chronic Type-I IFN

The Homeostatic Microglial Collapse thesis (Gustafsson, 2026) characterizes the loss of TGF-β/SMAD-maintained homeostatic identity as the defining event of Phase II. The thesis identifies several upstream drivers — amyloid accumulation, damage-associated molecular patterns from senescent neurons, oligodendrocyte ferroptosis — but the role of chronic viral antigenic load has been incompletely articulated. The framework developed here treats chronic viral antigenic exposure as a major upstream driver of the homeostatic collapse, with type-I interferon signaling as the principal molecular signal.

Type-I interferons (IFN-α, IFN-β) are produced in response to viral nucleic acid sensing through TLR3, TLR7/8, RIG-I, MDA5, and cGAS/STING. The type-I IFN signal binds the IFNAR receptor on microglia and triggers a transcriptional response that includes the interferon-stimulated genes (ISGs), the major histocompatibility class I machinery, and a set of microglial-specific genes that bias the cell toward an antigen-presenting and effector phenotype. Sustained type-I IFN signaling — the kind produced by chronic viral antigenic exposure across decades — drives microglia into a state that overlaps substantially with the DAM/MGnD transcriptional signature, including upregulation of complement components, lysosomal expansion, and downregulation of homeostatic surveillance functions.

Roy et al. (2020, *Nature Communications*) and Yin et al. (2023, *Cell*) characterized type-I IFN signaling in AD mouse models and demonstrated that pharmacological or genetic suppression of type-I IFN signaling rescues microglial homeostatic function and reduces neurodegeneration. The findings establish that chronic type-I IFN signaling is causally upstream of the microglial pathology in these models. The framework here extends this finding by identifying chronic viral reactivation as the principal physiological driver of the type-I IFN signal that produces the pathology.

The DAM/MGnD transition under chronic type-I IFN has several consequences for Phase II progression. First, it primes the microglia for the complement-mediated synaptic pruning that will dominate Phase III. Second, it reduces the synaptic surveillance and the neurotrophic support that healthy microglia normally provide, accelerating synaptic dysfunction. Third, it changes the cytokine output of the microglia from anti-inflammatory (TGF-β, IL-10) to pro-inflammatory (TNF, IL-1β,

IL-6), producing the cytokine environment in which BBB compromise and tau propagation accelerate.

6.4 Blood–Brain Barrier Compromise and Enhanced Viral CNS Access

The blood–brain barrier is progressively compromised in Phase II, with detectable changes in the hippocampus and entorhinal cortex preceding the cognitive prodrome by years (Nation et al., 2019, *Nature Medicine*; Montagne et al., 2015). The BBB compromise has multiple drivers — pericyte loss, endothelial dysfunction, astrocyte endfoot remodeling — but the viral framework identifies an additional driver and an additional consequence.

The driver: chronic inflammatory cytokine signaling from activated microglia and infiltrating monocytes acts on cerebrovascular endothelium to upregulate adhesion molecules, increase paracellular permeability, and reduce tight-junction integrity. The chronic inflammatory state of Phase II is therefore directly upstream of the BBB compromise that is increasingly recognized as an early feature of AD.

The consequence: the compromised BBB allows enhanced CNS access of peripheral pathogens that would normally be excluded. Subclinical HSV-1 reactivation in peripheral tissue can produce circulating viral particles, viral nucleic acids, and viral antigens that, in the presence of BBB compromise, reach the CNS in larger quantities than would otherwise be possible. The Phase II BBB compromise is therefore not just a downstream consequence of disease progression but an *amplifier* of the antigenic load that the framework identifies as causally upstream of the disease. The amplification loop — chronic antigenic load drives BBB compromise drives enhanced antigenic load — is one of the principal mechanisms by which Phase II accelerates once it has begun.

6.5 Prion-Like Tau Propagation in an Inflamed Milieu

The tau pathology characteristic of Phase II progresses from the entorhinal cortex through the hippocampal formation in a stereotyped Braak pattern that has long been interpreted as evidence of trans-synaptic spreading. The mechanism is now well-established: tau seeds released from one neuron are taken up by anatomically connected downstream neurons, where they template the misfolding of native tau and propagate the pathology along anatomical pathways. The propagation is enhanced by neuroinflammation: TNF, IL-1β, and complement components all increase tau uptake and templating in cell-culture and mouse-model assays (Asai et al., 2015; Maphis et al., 2015).

The framework advanced here identifies chronic viral antigenic load as a major driver of the neuroinflammation that accelerates tau propagation. The Phase II inflammatory milieu — driven in substantial part by chronic HSV-1 and HHV-6 reactivation — is the substrate in which tau propagation occurs at its fastest rates. Pure tau pathology in the absence of inflammation propagates slowly; tau pathology in the inflamed brain propagates fast. The acceleration is one of the principal mechanisms by which Phase II progresses, and it is targeted by both anti-tau (such as the anti-tau antibody trials in early AD) and anti-inflammatory (such as IL-1β blockade) therapeutics that the field is currently pursuing.

6.6 Late-Life Depression as the Serotonergic Prodrome

A robust epidemiological observation that has resisted satisfactory mechanistic interpretation is that late-life depression is a strong risk factor for subsequent dementia, with hazard ratios of approximately 2 in most cohorts (Diniz et al., 2013). The conventional interpretations have been that depression and dementia share genetic risk factors, that depression itself is an early symptom of underlying AD, or that depression produces vascular or metabolic perturbations that increase AD risk. The viral framework offers a different interpretation: late-life depression and AD are both consequences of the same chronic inflammatory IDO induction; depression is the early-Phase-II manifestation (serotonergic withdrawal), and AD is the late-Phase-II/Phase-III manifestation (microglial collapse and synaptic decompensation).

The interpretation has practical implications. SSRIs in late-life depression have produced mixed effects on subsequent dementia incidence in observational studies.

The framework predicts that SSRIs should be modestly effective at the symptom level (raising synaptic 5-HT in the face of substrate limitation) but limited in their capacity to prevent AD progression because they do not address the upstream IDO induction that drives both the serotonergic withdrawal and the microglial pathology. The framework further predicts that the combination of antiviral suppression with SSRIs should be substantially more effective than SSRI monotherapy — a testable prediction with substantial clinical implications.

6.7 The Cairns 3D Brain Models: HSV-1 Reactivation and VZV Transactivation

A particularly important line of evidence for the Phase II framework comes from the Cairns laboratory at Tufts (Cairns et al., 2020, 2022, *Science Advances*). The group developed three-dimensional bioengineered neural tissue models — composed of human induced pluripotent stem cell-derived neurons and glia cultured on a silk-collagen scaffold — and used these models to study HSV-1 reactivation and its consequences.

Cairns et al. (2020) demonstrated that HSV-1 infection of the 3D brain models produced cumulative AD-like pathology over weeks: amyloid plaques, neurofibrillary tangle-like structures, neuroinflammation, and electrophysiological abnormalities. The pathology was induced by repeated reactivation cycles triggered by withdrawal of immune-suppressing factors, and the cumulative effect over multiple cycles resembled human AD pathology. The model provides one of the strongest in vitro demonstrations that HSV-1 reactivation can drive AD-like pathology in human neural tissue.

Cairns et al. (2022) extended the model to varicella zoster virus and made the critical observation that VZV infection of the 3D brain tissue triggered reactivation of latent HSV-1 in the same tissue. VZV itself did not produce direct AD-like pathology; instead, it produced HSV-1 reactivation, and the reactivated HSV-1 then produced the AD-like pathology. The mechanism appears to involve VZV-induced inflammatory signaling that destabilizes HSV-1 latency. The "transactivation" finding is mechanistically critical because it supplies the interpretation of the zoster-vaccination natural experiments: zoster vaccination reduces VZV reactivation, which reduces HSV-1 transactivation, which reduces the cumulative HSV-1 antigenic load on brain — and reduces dementia incidence in the cohort.

The Cairns findings have not been independently replicated in 3D models from other laboratories, and the model has not been validated against human brain tissue at the molecular level. Both limitations are important. But the model provides a mechanistic substrate for the population-level findings in a way that the cell-culture and animal-model literatures had not, and it has substantially influenced the interpretation of the zoster-vaccine evidence.

6.8 What Phase II Looks Like in MCI

Phase II is the window of greatest current clinical attention because it is the window in which contemporary disease-modifying therapeutics (lecanemab, donanemab) are approved for use. The biomarker presentation of Phase II includes positive amyloid PET, declining CSF Aβ42, elevated CSF phospho-tau, and increasingly detectable plasma p-tau217. The cognitive presentation begins with subjective cognitive decline (SCD) — patients report memory complaints that are not yet detectable on standard cognitive testing — and progresses through mild cognitive impairment (MCI) and into mild dementia.

The viral framework predicts that Phase II patients should show additional biomarker abnormalities that the conventional panel does not capture: elevated plasma kynurenine-to-tryptophan ratio, elevated serum anti-HSV IgG titers and shedding rates, elevated CSF cytokines and complement components, and elevated peripheral monocyte expression of CD163 and other markers of monocyte activation. The framework also predicts that the phase-appropriate therapeutic intervention in Phase II includes antiviral suppression alongside anti-amyloid antibody therapy — a combination that has not been systematically tested in trials.

7. Chapter IV — Phase III: Immunosenescence, Decompensation, and the SARS-CoV-2 Accelerator

7.1 Immunosenescence: T-Cell Exhaustion, NK Senescence, CD38+ Macrophage Expansion

The transition from Phase II to Phase III is marked by the failure of the host's adaptive immune system to continue suppressing viral reactivation. The immunosenescence phenotype that characterizes elderly humans includes several distinct but interrelated features: clonal expansion of antigen-experienced memory T cells; loss of naive T-cell diversity (driven by thymic involution); accumulation of exhausted CD8+ T cells expressing PD-1, TIM-3, LAG-3, and other inhibitory receptors; loss of NK cell cytotoxic function; and expansion of CD38+ senescent macrophages whose CD38 ectoenzyme activity erodes systemic NAD+ levels (Chini et al., 2017, 2020).

The immunosenescent state is not merely an "old immune system" but a qualitatively different state in which the balance between viral suppression and viral reactivation has shifted decisively toward reactivation. The latent herpesviruses — HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, HHV-7 — each contribute to and exploit this state. CMV is the most aggressive driver of clonal T-cell expansion, with up to 30 percent of an elderly individual's CD8+ T cell repertoire devoted to CMV-specific clones (Brodin and Davis, 2017). The clonal expansion crowds out diversity and reduces the host's capacity to respond to novel pathogens — including, in the modern era, novel respiratory viruses such as SARS-CoV-2.

The CD38+ macrophage expansion is mechanistically important for the Bioenergetic Collapse thesis (Gustafsson, 2026, Ch. 1) and for the present framework. CD38 is an ectoenzyme that hydrolyzes NAD+ to nicotinamide and ADP-ribose; the expansion of CD38-expressing immune cells in aged tissue produces a substrate-level erosion of systemic NAD+ that the host's biosynthetic machinery cannot fully compensate. The Schwartz–Chini collaboration (Schwartz and Chini, 2025, *Nature Communications*) demonstrated that anti-CD38 antibody therapy in aged mice simultaneously rescues immune function, brain NAD+ levels, peripheral metabolism, and cognition — a cross-substrate rescue that is the cleanest contemporary demonstration of the immunometabolic coupling that the viral trajectory framework presupposes.

7.2 Gate et al. 2020: Clonally Expanded CD8+ T Cells in AD CSF

A particularly important piece of evidence for the Phase III framework comes from Gate et al. (2020, *Nature*). The study analyzed the T-cell repertoire in cerebrospinal fluid from Alzheimer's disease patients and matched controls, and identified clonally expanded CD8+ T cells in the AD CSF that were not present in controls. The clones were antigen-specific, and TCR sequencing combined with antigen prediction identified Epstein–Barr virus antigens as the principal target of the expanded clones.

The Gate finding is critical because it establishes that the AD brain is the site of antigen-specific adaptive immune activity directed against a chronic viral pathogen. The principal alternative interpretations — that the CSF T cells are responding to neuronal damage-associated patterns rather than to viral antigens, or that they are bystanders — are not well-supported by the data, which show specific TCR–MHC recognition of EBV-derived peptides. The finding has been replicated in subsequent cohorts and is now one of the strongest pieces of evidence for an active viral component in Phase III AD.

The framework here treats the Gate findings as the immunological fingerprint of Phase III viral reactivation. The clonal expansion is the residue of decades of chronic EBV antigenic exposure; the CSF localization is the consequence of BBB compromise and active CNS antigen presentation. The expansion does not necessarily indicate that EBV is *the* causal pathogen — HSV-1, HHV-6, and VZV could each be similarly active, with their own T-cell clones — but it establishes that adaptive immune activity against herpesvirus antigens is ongoing in the AD brain.

7.3 The Terminal Microglial State: PANTHOS and Lipid-Laden Microglia

Phase III is marked by the appearance of microglial states that are not present in Phase II: PANTHOS (panthos, the Greek-derived term for "all pathology"), characterized by Nixon and colleagues as the terminal failure of the autophagy-lysosomal system in microglia; lipid-laden microglia accumulating cholesterol esters and lipid droplets, characterized by Marschallinger and colleagues; and dystrophic microglia exhibiting cytoplasmic fragmentation and process retraction, characterized by Streit and colleagues. Each of these states represents the failure of the microglial response that Phase II had primed: the cells have been pushed beyond their adaptive capacity and are now contributing to pathology rather than mitigating it.

The Convergent Autophagic Collapse working paper (Gustafsson, 2026) develops the PANTHOS framework in detail; the present chapter notes that the autophagic collapse in Phase III microglia includes failure of viral antigen clearance. Microglia that cannot complete autophagy cannot clear engulfed viral particles, and the cells therefore accumulate viral material that further drives inflammatory signaling. The terminal microglial state is, on this account, both a *consequence* of cumulative viral antigenic load and a *cause* of continued viral antigenic accumulation. The bidirectional coupling is one of the principal drivers of the rapid decompensation that characterizes the late-Phase-III period.

7.4 Synaptic Loss in a Post-Viral Inflammatory Bed: Complement and MMP-9

The synaptic decompensation characteristic of Phase III is driven principally by complement-mediated pruning (Hong et al., 2016) and by MMP-9-mediated perineuronal net digestion (Vegh et al., 2014; Cabungcal et al., 2013). Both processes are accelerated by inflammatory signaling — complement components are upregulated under chronic type-I IFN and IL-1β, and MMP-9 is upregulated under chronic TNF and chemokine signaling. The Phase III synaptic loss therefore occurs in a post-viral inflammatory bed in which decades of chronic viral antigenic load have primed the brain for accelerated synaptic dysfunction.

The Stevens laboratory's complement knockout experiments (Hong et al., 2016) demonstrate that complement-mediated synaptic pruning is causally upstream of

cognitive decline in AD mouse models, independent of amyloid burden. The framework here extends this finding: the complement priming is itself causally downstream of chronic viral antigenic load, and the chain is therefore viruses ☐ microglial activation ☐ complement priming ☐ synaptic pruning ☐ cognitive decline. Anti-complement therapy (ANX005, pegcetacoplan) addresses the penultimate step in this chain; antiviral therapy addresses the first step. The combination is predicted to be substantially more effective than either alone.

7.5 PNN Digestion in an Inflammatory Landscape

The perineuronal nets that protect PV+ interneurons are digested in Phase III by MMP-9 and by chondroitinases produced by activated microglia. The PNN digestion exposes the underlying PV+ interneurons to oxidative damage and to extracellular proteolytic activity. The result is selective vulnerability of the PV+ population in cortex and hippocampus, with downstream consequences for gamma-oscillation generation and for the cortical–hippocampal communication that underlies memory consolidation.

Chronic viral antigenic load contributes to PNN digestion through multiple mechanisms. First, the chronic inflammatory environment upregulates MMP-9 expression in microglia and infiltrating monocytes. Second, HSV-1 itself encodes glycoproteins that bind heparan sulfate proteoglycans (the same class of molecules that form PNN backbone), and HSV-1 entry into cells through HSPG binding has been suggested to contribute to local extracellular matrix remodeling. Third, the type-I IFN signature in Phase III microglia includes upregulation of matrix-degrading enzymes as part of the antiviral response. The cumulative effect is accelerated PNN digestion and accelerated PV+ interneuron vulnerability.

7.6 SARS-CoV-2 as a Phase III Accelerator

The COVID-19 pandemic supplied a natural experiment in acute viral perturbation of an already-stressed Phase III population. The cohort evidence (Taquet et al., 2021, 2022; Wang et al., 2022) documents elevated dementia diagnoses in the months and years following SARS-CoV-2 infection, with the effect concentrated in older adults. The framework advanced here treats SARS-CoV-2 as an acute Phase III accelerator: patients already in late Phase II or early Phase III, whose brains are in a state of immunometabolic vulnerability, decompensate rapidly when acute SARS-CoV-2 infection adds an additional load.

The mechanisms include direct neuroinvasion through the olfactory and trigeminal routes (analogous to the chronic HSV-1 retrograde route but more acute); direct astrocyte infection (Crunfli et al., 2022) with attendant metabolic dysfunction; spike-protein-induced amyloid-like aggregation (Charnley et al., 2022); cytokine-storm-driven microglial activation; and reactivation of latent herpesviruses (HSV-1, VZV, EBV) triggered by the systemic inflammatory state and corticosteroid treatment that severe COVID-19 entails. The "two-hit" pattern — pre-existing Phase II vulnerability plus acute SARS-CoV-2 perturbation — is the predicted mechanism for the post-COVID dementia association in the cohort data.

7.7 What Phase III Looks Like at Autopsy: Viral Antigen Colocalization with Plaques

The autopsy literature on viral antigen colocalization with AD pathology has been one of the most contested areas of the viral hypothesis. The Wozniak et al. (2009) finding — HSV-1 antigen colocalizing with amyloid plaques in human AD brain — has been challenged on technical grounds (specificity of the HSV-1 antibodies used, validity of the colocalization analysis) but has been broadly replicated in subsequent studies (e.g., Bourgade et al., 2016). The framework here treats the colocalization as expected: if Aβ deposition is the antimicrobial response to viral neuroinvasion, then viral antigen should be detectable within the resulting plaques. The colocalization is not proof of viral causation, but it is the prediction of the antimicrobial Aβ hypothesis and it is broadly confirmed in the autopsy data.

The Phase III autopsy signature, on the framework advanced here, includes: HSV-1 antigen colocalization with amyloid plaques (variable detection); HHV-6 transcripts in a fraction of brains (the Readhead 2018 finding, with the Allnutt 2020

caveats); EBV antigens recognized by clonally expanded CSF CD8+ T cells (Gate 2020); SARS-CoV-2 antigens in brains of patients who died after COVID-19 infection (Crunfli 2022); and chronic type-I IFN transcriptional signatures in microglia and adjacent astrocytes. No single pathogen accounts for all Phase III pathology in all patients, but the cumulative pattern of multi-pathogen antigenic load is consistent with the framework's prediction of cumulative pathogen load as the principal Phase III driver.

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8. Chapter V — The Viral Cast: HSV-1, HHV-6, VZV, EBV, CMV, SARS-CoV-2

8.1 HSV-1: The Canonical Case

Herpes simplex virus type 1 is the canonical pathogen in the viral hypothesis of Alzheimer's disease and supplies the longest and richest evidentiary tradition. The case rests on five pillars: (i) the molecular evidence of HSV-1 DNA in human AD brain (Itzhaki and colleagues, since 1997); (ii) the colocalization of HSV-1 antigen with amyloid plaques (Wozniak et al., 2009); (iii) the gene–virus interaction with APOE ε4 (Itzhaki et al., 1997; Linard et al., 2020; Tsai et al., 2011); (iv) the in vitro and in vivo demonstration that HSV-1 infection of neuronal models produces AD-like pathology (Bourgade, Civitelli, De Chiara, Cairns); and (v) the cohort evidence of reduced dementia incidence among long-term users of anti-HSV antivirals (Tzeng, Lopatko Lindman, Linard, Bae).

The Phase-specific role of HSV-1 in the framework is as follows. In Phase I, HSV-1 latency in the trigeminal ganglion and periodic retrograde reactivation to the LC is the principal driver of the LC tau pathology and the antimicrobial Aβ deposition that defines the bioenergetic prodrome. In Phase II, increasing reactivation frequency drives the chronic IDO induction and type-I IFN signaling that produce the microglial homeostatic collapse. In Phase III, immunosenescence-driven unchecked HSV-1 reactivation contributes to the inflammatory milieu in which complement-mediated pruning and PNN digestion accelerate. HSV-1 is therefore not a Phase-specific pathogen but a cross-phase driver whose mechanism of action changes as the host phase changes.

8.2 HHV-6A and HHV-6B: Readhead, Allnutt, and the Replication Controversy

Human herpesvirus 6 was the subject of the Readhead et al. (2018, *Neuron*) paper that substantially elevated the field's attention to viral hypotheses of AD. The paper reported substantially elevated HHV-6A and HHV-7 transcript abundance in the Mount Sinai Brain Bank AD cohort relative to controls and proposed that HHV-6A was a load-bearing driver of disease. The paper used multiple RNA-seq cohorts, transcriptional network analysis, and mouse-model validation, and it was the most ambitious viral-AD claim of the modern era.

The Readhead findings were challenged by Allnutt et al. (2020, *Neuron*), who reanalyzed the same and additional RNA-seq datasets with stricter pathogen-detection methodology. The Allnutt analysis required higher minimum read counts for pathogen detection, used multiple control datasets, and applied corrections for batch effects that the original analysis had not. The reanalysis found HHV-6 detection in a substantially smaller fraction of brains than the original report had suggested, and the case-control differences did not reach statistical robustness in the reanalyzed data. The Readhead group defended its original findings, and the dispute has not been definitively resolved.

The framework here treats the HHV-6 evidence as partially supportive of the viral hypothesis. HHV-6 is detectable in a fraction of AD brains, and the magnitude of the contribution may have been overstated in the original Readhead paper, but the pathogen is real, its latency in the CNS is well-established, and it is a plausible contributor to the cumulative pathogen load that the framework treats as the operative variable. The framework does not require HHV-6 to be a major contributor in all patients; it requires only that cumulative pathogen load across multiple viruses produces the Phase II and Phase III pathology, which the existing evidence broadly supports.

8.3 VZV: The Zoster Vaccine Natural Experiment

Varicella zoster virus is the source of the strongest contemporary causal evidence for viral involvement in dementia. The Wales regression-discontinuity natural experiment (Eyting et al., 2025, *Nature*) and the Australian replication (Liu et al., 2025) demonstrate that vaccine-induced suppression of VZV reactivation produces substantial reductions in dementia incidence — approximately 20 percent over 7 years of follow-up. The effect size is substantially larger than any pharmacological intervention to date.

The mechanistic interpretation of the zoster-vaccine effect is the central question. The framework here treats the VZV transactivation finding (Cairns et al., 2022) as the operative mechanism: zoster vaccination reduces VZV reactivation, which reduces VZV-induced transactivation of latent HSV-1, which reduces cumulative HSV-1 antigenic load on brain, which reduces Phase II and Phase III progression. The interpretation predicts that the zoster-vaccine effect on dementia should be partially mediated by changes in HSV-1 reactivation markers, a prediction that has not yet been directly tested.

An alternative interpretation is that the zoster vaccine has nonspecific (trained immunity) effects on the innate immune system that reduce inflammatory tone over time, independent of any specific effect on HSV-1. The two interpretations are not mutually exclusive — both mechanisms may contribute — and the relative contribution of each is an empirical question for future research. The framework here treats the specific HSV-1 transactivation mechanism as the principal contributor but acknowledges the trained-immunity contribution as a likely secondary mechanism.

8.4 EBV: B-Cell Latency and the MS Lesson

Epstein–Barr virus establishes latency in B lymphocytes and is the canonical example of an oncogenic herpesvirus. The Bjornevik et al. (2022, *Science*) paper established EBV as a necessary cause of multiple sclerosis using prospective cohort data from 10 million U.S. military personnel. The methodology — serial serum sampling that captured the EBV seroconversion event — is not directly transferable to AD because the relevant AD exposure is reactivation rather than primary infection, but the result establishes that herpesvirus involvement in chronic neurological disease can be definitively demonstrated when the exposure is appropriately characterized.

The EBV–AD connection runs through the Gate et al. (2020) finding of clonally expanded EBV-specific CD8+ T cells in AD CSF. The interpretation here is that EBV reactivation in peripheral B cells — perhaps amplified in AD by the immune dysregulation of the chronic inflammatory state — produces antigenic load that drives the adaptive immune expansion that Gate identified. The framework predicts that anti-EBV interventions (the EBV vaccine programs currently in development; existing antivirals with anti-EBV activity such as ganciclovir) should reduce AD incidence in cohorts where EBV reactivation is substantial, a prediction that has not yet been tested at scale but that is increasingly tractable as anti-EBV interventions advance.

8.5 CMV: T-Cell Exhaustion Driver

Cytomegalovirus is the principal driver of T-cell exhaustion and clonal expansion in aged humans. Up to 30 percent of an elderly individual's CD8+ T-cell repertoire may be devoted to CMV-specific clones (Brodin and Davis, 2017), with corresponding crowding of the naive T-cell pool and reduced capacity to respond to novel pathogens. CMV seropositivity is associated with multiple aging-related phenotypes including cardiovascular disease, frailty, and — in some cohorts — dementia (Lurain et al., 2013).

The framework here treats CMV as a Phase III contributor through its effect on adaptive immunity. The clonal expansion that CMV drives reduces the host's capacity to control reactivation of *other* herpesviruses (HSV-1, VZV, EBV) and contributes to the immunosenescent state that defines Phase III. CMV is therefore an indirect driver: it does not produce AD pathology directly, but it accelerates the failure of viral control that allows the other herpesviruses to reactivate unchecked. The implication is that CMV-targeted interventions (existing antivirals such as valganciclovir; CMV vaccines in development) should reduce dementia incidence in CMV-seropositive cohorts.

8.6 SARS-CoV-2: Acute Neurotropism and the Phase III Accelerator

SARS-CoV-2 is, in the framework, an acute perturbation rather than a chronic driver. The pandemic supplied a natural experiment in acute viral exposure of a population that included millions of individuals already in Phase I, Phase II, or Phase III of underlying Alzheimer's pathology. The cohort evidence (Taquet et al., 2021, 2022; Wang et al., 2022) documents accelerated dementia incidence in the months and years following SARS-CoV-2 infection. The framework interprets this as the result of acute SARS-CoV-2 perturbation of a system already in the late-Phase-II or early-Phase-III window.

The mechanisms include direct neuroinvasion (olfactory and trigeminal routes), direct astrocyte infection (Crunfli et al., 2022), spike-protein-induced amyloid-like aggregation (Charnley et al., 2022), and reactivation of latent herpesviruses triggered by the systemic inflammatory state. The reactivation mechanism is particularly important because it integrates SARS-CoV-2 with the chronic-herpesvirus framework: SARS-CoV-2 acts as an acute trigger that unleashes reactivation of HSV-1, VZV, EBV, and CMV — pushing patients already in Phase II into accelerated Phase III. The framework therefore predicts that the post-COVID dementia association should be substantially mediated by herpesvirus reactivation markers, a prediction that has begun to be tested in COVID cohorts.

8.7 Pathogen-Pair and Cumulative-Load Effects

A unifying feature of the viral hypothesis as developed here is that no single pathogen is sufficient to cause AD, but the cumulative load of multiple pathogens across decades is the operative variable. The pathogen-pair literature is consistent with this view: combinations of HSV-1 + APOE ε4, HSV-1 + chlamydia pneumoniae, HSV-1 + periodontal disease (P. gingivalis), and HSV-1 + HHV-6 have each been associated with elevated dementia risk in cohort studies. The framework predicts that each pathogen contributes additively (or sub-additively) to cumulative antigenic load, that the cumulative load is the principal determinant of disease progression, and that interventions targeting any one pathogen should produce partial benefit proportional to that pathogen's contribution to the patient's cumulative load.

The cumulative-load framing also explains the population-attributable-fraction problem. If HSV-1 seropositivity is 70 percent in adults and HSV-1 alone is not sufficient to cause AD, then HSV-1 seropositivity is not predictive of AD at the

individual level. But if cumulative pathogen load is the operative variable, and HSV-1 reactivation frequency is a major component of cumulative load in many patients, then HSV-1 reactivation frequency (which is distinct from seropositivity) should predict AD incidence. The framework's prediction is that markers of HSV-1 reactivation frequency — anti-HSV IgG avidity, plasma viral DNA in subclinical-shedding cohorts, salivary HSV-1 RNA — should outperform seropositivity as predictors of subsequent dementia. This prediction has only begun to be tested.

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9. Chapter VI — The Integrated Viral Trajectory: A Phase-Coupled Framework

9.1 Three Phases, One Iterative Cycle

The central claim of this chapter is that the three temporal phases of Alzheimer's disease — Phase I bioenergetic, Phase II microglial, Phase III synaptic — are not three independent insults but three temporal expressions of a single iterative cycle of host–virus interaction. The cycle proceeds as follows. At each phase, viral reactivation produces an antigenic stimulus that the host immune system responds to. The response is initially adaptive but, over decades and across thousands of reactivation cycles, accumulates pathology that progressively damages the host. The damage at each phase weakens the host's defenses against the next reactivation, and the system spirals through the three phases in a roughly age-graded sequence.

The cycle has three load-bearing properties. First, it is *iterative*: the same basic mechanism (reactivation followed by immune response) repeats across decades, with cumulative rather than threshold consequences. Second, it is *self-amplifying*: each cycle weakens defenses against the next, and the rate of reactivation increases with age while the capacity to suppress reactivation decreases. Third, it is *phase-coupled*: the consequences of reactivation at each phase are different because the host is different at each phase — different in immune competence, different in BBB integrity, different in microglial state, different in synaptic infrastructure. The same antigenic stimulus produces different effects at age 30 versus age 50 versus age 70.

9.2 The Amplification Loop

The amplification loop that the framework predicts has three nested cycles operating on different timescales. The *short-cycle* amplification operates within a single reactivation event: viral antigen drives microglial activation, microglial activation produces inflammatory cytokines and complement components that recruit additional immune cells and that compromise the BBB locally, BBB compromise allows enhanced viral CNS access, and the cycle completes within days. The *medium-cycle* amplification operates across weeks to months: cumulative microglial activation drives DAM/MGnD transition, transition reduces microglial homeostatic surveillance, reduced surveillance allows enhanced viral persistence, and the cycle completes within the timescale of the Phase II inflection. The *long-cycle* amplification operates across decades: cumulative microglial pathology drives synaptic loss in Phase III, synaptic loss reduces cognitive reserve, reduced cognitive reserve increases stress vulnerability, stress vulnerability drives more frequent reactivation, and the cycle completes within the timescale of the full disease trajectory.

The three nested cycles operate concurrently and interact. The short cycle determines the response to any single reactivation event; the medium cycle determines the rate of Phase II progression; the long cycle determines the trajectory across the entire lifespan. Therapeutic intervention can target any of the three cycles: short-cycle interventions (acute antivirals during reactivation) reduce immediate consequences; medium-cycle interventions (chronic antiviral suppression, anti-inflammatory therapy) reduce Phase II progression; long-cycle interventions (lifestyle modification, stress management, vaccine programs) reduce lifetime cumulative load.

9.3 Coupling to the Collapse Trilogy Axes

The viral trajectory framework couples to the three substrate axes of the Collapse trilogy through phase-specific mechanisms.

Bioenergetic axis (Phase I): Chronic viral antigenic exposure of the LC drives PARP-1 hyperactivation on inflammatory DNA damage, NAD+ depletion below the salvage threshold, and ISR engagement. The coupling to the bioenergetic axis is most direct in Phase I, where LC neurons are the principal site of both viral antigenic load and bioenergetic vulnerability. The Tryptophan Partition companion volume

(Gustafsson, 2026) develops the metabolic substrate of this coupling: chronic IDO induction shifts the tryptophan partition toward the kynurenine branch, providing de novo NAD+ at the same time as it withdraws substrate from the serotonergic branch. The viral driver, the bioenergetic axis, and the tryptophan partition are therefore three views of the same molecular system.

Microglial axis (Phase II): Chronic viral antigenic exposure of forebrain microglia drives the homeostatic-to-DAM/MGnD transition through sustained type-I IFN signaling. The coupling to the microglial axis is the central mechanism of Phase II, and it is the phase in which the viral trajectory framework has the most direct overlap with the Homeostatic Microglial Collapse thesis. The intervention point in Phase II is most plausibly through antiviral suppression combined with microglial-state-stabilizing therapy (TREM2 agonists, anti-inflammatory cytokine modulation, anti-CD38 to address the immunometabolic substrate).

Synaptic axis (Phase III): Chronic viral antigenic exposure produces the inflammatory milieu in which complement priming and MMP-9 expression are sustained, accelerating synaptic loss and PNN digestion. The coupling to the synaptic axis is less direct than in Phase I or Phase II because the immediate driver of synaptic loss is complement and MMP-9 activity rather than viral antigen per se, but the chronic viral antigenic load is the upstream driver of the complement and MMP-9 priming. The intervention point in Phase III combines antiviral suppression with anti-complement (ANX005, pegcetacoplan) and MMP-9 inhibition (JNJ0966, others in development).

9.4 The Locus Coeruleus as Anatomical Lynchpin

The LC is the anatomical lynchpin of the integrated framework. It is the principal target of Phase I viral antigenic load (through the trigeminal–LC retrograde axis); it is the principal site of Phase I bioenergetic vulnerability (PARP-1 hyperactivation, NAD+ depletion); and it is the principal source of the descending noradrenergic anti-inflammatory tone whose loss permits Phase II microglial activation. The LC therefore couples Phase I to Phase II through the descending projection: as Phase I LC degeneration progresses, the descending noradrenergic tone weakens, and the forebrain microglia transition more readily into the DAM/MGnD state. The framework predicts that interventions preserving LC function in Phase I should delay Phase II onset.

9.5 The Microglial Transition as Immunological Lynchpin

The microglial homeostatic-to-DAM/MGnD transition is the immunological lynchpin of the integrated framework. It is the consequence of cumulative Phase I and Phase II antigenic load; it is the principal mechanism of Phase II progression; and it is the upstream driver of Phase III complement priming and PNN digestion. The transition is therefore the point in the trajectory at which intervention can most plausibly modify the entire downstream course of the disease. The framework predicts that interventions that stabilize the microglial homeostatic state — antiviral suppression to reduce antigenic drive, TREM2 agonists to maintain microglial fitness, anti-CD38 to address the immunometabolic substrate, anti-complement to reduce the consequence of the transition — should produce substantial delays in Phase III decompensation.

9.6 The Synaptic Decompensation as Functional Lynchpin

The synaptic decompensation in Phase III is the functional lynchpin: it is the level at which cognitive deficits emerge and at which clinical disease becomes manifest. The intervention in Phase III is more constrained because the upstream pathology has already accumulated, but the framework predicts that anti-complement therapy (addressing the immediate driver of synaptic loss) combined with continued antiviral suppression (addressing the antigenic drive) should produce meaningful clinical benefit in early Phase III. The Phase III interventions are unlikely to halt disease progression, but they can plausibly slow it substantially.

9.7 A Formal Account of Phase Coupling

The framework can be formalized as follows. Let \(V(t)\) be the cumulative viral antigenic load on brain at time \(t\), with \(V(t) = \int_0^t r(s)\, ds\), where \(r(s)\) is the rate of reactivation at time \(s\). Let \(P_1(t), P_2(t), P_3(t)\) be the pathological burdens at Phase I, Phase II, and Phase III respectively. The framework predicts:

- \(P_1(t) = f_1(V(t), \alpha_1(t))\), where \(\alpha_1(t)\) is the LC-specific vulnerability (APOE genotype, bioenergetic reserve, individual variation).
- \(P_2(t) = f_2(V(t), P_1(t), \alpha_2(t))\), where \(\alpha_2(t)\) is the microglial-specific vulnerability and where Phase I pathology contributes to Phase II progression through the descending-LC and inflammatory mechanisms.

- $P_3(t) = f_3(V(t), P_2(t), \alpha_3(t))$, where $\alpha_3(t)$ is the synaptic-specific vulnerability and where Phase II pathology contributes to Phase III progression through complement priming and PNN digestion.

The reactivation rate $r(t)$ is itself a function of host state: $r(t) = g(t, V(t), P_1(t), P_2(t))$ — that is, reactivation rate increases with age and with accumulating pathology, producing the self-amplifying long-cycle behavior. The full system is a set of coupled differential equations with positive feedback that produces the observed trajectory of the disease.

The therapeutic implications follow from the formalism. Interventions that reduce $r(t)$ at any age reduce $V(t)$ for all subsequent times and therefore reduce P_1, P_2, P_3 at all subsequent times. The earlier the intervention, the larger the cumulative benefit. The framework therefore predicts that prophylactic antiviral suppression in middle age — when reactivation rates are rising but cumulative load is still modest — should produce the largest population-level reduction in lifetime dementia incidence. The zoster-vaccine natural experiments are consistent with this prediction: they intervened on $r(t)$ at ages 70+, and they observed a 20 percent reduction in subsequent dementia. The framework predicts that intervention at earlier ages should produce larger effects.

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10. Chapter VII — Critical Reassessment: What the Viral Hypothesis Does and Does Not Explain

10.1 The Seroprevalence Problem

The most frequent objection to the HSV-1 hypothesis of Alzheimer's disease is the seroprevalence problem. HSV-1 seropositivity in adults exceeds 70 percent in most populations and approaches 95 percent in some. If HSV-1 were a sufficient cause of AD, the population-attributable fraction would be implausibly large; if HSV-1 were a necessary cause, almost all adults should develop AD. Neither prediction matches the epidemiology, which estimates the lifetime risk of AD at approximately 10–15 percent in unselected populations.

The framework's response to the seroprevalence problem is that HSV-1 *seropositivity* is not the operative variable; HSV-1 *reactivation frequency* across decades is. The seroprevalence problem rests on the conflation of two distinct

exposure measures. Seropositivity records whether an individual has ever been infected; it does not record how frequently the latent virus has reactivated over the subsequent decades. The viral pathogenicity, on the framework, is a function of cumulative reactivation, not of binary seropositivity. Individuals who have been HSV-1-seropositive for sixty years but have reactivated rarely have minimal cumulative antigenic load on brain; individuals seropositive for the same period who have reactivated frequently have substantial cumulative load. The framework predicts that the latter group should be substantially overrepresented in AD incidence — a prediction that the antiviral cohort studies (which observe the protective effect of anti-HSV antivirals in HSV-positive patients) are consistent with.

The seroprevalence problem is therefore not a refutation of the viral hypothesis but a clarification of which exposure variable is operative. The reactivation-frequency framing is consistent with the high seroprevalence (which is universal) and with the modest AD incidence (which depends on reactivation frequency, which varies widely across individuals). The framing is also consistent with the gene–environment interaction with APOE ε4, which modifies reactivation efficiency.

10.2 Population Attributable Fraction Estimates

The population-attributable fraction (PAF) for HSV-1 in AD is difficult to estimate with the available data, but the available evidence suggests it is substantial. The Lopatko Lindman et al. (2021) Swedish cohort analysis estimated that approximately 20 percent of AD cases in their cohort were attributable to HSV-1-associated mechanisms; the Linard et al. (2020) French analysis produced a similar estimate. The Eyting et al. (2025) zoster-vaccine natural experiment supplies a lower bound on the PAF for VZV-associated mechanisms of approximately 20 percent. The combined PAF across multiple herpesviruses, with overlap and interaction, is plausibly in the 30–50 percent range — substantial but not exclusive of other mechanisms.

The PAF estimates support the framework's claim that viruses are a load-bearing input to AD without supporting the stronger claim that they are *the* exclusive cause. A 30–50 percent PAF is consistent with a model in which viral exposure is necessary in many cases but in which other mechanisms (vascular, metabolic, genetic) contribute the remainder.

10.3 Failed and Equivocal Antiviral Trials

The principal evidentiary weakness of the viral hypothesis is the absence of definitive randomized trial evidence. The VALAD trial (Devanand et al., 2020) is the only randomized trial of antiviral therapy in symptomatic AD patients to date, and it was small (n=130), short-duration (78 weeks), and underpowered to detect modest clinical effects. The primary outcomes were equivocal, with non-significant trends favoring valacyclovir on some measures and not others. The trial cannot be cited as positive evidence for antiviral benefit, but it also cannot be cited as definitive negative evidence: the trial was not powered to detect the effect sizes that the framework predicts.

The framework's response to the failed trials is that antiviral therapy in symptomatic AD addresses the disease at the wrong phase. The viral driver is cumulative across decades, and intervention in Phase III after substantial cumulative pathology has already accumulated is unlikely to produce substantial clinical benefit. The framework predicts that antiviral therapy will be most effective when administered prophylactically in middle age — before substantial cumulative load has accumulated — and that randomized trials with such an enrollment criterion have not yet been conducted. The Eyting natural experiment is the closest available approximation, and it produced a substantial positive effect.

10.4 The Allnutt Critique of Readhead

The Allnutt et al. (2020) reanalysis of the Readhead et al. (2018) HHV-6 findings is the most important methodological challenge to the modern viral hypothesis. The Allnutt analysis used stricter pathogen-detection methodology, additional control datasets, and corrections for batch effects that the original analysis had not applied. The reanalysis found HHV-6 detection in a substantially smaller fraction of brains than the original report had suggested, and the case-control differences did not reach statistical robustness.

The framework's response is that the Readhead findings may have been overstated in their original form but that the underlying observation — HHV-6 transcripts detectable in a fraction of AD brains — remains valid. The framework does not require HHV-6 to be a major contributor in all patients; it requires only that cumulative pathogen load across multiple viruses produces the Phase II and Phase III pathology. The framework is therefore robust to the Allnutt critique: even if

HHV-6 contributes in a smaller fraction of cases than the original Readhead report suggested, the cumulative pathogen-load framing absorbs the smaller contribution without difficulty.

The dispute is, however, a useful reminder that the viral evidence has come substantially from a small set of laboratories and that broader replication would strengthen the field. The Cairns 3D-brain-model findings, the Itzhaki-Wozniak colocalization findings, and the antimicrobial-Aβ findings would all benefit from independent replication across multiple groups.

10.5 Causal Direction: Does AD Pathology Increase Reactivation?

A serious challenge to the viral hypothesis is the causal-direction question. The observed correlation between HSV-1 reactivation markers and AD pathology could reflect either direction of causation: viral reactivation could drive AD pathology, or AD pathology could increase viral reactivation by impairing immune surveillance. The framework as developed here treats both directions as operative — Phase III immunosenescence does increase reactivation rates, and Phase II microglial pathology does reduce antiviral surveillance — but the framework also requires that the *initial* direction of causation be viral-to-pathology rather than the reverse, since the iterative cycle has to start somewhere.

The strongest evidence for the viral-to-pathology direction is the antiviral-cohort literature, which observes reduced subsequent AD incidence in patients prescribed anti-HSV antivirals years before AD diagnosis. The pre-diagnostic timing makes the reverse-causation interpretation difficult: if AD pathology drove the antiviral prescriptions, the prescriptions would be expected to follow rather than precede the dementia diagnosis. The Eyting et al. (2025) regression-discontinuity design provides even stronger evidence for the viral-to-pathology direction, because the policy-induced vaccine exposure is unrelated to any pre-existing AD pathology in the cohort.

The framework therefore treats the causal direction as established for the *initial* perturbation but acknowledges that bidirectional coupling operates once the disease is underway. The bidirectional coupling is part of what makes Phase III progression so rapid — the failure of viral suppression at one level produces additional viral antigenic load that drives further failure.

10.6 The Limits of the Tanzi–Moir Antimicrobial Hypothesis

The antimicrobial Aβ hypothesis advanced by Soscia, Kumar, Eimer, Moir, and Tanzi has substantial in vitro and in vivo support but is not without limitations. The principal limitations are:

First, the in vitro concentrations of Aβ required to demonstrate antimicrobial activity in cell-free assays are substantially higher than those measured in plasma or CSF under physiological conditions. The response is that the relevant concentrations are those achieved *locally*, in proximity to microbial surfaces, but the local concentration measurements that would directly validate this response have not been performed in vivo.

Second, the antimicrobial framing does not by itself explain the specific spatial distribution of plaques. Why are plaques concentrated in cortex and hippocampus rather than in the regions of highest pathogen exposure (e.g., olfactory bulb, brainstem)? The framework's response is that the spatial distribution reflects the connectomic propagation of pathology along anatomical pathways rather than the geography of initial infection, but the response is not yet fully empirically validated.

Third, the antimicrobial framing does not explain why some individuals with substantial viral exposure do not develop AD. The framework's response is that cumulative load, APOE genotype, microglial transcriptional landscape, and other host factors modify the response to viral exposure — but the response shifts the explanatory burden onto these modifying factors and weakens the predictive specificity of the antimicrobial framing alone.

The framework here treats the antimicrobial Aβ hypothesis as strongly suggestive and increasingly well-supported in vivo but not yet definitively established. The hypothesis is the strongest available mechanistic interpretation of the Aβ–virus relationship, but its strongest claims (Aβ deposition is *strictly* an antimicrobial response and would not occur in the absence of pathogen exposure) require additional evidence. The framework adopts the weaker form: Aβ has an antimicrobial role, and the antimicrobial role contributes substantially to AD amyloid deposition, but other mechanisms of Aβ deposition cannot yet be ruled out.

10.7 The Eyting et al. 2025 Nature Paper: Strongest Causal Evidence to Date

The Eyting et al. (2025, *Nature*) regression-discontinuity analysis of the Welsh zoster vaccination program is the strongest piece of causal evidence in the contemporary viral-hypothesis literature. The methodology is uncommonly powerful: the program's sharp birth-date eligibility cutoff produced two demographically nearly-identical groups separated only by policy-induced vaccine exposure, and the cumulative dementia incidence over the subsequent seven years differed substantially between the two groups (approximately 20 percent reduction in the vaccinated group). The design approximates randomization in a way that pharmacological trials of disease-modifying therapy in mid-stage AD have not achieved.

The Eyting result has been replicated in Australian data (Liu et al., 2025), and concordant findings have been reported for the older Zostavax formulation (Schnier et al., 2024). The convergence of three independent national-level natural experiments on a substantial reduction in dementia incidence following zoster vaccination is the strongest case yet made for a load-bearing role of viruses in AD pathogenesis.

The Eyting result does not by itself prove that HSV-1 reactivation is the operative mechanism — the vaccine targets VZV, not HSV-1 — but it establishes that suppression of one herpesvirus produces substantial reduction in dementia incidence. The mechanistic interpretation through VZV-induced transactivation of HSV-1 (Cairns et al., 2022) supplies a plausible explanation but is not yet directly validated in the vaccinated population. The interpretation predicts that the Eyting effect should be partially mediated by reductions in HSV-1 reactivation markers — a prediction that future analyses of the Welsh and Australian cohorts could test directly.

10.8 What the Framework Predicts That the Amyloid-Cascade and Tau-Propagation Frameworks Do Not

The viral trajectory framework makes several predictions that the conventional amyloid-cascade and tau-propagation frameworks do not. First, it predicts that prophylactic antiviral suppression in middle age should reduce subsequent dementia incidence — a prediction the amyloid-cascade framework does not make. Second, it predicts that the combination of antiviral suppression with anti-amyloid therapy should be substantially more effective than either alone in late Phase II patients. Third, it predicts that vaccination programs against herpesviruses should reduce dementia incidence, with effect sizes proportional to the vaccine's efficacy at reducing viral reactivation. Fourth, it predicts that markers of chronic viral antigenic load — kynurenine-to-tryptophan ratio, anti-viral IgG titers and avidity, CSF T-cell clones — should outperform amyloid and tau biomarkers as early predictors of disease progression in middle-aged adults. Fifth, it predicts that acute viral perturbations (SARS-CoV-2, severe influenza) should accelerate dementia incidence in patients in late Phase II — a prediction the cohort data are broadly consistent with. Sixth, it predicts that the protective effect of education and cognitive engagement (the "cognitive reserve" effect) may be partially mediated by stress reduction and improved immune competence, which reduce reactivation frequency.

Each of these predictions is testable. Several are already partially confirmed. The framework's distinctive contribution is to organize the available evidence around a single temporal scaffolding that supplies a coherent set of testable predictions across the disease trajectory.

11. Chapter VIII — Therapeutic Implications and Falsifiable Predictions

11.1 Prophylactic Antiviral Suppression in APOE ε4 Carriers

The framework's most direct therapeutic implication is prophylactic antiviral suppression in middle-aged APOE ε4 carriers. The argument runs as follows. APOE ε4 carriers have elevated HSV-1 reactivation rates and elevated cumulative viral antigenic load on brain across decades. Chronic low-dose valacyclovir (typically 500 mg daily, the dose used for HSV-1 outbreak prophylaxis in cold-sore-prone patients) suppresses HSV-1 reactivation substantially and is well-tolerated for years of continuous use. The framework predicts that chronic prophylactic valacyclovir in APOE ε4 carriers from age 40 onward should produce substantial reduction in subsequent dementia incidence.

The trial design implied by this prediction is a randomized controlled trial in cognitively normal APOE ε4 carriers aged 40–55, randomized to chronic valacyclovir or placebo, with follow-up of 10–15 years and primary outcomes including subjective cognitive decline, MCI conversion, and amyloid PET status. The trial is feasible — the population is large (APOE ε4 heterozygotes constitute approximately 15 percent of European-descent populations), the intervention is inexpensive and well-tolerated, and the outcome measures are well-established. The trial has not yet been conducted, in part because the pharmacoeconomics of generic valacyclovir do not support industry investment.

11.2 Vaccine Repurposing: Zoster, Influenza, BCG

The vaccine evidence supports a parallel therapeutic implication: targeted vaccination programs to suppress reactivation of the highest-impact pathogens. The zoster vaccine has the strongest evidence base (Eyting et al., 2025; Liu et al., 2025; Schnier et al., 2024) and should be deployed broadly in age-appropriate populations. The flu vaccine has weaker but suggestive evidence (Lehrer and Rheinstein, 2022; Wilkinson et al., 2022) for an anti-dementia effect, plausibly mediated by reduced inflammatory perturbations from severe influenza. The BCG vaccine has been associated with reduced dementia incidence in some cohorts (Klinger et al., 2021), plausibly through trained-immunity effects on innate immunity.

The framework predicts that combination vaccination programs — zoster + flu annually + targeted herpesvirus vaccines as they become available — should produce additive reductions in dementia incidence. The trial design would test the combination against single-vaccine or placebo arms in age-appropriate cohorts.

11.3 Phase-Specific Therapeutic Windows

The framework's most distinctive therapeutic implication is that interventions are *phase-specific*: the appropriate intervention depends on the patient's current disease phase, and an intervention appropriate for one phase may be ineffective or counterproductive in another. The phase-specific recommendations are:

- **Phase I (ages 20–50, subclinical):** Prophylactic antiviral suppression, stress management, sleep optimization, and lifestyle interventions to reduce reactivation rate. NAD+ precursor supplementation to support LC bioenergetic function. Targeted vaccination as available.
- **Phase II (ages 50–70, SCD/MCI):** Continued antiviral suppression combined with anti-amyloid monoclonal antibodies (lecanemab, donanemab) and emerging anti-tau therapeutics. Anti-CD38 antibody therapy to address the immunometabolic substrate. Anti-inflammatory cytokine modulation (e.g., IL-1β blockade) in carefully selected patients. KMO inhibition to rebalance the tryptophan partition.
- **Phase III (ages 70+, dementia):** Anti-complement therapy (ANX005, pegcetacoplan) to address the immediate driver of synaptic loss. Continued antiviral suppression to reduce ongoing antigenic load. Symptomatic therapy (cholinesterase inhibitors, memantine) for cognitive symptoms.

11.4 Combination with Tryptophan Partition Therapy

The Tryptophan Partition companion volume (Gustafsson, 2026) develops the case for tryptophan-partition therapy: IDO inhibitors, KMO inhibitors, NAD+ precursors (nicotinamide riboside, NMN), and tryptophan supplementation. The viral framework predicts that tryptophan-partition therapy and antiviral therapy should be combinatorially effective because antiviral therapy reduces the upstream IDO induction signal (chronic viral antigenic load) while tryptophan-partition therapy addresses the downstream metabolic consequences. The combination is therefore not redundant but synergistic.

11.5 Combination with Anti-CD38

The Schwartz–Chini collaboration (Schwartz and Chini, 2025) demonstrated that anti-CD38 antibody therapy in aged mice simultaneously rescues immune function, brain NAD+ levels, peripheral metabolism, and cognition. The cross-substrate rescue is the cleanest contemporary demonstration of the immunometabolic coupling that the viral trajectory framework presupposes. The framework predicts that anti-CD38 therapy combined with antiviral suppression should be substantially more effective in Phase II than either alone, because the antiviral component reduces the upstream antigenic drive while the anti-CD38 component addresses the immunometabolic substrate erosion.

11.6 Combination with Anti-Complement

The Stevens laboratory's anti-complement therapy (ANX005, pegcetacoplan) addresses the immediate driver of synaptic loss in Phase III. The framework predicts that anti-complement therapy combined with continued antiviral suppression should produce meaningful clinical benefit in early Phase III, because the antiviral component reduces the ongoing inflammatory drive that sustains complement priming while the anti-complement component addresses the immediate cytotoxic consequence.

11.7 Six Falsifiable Predictions

The framework generates six falsifiable predictions that can be tested with currently available or near-term-feasible methodology:

- **Reactivation-frequency prediction.** Markers of HSV-1 reactivation frequency (anti-HSV IgG avidity, salivary viral RNA shedding rates, plasma HSV-1 DNA in subclinical-shedding cohorts) should outperform HSV-1 seropositivity as predictors of subsequent dementia incidence in middle-aged cohorts. Falsification: if reactivation-frequency markers do not predict dementia incidence above seropositivity, the framework's central premise (that reactivation rather than infection is the operative variable) is undermined.
- **APOE × reactivation interaction.** The dementia-protective effect of antiviral therapy should be substantially larger in APOE ε4 carriers than in non-carriers. Falsification: if the protective effect is equivalent across APOE genotypes, the gene–virus interaction interpretation is undermined.

• **Zoster mechanism prediction.** The dementia-protective effect of zoster vaccination should be partially mediated by reductions in HSV-1 reactivation markers (the Cairns transactivation mechanism). Falsification: if the zoster-vaccine effect on dementia is not mediated by HSV-1 reactivation markers, the transactivation interpretation is undermined and the trained-immunity interpretation gains weight.

• **Phase III combination prediction.** Anti-complement therapy combined with continued antiviral suppression should produce substantially greater clinical benefit in early Phase III patients than anti-complement monotherapy. Falsification: if the combination is no more effective than anti-complement alone, the framework's claim that ongoing antigenic drive sustains Phase III progression is undermined.

• **COVID accelerator prediction.** SARS-CoV-2 infection should accelerate dementia incidence specifically in patients with elevated baseline markers of chronic viral antigenic load (kynurenine ratio, anti-HSV IgG avidity); patients without elevated baseline markers should show smaller post-COVID dementia incidence elevation. Falsification: if the post-COVID dementia association is independent of baseline antigenic-load markers, the "two-hit" interpretation is undermined.

• **Tryptophan-partition mediation.** The dementia-protective effect of antiviral therapy should be partially mediated by reductions in plasma kynurenine-to-tryptophan ratio over time. Falsification: if the antiviral effect on dementia is not mediated by kynurenine-pathway markers, the coupling between viral antigenic load and tryptophan partition is weakened.

Each prediction is testable with currently available or near-term-feasible methodology. The framework therefore makes a substantial empirical commitment and is genuinely falsifiable.

12. Conclusion

The viral hypothesis of Alzheimer's disease has been advanced in one form or another since Oskar Fischer's observation of inflammatory glial responses around plaques in 1907. The hypothesis has been variably suppressed and revived through the twentieth century, and it has been substantially clarified by the molecular evidence accumulated since Itzhaki's 1997 paper. The contemporary form of the hypothesis — developed in this dissertation as the "viral trajectory framework" — treats viruses neither as the unique cause of Alzheimer's disease nor as incidental passengers, but as a *temporal driver* whose interaction with the host changes mechanism, anatomy, and consequence at each of the three temporal phases of the disease.

The framework integrates the Itzhaki HSV-1 molecular tradition, the Tanzi–Moir antimicrobial Aβ tradition, the Readhead HHV-6 program (with the Allnutt caveats), the Bjornevik EBV/MS tradition, the Gate adaptive-immunity tradition, the Cairns 3D-brain-model tradition, the antiviral cohort literature, and the regression-discontinuity zoster-vaccine evidence. The integrating principle is the three-phase temporal architecture: Phase I bioenergetic prodrome (LC, antimicrobial Aβ deposition); Phase II microglial inflection (hippocampus, DAM transition, chronic IDO induction); Phase III synaptic decompensation (PV+/PNN, complement priming, immunosenescence-driven reactivation). Each phase has phase-specific viral mechanisms; each phase couples to the next through identifiable molecular and anatomical pathways.

The framework retains the amyloid and tau pathologies as central to the disease but reinterprets them as the host's responses to a chronic antigenic drive distributed across decades, rather than as autonomous proteinopathies that happen to occur in the same brain. The reinterpretation explains the modest clinical efficacy of pure anti-amyloid monotherapy in late-Phase trials — these therapies address the host response without addressing the antigenic drive that triggers it — and it predicts that combination therapy with antiviral suppression, anti-CD38, anti-complement, and tryptophan-partition rebalancing should be substantially more effective in phase-appropriate windows.

The framework is testable. Six falsifiable predictions are developed in Chapter VIII, each tractable with currently available or near-term-feasible methodology. The strongest contemporary causal evidence — the Eyting et al. (2025)

regression-discontinuity natural experiment in Wales, the Liu et al. (2025) Australian replication, and the Schnier et al. (2024) findings — already partially confirms the framework's central prediction that suppression of herpesvirus reactivation reduces dementia incidence. The framework does not claim that the question is settled; it claims that the question is now substantially clearer than it has been at any previous point in the field's history, and that the evidence increasingly supports the *temporal* viral interpretation that this dissertation has developed.

The Collapse trilogy of which this dissertation is the fifth companion volume — alongside *Convergent Synaptic Collapse*, *Homeostatic Microglial Collapse*, *Bioenergetic Collapse*, and the *Tryptophan Partition* — was an attempt to articulate the convergent infrastructure on which the proteinopathy-specific mechanisms of neurodegeneration run. The trilogy identified three substrate axes (synaptic, microglial, bioenergetic); the Tryptophan Partition companion identified a shared metabolic substrate that couples the three axes through tryptophan allocation; the present Viral Trajectory companion identifies a shared *temporal driver* that runs the system through its three phases. The two companions are complementary rather than competing: tryptophan partition is the metabolic substrate, viral trajectory is the temporal driver, and together they supply the molecular and temporal scaffolding that the substrate-level Collapse axes operate within.

The clinical implication of the integrated framework is that Alzheimer's disease will be substantially better controlled when therapeutics are deployed in *phase-appropriate combinations*: prophylactic antiviral suppression in middle age for those at elevated genetic and exposure risk; combination antiviral + anti-amyloid + anti-CD38 + tryptophan-partition therapy in Phase II; combination anti-complement + continued antiviral + symptomatic therapy in Phase III. The era of monotherapy targeting a single molecular endpoint is, on this account, ending; the era of phase-appropriate combination therapy targeting the temporal viral driver, the metabolic substrate, and the substrate-level collapse axes simultaneously is beginning.

Oskar Fischer's century-old observation that the inflammatory glial response in senile dementia was not a bystander but a participant has, after a long interval, been substantially vindicated. The framework developed here is the contemporary articulation of Fischer's intuition, refined by the molecular biology, the genetics, the epidemiology, and the natural-experiment evidence accumulated in the intervening

120 years. The question Fischer left open — *what is the inflammatory stimulus that drives the chronic glial response* — now has a partial answer: latent and reactivating herpesviruses, principally HSV-1, distributed across decades, exploiting phase-specific weaknesses of the host immune and metabolic systems. The answer is not yet definitive, but it is substantially more defensible than at any previous point in the field's history, and the therapeutic implications are substantial.

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