Keystone Epitope Theory in Deep Time: How Viral Endogenization and Sexual Dimorphism Wrote the Genomic Syllabus of Immunity.

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Abstract

Persistent infections and their antigenic "teaching sets" can dominate immune memory, but immunodominance often fails as a proxy for protection. Keystone Epitope Theory (KET) reframes this gap by treating immunity as an attention-allocation system operating in an ecological landscape of (i) long-lived "keystone organisms" that engage immunity repeatedly using relatively stable epitopes and (ii) rapidly evolving "adaptable organisms" that can deploy decoy epitopes to divert immune attention. This review extends KET into evolutionary time. We integrate evidence that "silent" sequence space is not silent (synonymous selection, codon usage, RNA-structure constraints), that host genomes are heavily shaped by viral sequence acquisition (endogenous retroviruses and other integrated viral DNA), and that perturbations such as drug hypersensitivity, critical illness, and SARS-CoV-2 infection are followed by ordered viral reactivation dynamics. We then propose non-exclusive models for why hosts retain and sometimes express endogenized viral sequences, including established mechanisms (regulatory exaptation; restriction modules; innate "viral mimicry") and KET-motivated hypotheses (decoy detox through negative selection; immune calibration via reference epitopes). Finally, we outline

experiments and multi-omic cohort designs that can discriminate among competing mechanisms and convert KET from a descriptive framework into a predictive science.

Terminology and scope

Keystone Epitope Theory employs a specific vocabulary that warrants standardization up front. In KET, **keystone organisms** are persistent infections that establish long-term residence and repeatedly engage immune surveillance using relatively **stable epitopes**; **adaptable organisms** are rapidly evolving pathogens (often RNA viruses) that can exploit immunodominance by presenting **decoy epitopes** (immunodominant but non-protective) while **constrained protective epitopes** remain subdominant or harder to access [1] [2]. KET is designed to explain why immune memory can be "strong" yet strategically misallocated, and why protection sometimes comes from epitopes that are not the most immunodominant.

Clarification on tolerance: KET does not assume keystone epitopes are inherently untolerizable within their niches. Instead, keystone-trained responses are typically managed as regulated equilibrium with niche-specific inhibitory set-points. Keystone-mimetic stimuli can remain clinically silent when subthreshold, but high mimic burden (for example, many mimicking targets or high presentation density) can overwhelm that control and trigger pathology.

This review focuses on three connected questions:

1. **Deep-time coevolution:** How might persistent DNA viruses and rapidly adapting RNA viruses co-shape host immune architecture over evolutionary time?
2. **Endogenization:** Why do host genomes retain large amounts of viral sequence, and when does expression of those sequences plausibly benefit the host?
3. **Perturbation readouts:** Can ordered viral reactivation after stress, hypersensitivity reactions, and COVID-19 provide measurable fingerprints of immune "keystone circuitry," and how might this inform KET?

These three threads are integrated in a deep-time schematic that frames the remainder of the Perspective (Fig. 1).

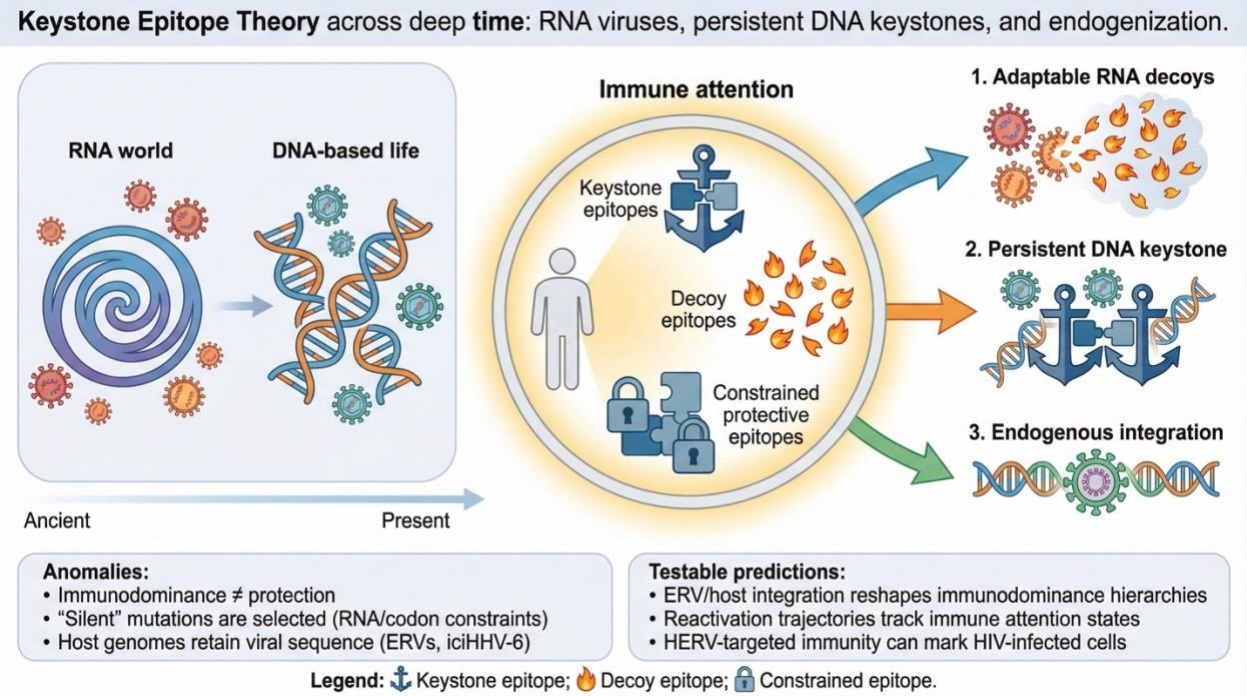

Figure 1 | Deep-time framing of Keystone Epitope Theory across the RNA-to-DNA transition.

Conceptual schematic linking (left) the proposed RNA world and emergence of RNA viruses with (bottom) DNA-based life and persistent DNA viruses. The central "immune attention" lens represents the host immune system as an allocation process shaped by prior antigenic experience. Keystone epitopes (anchor icon) represent conserved, repeatedly encountered epitopes that can reinforce durable immune circuits, whereas decoy epitopes (flame/leaf icons) represent targets that can become immunodominant yet fail to provide protection. The right side illustrates three non-exclusive long-term outcomes: **(1)** adaptable RNA viruses exploit immune attention by generating decoy epitopes; **(2)** persistent DNA viruses act as long-lived "keystone" exposures that stabilize immune circuitry via conserved epitopes; and **(3)** endogenous integration incorporates viral sequence into host genomes, enabling long-term regulatory and immunological consequences, including potential effects on antigen presentation, tolerance, and baseline immune set-points that can be breached under high mimicry burden.

1. The unmet need: immunodominance is reliable biology, but an unreliable strategy

Immunodominance is one of immunology's most reproducible patterns: for any complex antigenic mixture, immune responses concentrate on a minority of epitopes [3 4]. Yet "dominant" is not synonymous with "protective." Across multiple viral systems, strongly targeted epitopes can be mutable, functionally dispensable, or structurally positioned to

absorb immune pressure without meaningful loss of pathogen fitness, which is the operational definition of a decoy [3] [5]. This mismatch is particularly acute in chronic infections, where immune engagement is sustained long enough for both pathogen evolution and host immunological reinforcement to occur [6] [7].

KET's core move is to treat this mismatch as a **systems property**: immune memory is built under constraints (developmental timing, antigen persistence, competition among clones, and network reinforcement), and pathogens can exploit the resulting "attention economy" by presenting attractive but strategically low-value targets [1] [1]. The long-term consequence is that coevolution is not only about "escape mutations," but also about **who gets to write the immune system's syllabus**.

2. A deep-time reframing: from an RNA world to DNA-based immune memory

2.1 RNA predates DNA, but DNA made long-term information storage cheap

The "RNA world" hypothesis proposes that early life relied on RNA for both information storage and catalysis, with DNA arising later as a more stable information medium [8] [9]. Multiple evolutionary models argue that viruses may have contributed key innovations in DNA replication and the transition to DNA genomes, turning viruses from mere parasites into evolutionary engineers [10] [11].

KET is of interest in this context because immunity is itself a **memory system**. In vertebrates, adaptive immunity stores information in long-lived lymphocyte populations and their clonal lineages. Persistent DNA viruses, especially herpesviruses, are masters of **long-lived antigenic presence** and immune modulation [6] [12]. From a KET perspective, they are plausible candidates to serve as keystone organisms whose repeated exposures reinforce stable immune circuits.

Over deep evolutionary time, host-microbe relationships have been dynamic, with some lineages tightening toward structured mutualistic persistence and others exploiting transient ecological opportunity [1]. Keystone organisms represent one outcome of this churn, but immune calibration likely reflects layered exposures. Specialist niche residents (for example chronic colonizers such as *H. pylori*) and long-lived helminth and protozoan infections (for example *Schistosoma*, *Strongyloides*, *Toxoplasma*) can occupy hosts for decades and deploy immune-modulating and mimicry strategies [1]. These organisms may not generate the same species-wide, multi-arm imprinting profile as keystones, but they plausibly contribute to compartmental regulatory setpoints and developmental timing effects that shape later susceptibility to allergy, hypersensitivity, and autoimmunity [13].

2.2 Persistent DNA viruses as “keystones” and fast RNA viruses as “attention hackers”

Herpesviruses provide canonical persistence: lifelong latency with intermittent reactivation, antigen presentation during both lytic bursts and low-level persistence, and strong imprinting of T-cell repertoires [14] [15]. CMV further drives “memory inflation,” in which large fractions of the T-cell pool become CMV-specific over time [16] [15]. In KET terms, this is not just “a big response,” it is a **structural reallocation of immune capacity**.

RNA viruses, by contrast, frequently operate under high mutation rates and shorter generation times. This makes them well suited to produce and refine decoy epitopes, particularly in regions where mutations are tolerated and can be shaped by immune selection [17]. KET’s deep-time claim is not that RNA viruses always deploy decoys, but that the evolutionary affordances of RNA viruses make decoy deployment a recurrent, selectable strategy in the presence of reinforced immune attention. We summarize this ‘immune attention’ allocation problem as reinforced keystone circuitry confronted by adaptable decoy pressure and constrained protective targets (Fig. 2).

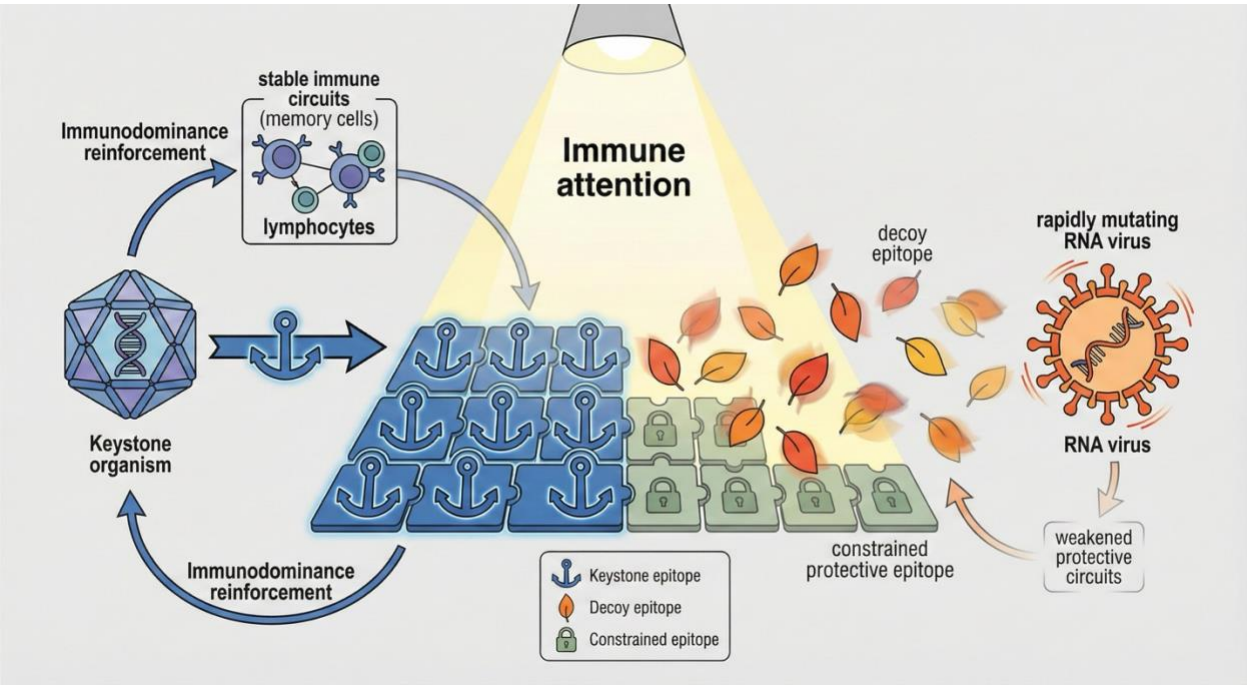

Figure 2 | Immune attention as a reinforced allocation problem: keystone, decoy, and constrained epitopes.
A schematic illustrating how persistent keystone organisms can reinforce stable immune circuits (memory cell pools and immunodominance hierarchies) that are beneficial when they focus on protective epitopes but become exploitable when adaptable pathogens supply abundant, mutable decoy epitopes. Keystone epitopes (anchor blocks) represent

reinforced, stable targets; constrained protective epitopes (locked blocks) represent protective targets with limited mutational room but that may be under-targeted; decoy epitopes (floating flames/leaves) represent adaptable targets that capture immune attention. The spotlight metaphor emphasizes that immune attention is finite: disproportionate allocation to decoys can weaken protective circuits and reshape downstream control of the broader virome.

3. "Silent" sequence space is not silent: synonymous selection and RNA constraints as coevolutionary levers

A recurring failure mode in immunology–evolution conversations is to implicitly equate "antigenic evolution" with amino-acid change. That assumption is increasingly untenable.

3.1 Synonymous selection and codon usage can be adaptive

HIV is a classic case where synonymous variation can carry biological meaning. Codon usage bias, context-dependent mutation pressures, and selection on RNA-level features (including splicing, packaging signals, and RNA structure) can constrain or channel evolution even when protein sequences remain unchanged [18] [19]. In practical terms, a pathogen can explore synonymous space to adjust expression, replication kinetics, or immune visibility without incurring the cost of amino acid substitutions that compromise protein function.

3.2 RNA structure imposes selection that can shape recombination and evolution

For coronaviruses, growing evidence indicates that conserved RNA structures, covarying base pairs, and genome-scale constraints can influence evolution and recombination landscapes [20] [21] [22]. This matters for KET because **constraints create predictable immovable targets**: regions that cannot change easily (even synonymously) become candidate constrained epitopes or constrained antigen-processing contexts. Conversely, unconstrained regions are candidate decoy playgrounds.

3.3 KET implication: decoys and constraints can be encoded at multiple layers

KET is often discussed in peptide-epitope language, but the mechanism can operate through RNA-level constraints that shape which peptides are produced, processed, or expressed at high abundance. The broad claim is straightforward: selection on synonymous sites and RNA structure can modulate antigen availability and mutational accessibility, thereby modulating which epitopes are attractive decoys and which are constrained protective targets [18] [20].

Three recurring anomalies motivate treating this as a coevolutionary systems problem rather than a purely protein-centric one (Fig. 3).

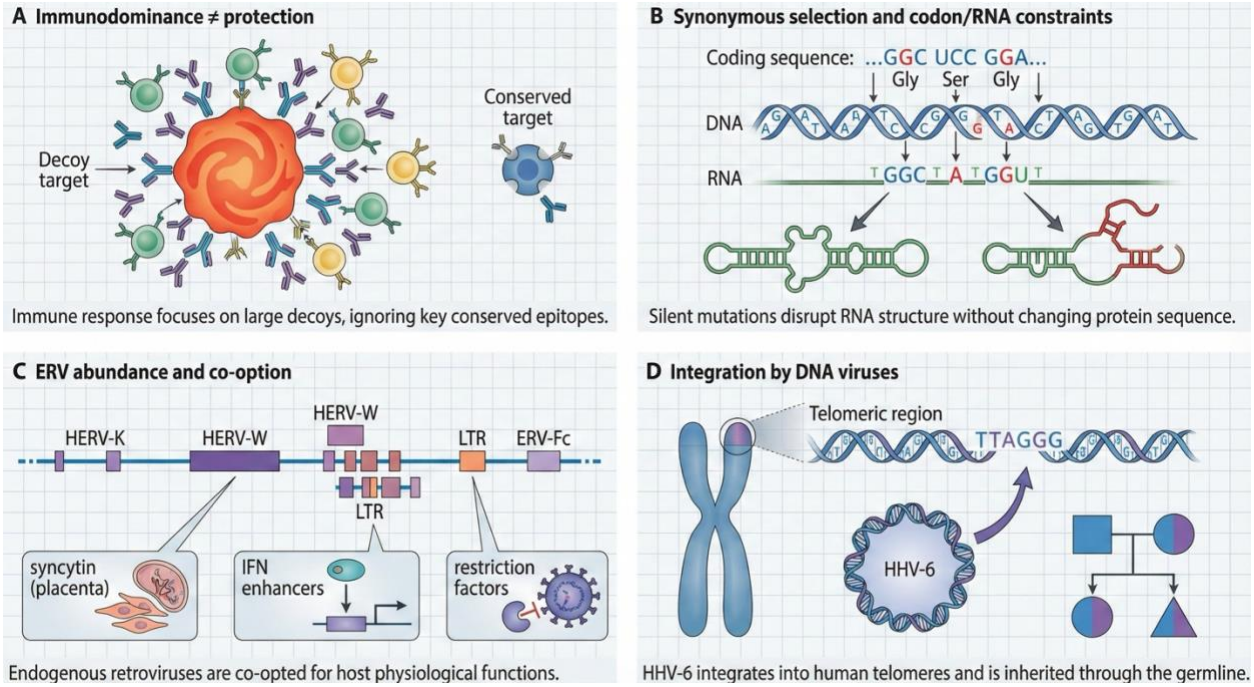

Figure 3 | Three anomalies motivating Keystone Epitope Theory in evolution and immunology.

(A) Immunodominance does not necessarily imply protection: immune responses can concentrate on highly visible decoy targets while ignoring conserved protective targets. **(B)** Synonymous selection and RNA-level constraints: “silent” mutations can be adaptive or constrained by codon usage, RNA structure, splicing, packaging signals, or other RNA functions, decoupling evolutionary inference from protein change alone. **(C)** Endogenous retrovirus (ERV) abundance and co-option: viral-derived sequence is widespread in vertebrate genomes and can be repurposed for host functions (illustrated examples include placental syncytins, interferon-linked enhancer activity, and restriction factor modules). **(D)** Integration by DNA viruses: inherited chromosomally integrated HHV-6 (iciHHV-6) illustrates that non-retroviral DNA viruses can integrate into telomeric regions and be transmitted through the germline, creating durable, measurable host–virus integration states.

4. Endogenization as evolutionary memory: why host genomes keep viral sequence

4.1 The empirical fact: viral sequence is a major component of vertebrate genomes

Endogenous retroviruses (ERVs) and other retroelements are pervasive in mammalian genomes. Estimates vary by annotation method, but ERV-derived sequences account for a substantial fraction of the human genome, and transposable element sequences constitute an even larger fraction [23] [24] [25]. Most insertions are neutral or deleterious; some are domesticated.

4.2 The established benefits: regulatory exaptation, restriction modules, and innate "viral mimicry"

Several host-beneficial roles for endogenized viral sequences are well supported:

Regulatory exaptation. ERV long terminal repeats and other transposon-derived elements can serve as promoters, enhancers, and insulators that rewire host gene regulation, including in immunity [25] [26]. In some contexts, ERV-derived regulatory elements act as interferon-inducible enhancers, effectively embedding antiviral response modules into the genome [26].

Physiological domestication. The syncytin genes, derived from ERV envelope proteins, are central to placental development and represent a canonical domestication event [27] [28].

Restriction modules. Some endogenous retroviral proteins can interfere with related exogenous viruses through receptor interference or other mechanisms, providing a form of "vaccination by fossilization" [29] [30].

Innate viral mimicry. ERV expression can generate dsRNA-like stimuli and activate pattern recognition receptors, thereby inducing interferon programs. This phenomenon has been exploited therapeutically in cancer to enhance antitumor immunity [31] [32].

These mechanisms already justify why endogenization is not merely a record of past infection, but a substrate for adaptation.

Building on these established mechanisms, we outline five non-exclusive models that add KET-motivated hypotheses to the canonical explanations for endogenization (Fig. 4).

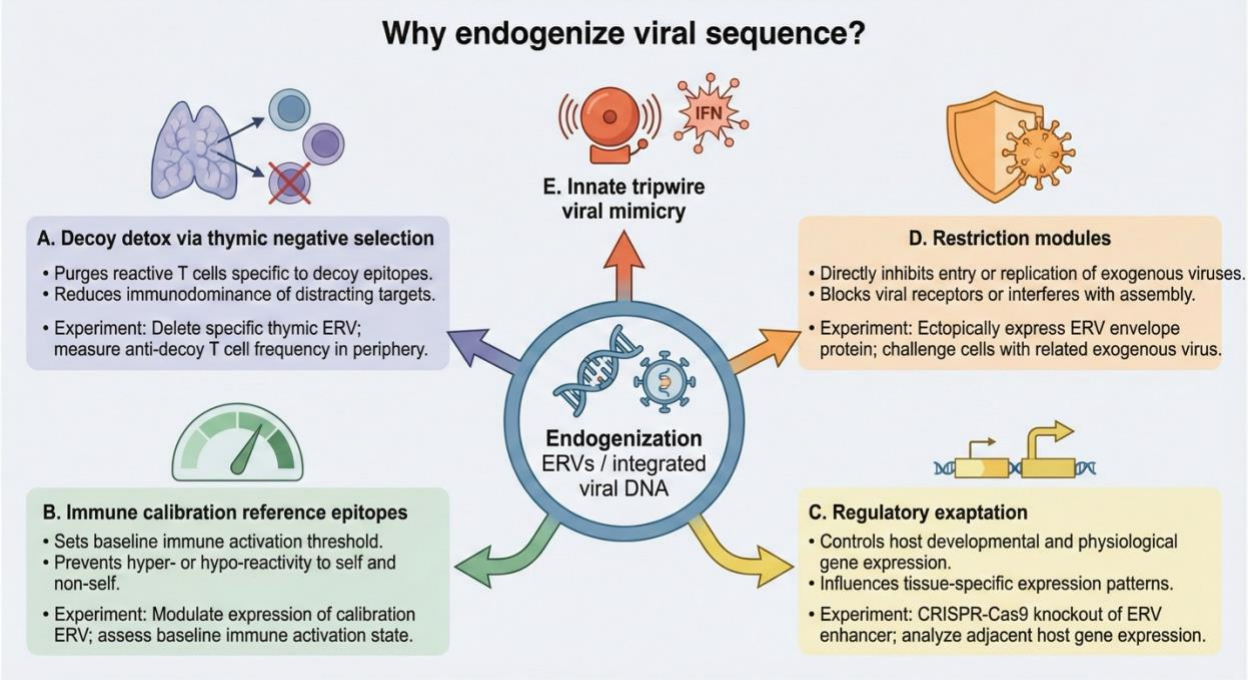

Figure 4 | Why endogenize viral sequence? Five non-exclusive models.
Five non-exclusive models for potential host-level benefit from retaining and expressing endogenized viral sequence (center circle: "Endogenization: ERVs / integrated viral DNA"). **(A)** *Decoy detox via thymic negative selection* (hypothesis): thymic expression of endogenized viral epitopes may delete T cells that would otherwise preferentially target decoy-like motifs. **(B)** *Immune calibration via reference epitopes* (hypothesis): persistent endogenous expression may tune immune activation thresholds or stabilize specific repertoire set-points. **(C)** *Regulatory exaptation* (established): viral regulatory elements are co-opted to shape host gene expression programs. **(D)** *Restriction modules* (established): endogenized viral proteins or fragments can interfere with related exogenous viruses. **(E)** *Innate "tripwire" viral mimicry* (established): endogenous transcription can generate nucleic-acid patterns that engage innate antiviral pathways. Hypothesis-labeled mechanisms are explicitly proposed interpretations that require causal tests.

5. KET-motivated hypotheses for why endogenized viral expression might benefit the host

In addition to the established benefits above, KET suggests further, non-exclusive possibilities. The following are explicitly **hypotheses**, not settled facts.

5.1 “Decoy detox” via negative selection

If adaptable pathogens repeatedly exploit a particular structural motif that reliably produces decoy epitopes, the host may benefit from endogenizing and expressing related sequences in thymic or tolerogenic contexts to delete, re-route into regulatory phenotypes, or raise activation thresholds in the most easily diverted clones. Mechanistically, this would resemble an evolutionary extension of central tolerance, where the host proactively subtracts immune options that pathogens are most able to mislead.

This hypothesis is compatible with known principles (thymic negative selection; ectopic antigen expression via AIRE) but requires specific evidence that (i) relevant ERV-derived peptides are presented during thymic selection and (ii) deletion of corresponding clones reduces pathogen decoying without unacceptable collateral costs [33] [34].

5.2 Immune calibration via “reference epitopes”

A host might use persistently expressed endogenous viral epitopes as stable reference points that tune activation thresholds, maintain memory homeostasis, or stabilize cross-reactive repertoires. This framing implies a dose- and context-dependent threshold: the same geometry can reinforce regulated readiness under tonic exposure, yet drive effector activation if cumulative keystone-mimetic input exceeds the niche’s inhibitory set-point. This could function as a “metronome” for immune readiness, in the same way that tonic signaling and persistent antigen can maintain memory phenotypes.

5.3 Endogenization as a host–keystone détente

This conjecture can be formalized as follows. If a persistent keystone organism becomes too frequently mimicked by decoy epitopes from adaptable pathogens, then the keystone’s epitopes may become liabilities that repeatedly misdirect immunity. Under that pressure, endogenization of the keystone organism (or parts of its epitope repertoire) could, in principle, shift the balance toward tolerogenic conditioning or higher inhibitory set-points and reduce exploitability. This is conceptually plausible but currently speculative.

6. Integrated DNA viruses beyond retroviruses: the special case of inherited chromosomally integrated HHV-6

6.1 What is known: iciHHV-6 exists and integrates into telomeres

Human herpesvirus 6A/6B can integrate into telomeric regions of human chromosomes, and in some cases the integrated viral genome is inherited through the germline [35] [36] [37]. This phenomenon, commonly called **inherited chromosomally integrated HHV-6 (iciHHV-6)**, is estimated to occur in a non-trivial minority of individuals in some populations [36] [37].

Integrated HHV-6 can retain the capacity for transcriptional activity and, in some settings, reactivation, although the clinical significance is still being defined [36] [38].

6.2 Why this matters for KET

iciHHV-6 provides a rare, measurable bridge between (i) persistent DNA viruses as potential keystone organisms and (ii) endogenization as a host–virus equilibrium state. It also creates a natural experiment: individuals with iciHHV-6 carry a stable copy of a herpesvirus genome in every cell, which may alter immune calibration, antigen availability, and reactivation dynamics under stress.

KET-relevant questions are immediate and testable: do iciHHV-6 carriers show different immunodominance hierarchies to HHV-6 epitopes, different cross-reactivity patterns, or different downstream effects on immune attention to other pathogens?

A side-by-side comparison highlights how retroviral endogenization and inherited chromosomally integrated HHV-6 converge on shared questions about transcription, immunity, and fitness tradeoffs (Fig. 5).

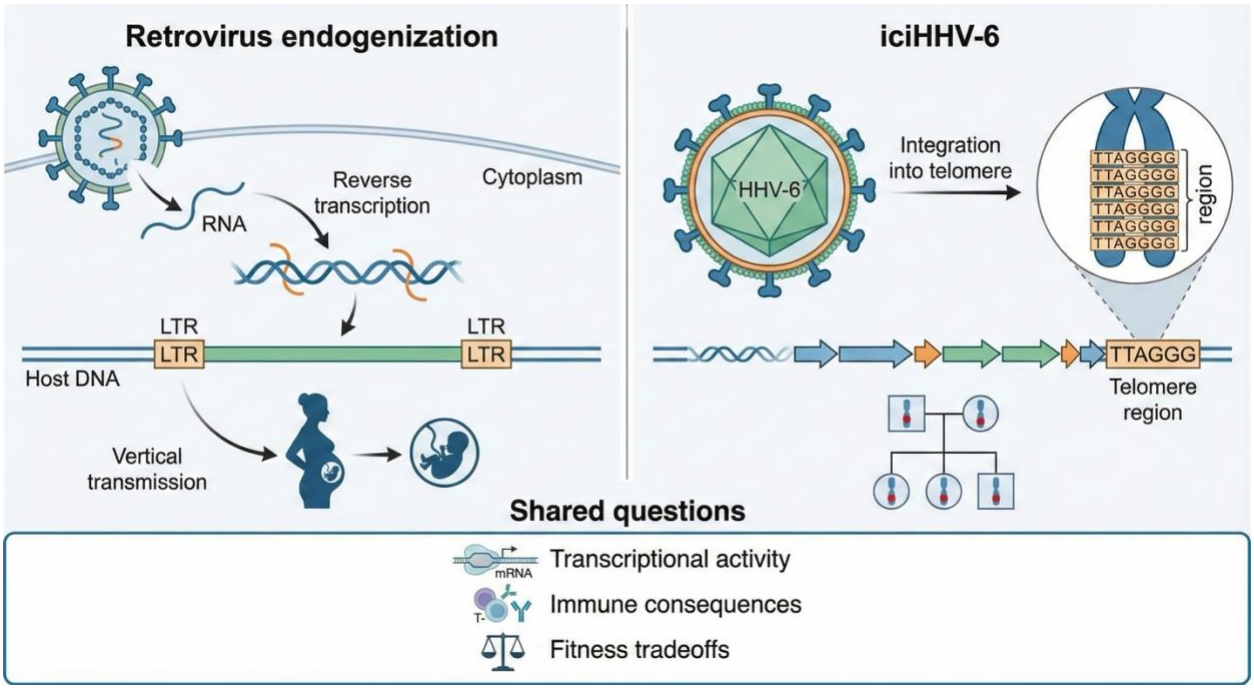

Figure 5 | Retrovirus endogenization and iciHHV-6: convergent integration phenomena and shared questions.
Side-by-side comparison of two routes by which viral sequence becomes heritable. **Left (retrovirus endogenization):** infection introduces viral RNA, reverse transcription produces DNA, and integration into host DNA (flanked by long terminal repeats, LTRs) enables vertical transmission after germline entry. **Right (iciHHV-6):** HHV-6 can integrate

into human telomeric regions and be inherited through the germline, creating carriers with integrated HHV-6 sequence in every nucleated cell. **Bottom:** shared questions relevant to KET and host–pathogen coevolution: (i) what governs transcriptional activity of integrated sequence across tissues and life stages, (ii) how integration shapes antigen presentation, tolerance, and immune attention, and (iii) what fitness tradeoffs determine whether integration is neutral, harmful, or adaptive.

If integration is a deep-time strategy, then HIV provides a rare contemporary perturbation in which an exogenous retrovirus may expose endogenous retroviral dynamics in real time.

7. HIV as a perturbation experiment: when an exogenous retrovirus illuminates endogenous retroviral biology

7.1 What is known: HERV-K expression and immunity in HIV infection

A substantial literature links HIV infection to increased expression of certain HERV families, particularly HERV-K (HML-2), via inflammatory signaling, epigenetic derepression, and direct or indirect effects of HIV proteins [39] [40] [41]. Critically, HERV-derived peptides can be presented on MHC class I, and HERV-specific CD8 T cells can recognize and kill HIV-infected cells in vitro, suggesting that HERV expression can create “non-self” targets on infected cells [42] [43].

This aligns with a practical therapeutic concept: endogenous retroviral antigens may be less mutable than HIV and may mark infected cells even when HIV itself downregulates antigen presentation. Several groups, including Doug Nixon’s, have contributed to this line of work and its implications for immunotherapy and cure strategies [42] [43].

7.2 KET framing: HERV expression as a “forced epitope reveal”

KET interprets the HIV–HERV interaction as a perturbation that can expose hidden layers of immune ecology:

- HIV may drive host-cell states that derepress ERVs, generating additional antigenic channels.
- Those ERV antigens can become immunodominant or at least immunologically actionable.
- The net effect could be beneficial (ERV-targeted killing of infected cells), neutral (biomarker of inflammation), or harmful (attention sink away from protective HIV epitopes).

The direction likely depends on timing (acute vs. chronic), tissue compartment, antigen abundance, and the host's pre-existing keystone imprint.

A stylized time course makes the competing interpretations explicit and anchors the HIV–HERV discussion to testable measurements (Fig. 6).

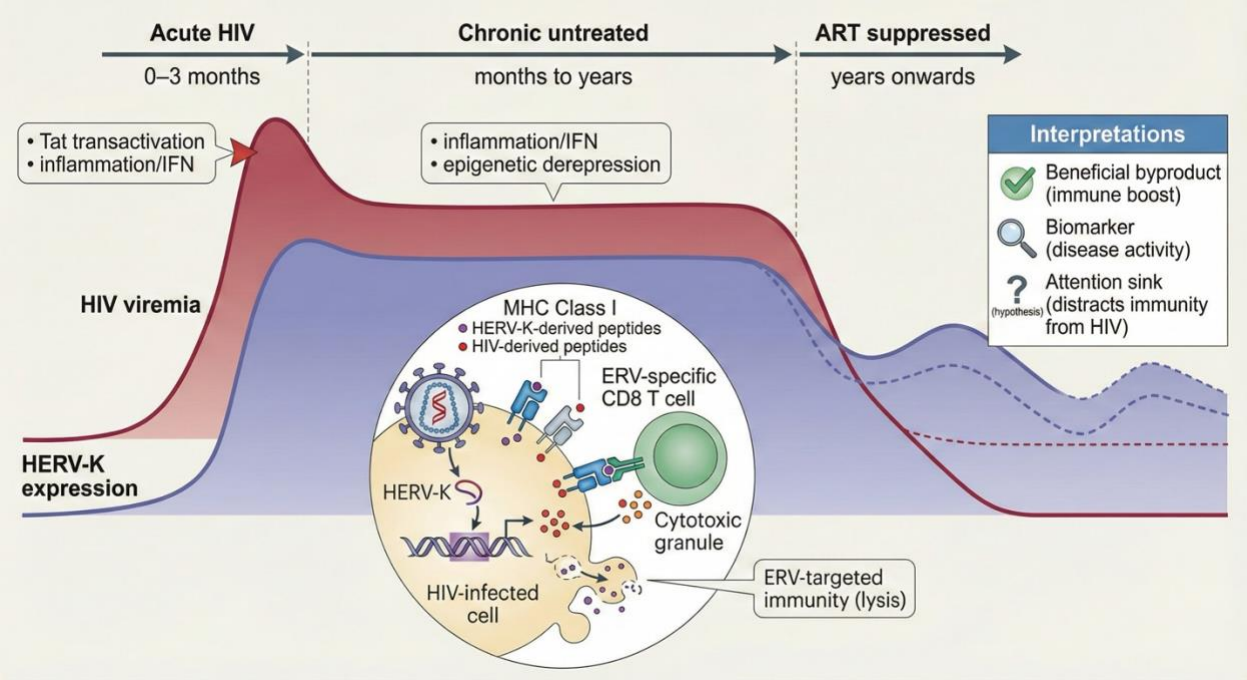

Figure 6 | HIV as a perturbation revealing endogenous retroviral dynamics. Illustrative time course spanning acute HIV infection (months), chronic untreated infection (months to years), and long-term ART-suppressed states (years). The schematic contrasts HIV viremia dynamics with increased HERV-K expression, highlighting plausible drivers including inflammation/interferon signaling and epigenetic derepression. The inset depicts antigen presentation of HERV-K-derived peptides on MHC class I in HIV-infected cells and recognition by ERV-specific CD8 T cells, providing a potential pathway for indirect targeting of HIV-infected cells. The interpretation box summarizes three non-exclusive views of ERV upregulation in HIV: **beneficial byproduct** (immune augmentation), **biomarker** (immune activation and disease state), or **attention sink** (hypothesis) that diverts immune resources from protective HIV epitopes.

Viewed through KET, HIV is useful not because it is 'representative,' but because it is disruptive in a stereotyped way: it perturbs interferon signaling, antigen presentation, and epigenetic control, and thereby exposes endogenous antigenic channels that are usually partially silent. This kind of perturbation framing naturally generalizes beyond HIV. Severe inflammatory states, hypersensitivity reactions, and acute viral infections act as repeatable

stress tests of immune attention, and the virome's response can be read as a structured output rather than noise.

HIV is only one perturbation. Stress biology, hypersensitivity reactions, and SARS-CoV-2 provide additional, partially standardized disruptions that can reveal whether virome dynamics follow ordered, interpretable trajectories.

8. Viral reactivation kinetics after stress, hypersensitivity, and COVID-19: ordered patterns as a readout of immune disruption

A central promise of KET is that immune attention has structure. Perturbations that disrupt immune regulation should therefore produce structured, not random, changes in the virome.

8.1 Hypersensitivity reactions and herpesvirus reactivation (DRESS/DIHS)

Drug reaction with eosinophilia and systemic symptoms (DRESS), and the closely related drug-induced hypersensitivity syndrome (DIHS), are characterized by systemic inflammation and frequent **sequential herpesvirus reactivation**, particularly HHV-6, followed by other herpesviruses in some cases [44] [45] [46]. Multiple reviews report that HHV-6 reactivation often occurs roughly **2–4 weeks** after symptom onset, with estimates around ~3 weeks in case-series syntheses [47] [48].

From a KET perspective, DRESS can be interpreted as an extreme immune "reallocation event," where regulatory failure and inflammatory amplification permit latent viruses (candidate keystone organisms) to reactivate in an ordered sequence that reflects both virus-specific latency biology and host immune control hierarchies.

8.2 Stress and critical illness: herpes reactivation is common and temporally patterned

Herpesvirus reactivation in critically ill but otherwise "immunocompetent" patients is well documented. HSV, CMV, and EBV reactivation can occur in ICU settings and is often associated with severity markers [49]. Time-to-reactivation varies across viruses, with reports of CMV reactivation occurring around days to a few weeks after ICU admission in some cohorts, and HSV reactivation is often associated with prolonged ventilation [50] [51].

Stress biology can directly impair CD8 T cell control of latency in animal models, and human studies link stress hormones (e.g., cortisol) to EBV reactivation markers [52] [53] [54].

8.3 SARS-CoV-2 as a population-scale perturbation: multi-omic evidence for viral reactivation dynamics

Large longitudinal cohort studies from the IMPACC network report widespread evidence of chronic viral reactivation signals during acute COVID-19 and post-acute sequelae, including herpesviruses and Anelloviridae [55] [56]. In this framework:

- EBV reactivation signals can appear early in hospitalization, and associations have been reported between EBV reactivation markers and clinical trajectories in subsets of patients [55] [57].
- CMV and HSV reactivation signals may emerge later in some hospitalized cohorts, consistent with a second phase of immune dysregulation or critical illness effects [55] [58].
- Anelloviruses (including torque teno virus, TTV) behave as **immune status reporters**: their loads tend to increase with immunosuppression and decrease with stronger immune control, a relationship used clinically in transplant medicine [59] [60].

Importantly, a study of first-time SARS-CoV-2 infection reported a significant **decrease** in anellovirus load in the first weeks after infection, followed by recovery toward baseline by ~12 weeks, suggesting that anellovirus kinetics can encode time-resolved information about immune state transitions [61].

8.4 Connecting the time courses: what can and cannot be inferred

Across DRESS/DIHS, critical illness, and COVID-19, the virome often exhibits temporally structured dynamics rather than indiscriminate bloom. Herpesvirus reactivation can appear in sequences, and anellovirus loads frequently track immunosuppression intensity and recovery. These patterns support the narrow claim that host immune disruption has detectable virome kinetics.

A KET-consistent interpretation is that such ordering reflects differences in how tightly distinct viral families are controlled by pre-existing, reinforced immune circuits that were shaped by persistent “keystone” exposures. Under this interpretation, standardized perturbations first relax control over viruses most dependent on the most reinforced arms of immunity, with broader reactivation emerging if immune dysfunction persists or evolves.

What remains unproven is causality at the level KET ultimately requires: that reactivation order is determined by immune attention allocation, rather than by virus-intrinsic latency programs, tissue tropism, sampling biases, or clinical confounding. The value of the framework, therefore, is predictive: it implies that viral reactivation trajectories should correlate with measurable shifts in antigen presentation and epitope-specific immunity,

and that these correlations should vary across hosts with different keystone-imprint histories.

The practical implication is that virome trajectories can be treated as dynamic biomarkers of immune allocation: not merely 'immunosuppression,' but shifts in which antigenic channels are permitted to expand, when, and for how long. That framing also creates an unusually testable opportunity for KET: it translates a conceptual model of keystones and decoys into measurable time series (peptides presented, clones expanded, viruses reactivated). The key question is not whether reactivation occurs, but whether its timing and ordering encode information about immune allocation and constraint.

A developmental 'immune calibration' hypothesis that links early-life barrier onboarding and keystone acquisition timing to later stress-test virome readouts is summarized in Fig. 7.

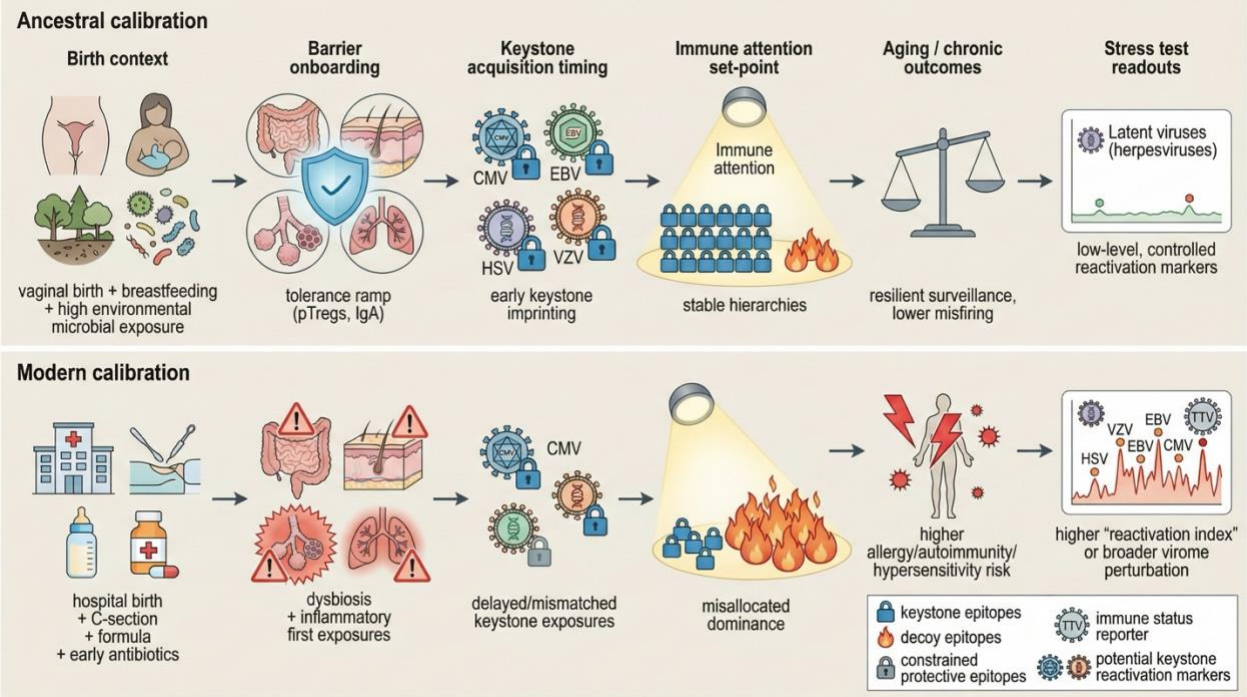

Figure 7 | Developmental calibration of immune attention and stress-test virome readouts. Conceptual model. In an ancestral calibration trajectory, high environmental microbial exposure at birth and early life supports barrier onboarding programs (including peripheral regulatory circuits and non-inflammatory mucosal control) and is followed by timely acquisition of persistent, human-adapted DNA-virus keystones. This sequence is proposed to stabilize immune attention hierarchies toward constrained, high-value targets, supporting resilient long-term surveillance with fewer misdirected inflammatory responses. In a modern calibration trajectory, disrupted early-life exposures (for example, altered birth context, early antibiotics, or dysbiosis) and delayed or mismatched keystone

acquisition are proposed to increase the risk of misallocated dominance, in which immune attention is drawn toward decoy-like targets during later perturbations. In both trajectories, acute stressors can be operationalized as "stress tests," with latent herpesvirus reactivation markers and anellovirus (TTV) kinetics serving as measurable readouts of immune system perturbation and recovery.

Callout box: Anomalies (3 items)

1. **Immunodominance frequently fails as a proxy for protection**, especially in chronic infection and reinfection settings [3] [7].
2. **Synonymous sites and RNA structure show functional selection**, challenging "protein-only" narratives of immune escape and constraint [18] [20].
3. **Host genomes retain and repurpose large amounts of viral sequence**, implying that viral acquisition can be adaptive, not only parasitic [25] [27].

Callout box: Testable predictions (3 items)

1. Individuals (or animal models) with higher thymic/tolerogenic expression of specific ERV loci will show reduced susceptibility to pathogen decoy strategies that exploit homologous motifs, measurable as shifts in immunodominance hierarchies and protection.
2. After standardized perturbations (vaccination, controlled stress, acute infection), **ordered viral reactivation trajectories** (EBV/HHV-6/CMV/HSV and TTV kinetics) will correlate with quantifiable shifts in epitope-specific immune attention and exhaustion phenotypes.
3. In HIV, the magnitude and quality of HERV-K–specific CD8 responses will predict reservoir metrics and clearance of infected cells under latency-reversal or immune-enhancing interventions, beyond what is predicted by HIV-specific responses alone [42] [43].

9. Experimental agenda: how to turn KET from narrative to mechanism

A KET-informed research program should be judged by whether it generates **discriminating tests**, not just plausible stories. The following experiments are high yield because they differentiate competing models.

9.1 Map “immune attention” directly with immunopeptidomics and repertoire sequencing

- Quantify peptide presentation (MHC-I and MHC-II) across key states: baseline, acute infection, chronic infection, post-infection, and after perturbations (e.g., corticosteroids, hypersensitivity).
- Simultaneously measure TCR/BCR repertoires and functional phenotypes (exhaustion markers, memory subsets).
- Test whether decoy epitopes show higher presentation abundance and stronger clonal reinforcement than constrained protective epitopes, and whether this relationship changes with keystone-virus reactivation.

9.2 Use natural experiments: iciHHV-6 carriers and longitudinal virome trajectories

iciHHV-6 carriers offer an unusually clean human model in which an integrated viral genome is present in every nucleated cell, allowing direct tests of whether integration state correlates with immune set-points and virome control [35] [37]. In longitudinal cohorts, compare baseline immune activation thresholds, epitope-specific hierarchies, and the kinetics of herpesvirus and anellovirus signals after standardized perturbations such as vaccination, intercurrent infections, pregnancy, surgery, or corticosteroid exposure. If KET is mechanistically relevant, integration state should not merely associate with bulk inflammation, but should map onto predictable differences in antigen presentation and immunodominance structure.

9.3 Perturb ERV loci with CRISPR in organoids and humanized models

To discriminate between “decoy detox” and “immune calibration” mechanisms, causality is essential. Candidate ERV loci, their promoters, or their LTR enhancers can be deleted or silenced in thymic epithelial cell organoids or in humanized mouse systems, followed by quantification of central tolerance outputs and downstream immunodominance in response to engineered pathogens containing decoy-like motifs. A key control is to distinguish tolerance effects from innate priming effects, since endogenous transcription can also engage antiviral sensing pathways. A convincing test will connect locus-specific perturbation to a predictable shift in epitope hierarchy and functional protection, not only to changes in baseline interferon signatures.

9.4 Integrate virome dynamics into hypersensitivity and post-viral syndromes

DRESS/DIHS and post-COVID syndromes provide clinically grounded contexts where immune disruption, viral reactivation, and symptom trajectories can be sampled over time.

Pair standardized clinical phenotyping with time-resolved quantification of herpesvirus DNA/RNA, anellovirus loads, and host interferon-linked signatures. Explicit temporal modeling is essential: the question is whether reactivation events cluster around identifiable immune state transitions, and whether these transitions coincide with changes in epitope-specific exhaustion, antigen presentation, or repertoire skewing. A KET-facing endpoint would be an association between keystone-imprint signatures and persistent symptoms that remains after adjustment for baseline severity and sampling intensity.

10. Outlook: from metaphor to measurement

Keystone Epitope Theory becomes scientifically useful only insofar as it identifies measurable constraints on immune allocation and makes falsifiable predictions about how those constraints shape pathogen evolution and host outcomes. The deep-time perspective proposed here suggests that persistent infections, genome-integrated viral sequence, and episodic perturbations are not separate curiosities, but parts of a coupled system that writes and rewrites immune attention across timescales. The near-term opportunity is methodological: combine immunopeptidomics, repertoire analysis, and longitudinal virome measurement to test whether "reactivation order," ERV expression, and integration state map onto predictable, mechanistic changes in epitope hierarchy and protection. If these predictions fail, KET should be revised or discarded. If they hold, KET offers a route to rationally manipulating immune attention, which is a scarce resource that pathogens have been optimizing against for a very long time.

References

1 Asiaee, A., Mallal, N., Phillips, E. & Mallal, S. Co-evolved Partners of Immunity: A Trait-Based Map of Human Keystone Organisms. *bioRxiv* (2025). https://doi.org/10.1101/2025.08.19.671142

2 Mallal, S. & Asiaee, A. Keystone Epitope Theory: An Ecological Perspective on RNA Viruses, Tumor Immunoediting, and Vaccine Design. *Zenodo* (2025). https://doi.org/10.5281/zenodo.17082095

3 Yewdell, J. W. Confronting complexity: real-world immunodominance in antiviral CD8+ T cell responses. *Immunity* **25**, 533–543 (2006). https://doi.org/10.1016/j.immuni.2006.09.005

4 Akram, A. & Inman, R. D. Immunodominance: a pivotal principle in host response to viral infections. *Clin Immunol* **143**, 99–115 (2012). https://doi.org/10.1016/j.clim.2012.01.015

5 Tan, H. X. *et al.* Immunodominance is a poor predictor of vaccine-induced T follicular helper cell quality. *bioRxiv* (2025). https://doi.org/10.1101/2025.07.21.666029

6 Virgin, H. W., Wherry, E. J. & Ahmed, R. Redefining chronic viral infection. *Cell* **138**, 30–50 (2009). https://doi.org/10.1016/j.cell.2009.06.036

7 Wherry, E. J. & Kurachi, M. Molecular and cellular insights into T cell exhaustion. *Nat Rev Immunol* **15**, 486–499 (2015). https://doi.org/10.1038/nri3862
8 Gilbert, W. Origin of life: The RNA world. *Nature* **319**, 618–618 (1986). https://doi.org/10.1038/319618a0
9 Joyce, G. F. The antiquity of RNA-based evolution. *Nature* **418**, 214–221 (2002). https://doi.org/10.1038/418214a
10 Forterre, P. The origin of viruses and their possible roles in major evolutionary transitions. *Virus Res* **117**, 5–16 (2006). https://doi.org/10.1016/j.virusres.2006.01.010
11 Koonin, E. V., Senkevich, T. G. & Dolja, V. V. The ancient Virus World and evolution of cells. *Biol Direct* **1**, 29 (2006). https://doi.org/10.1186/1745-6150-1-29
12 Cohen, J. I. Herpesvirus latency. *The Journal of clinical investigation* **130**, 3361–3369 (2020). https://doi.org/10.1172/jci136225
13 Mallal, S. & Phillips, E. Keystone Epitope Theory: Implications for Hypersensitivity, Autoimmunity and Transplantation. *Zenodo* (2025). https://doi.org/10.5281/zenodo.17082090
14 Moss, P. 'From immunosenescence to immune modulation': a re-appraisal of the role of cytomegalovirus as major regulator of human immune function. *Med Microbiol Immunol* **208**, 271–280 (2019). https://doi.org/10.1007/s00430-019-00612-x
15 Klenerman, P. & Oxenius, A. T cell responses to cytomegalovirus. *Nat Rev Immunol* **16**, 367–377 (2016). https://doi.org/10.1038/nri.2016.38
16 Karrer, U. *et al.* Memory inflation: continuous accumulation of antiviral CD8+ T cells over time. *Journal of immunology* **170**, 2022–2029 (2003). https://doi.org/10.4049/jimmunol.170.4.2022
17 Domingo, E. & Perales, C. Viral quasispecies. *PLoS Genet* **15**, e1008271 (2019). https://doi.org/10.1371/journal.pgen.1008271
18 Kijak, G. H. *et al.* Lost in translation: implications of HIV-1 codon usage for immune escape and drug resistance. *AIDS Rev* **6**, 54–60 (2004).
19 Plotkin, J. B. & Kudla, G. Synonymous but not the same: the causes and consequences of codon bias. *Nat Rev Genet* **12**, 32–42 (2011). https://doi.org/10.1038/nrg2899
20 Leary, S. *et al.* Generation of a Novel SARS-CoV-2 Sub-genomic RNA Due to the R203K/G204R Variant in Nucleocapsid: Homologous Recombination has Potential to Change SARS-CoV-2 at Both Protein and RNA Level. *Pathog Immun* **6**, 27–49 (2021). https://doi.org/10.20411/pai.v6i2.460
21 Simmonds, P. Pervasive RNA Secondary Structure in the Genomes of SARS-CoV-2 and Other Coronaviruses. *mBio* **11**, 10.1128/mbio.01661–01620 (2020). https://doi.org/10.1128/mBio.01661-20
22 Malone, B., Urakova, N., Snijder, E. J. & Campbell, E. A. Structures and functions of coronavirus replication-transcription complexes and their relevance for SARS-CoV-2 drug design. *Nat Rev Mol Cell Biol* **23**, 21–39 (2022). https://doi.org/10.1038/s41580-021-00432-z

23 Lander, E. S. *et al.* Initial sequencing and analysis of the human genome. *Nature* **409**, 860–921 (2001). https://doi.org/10.1038/35057062
24 Bannert, N. & Kurth, R. The evolutionary dynamics of human endogenous retroviral families. *Annu Rev Genomics Hum Genet* **7**, 149–173 (2006). https://doi.org/10.1146/annurev.genom.7.080505.115700
25 Feschotte, C. Transposable elements and the evolution of regulatory networks. *Nat Rev Genet* **9**, 397–405 (2008). https://doi.org/10.1038/nrg2337
26 Chuong, E. B., Elde, N. C. & Feschotte, C. Regulatory evolution of innate immunity through co-option of endogenous retroviruses. *Science* **351**, 1083–1087 (2016). https://doi.org/10.1126/science.aad5497
27 Mi, S. *et al.* Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. *Nature* **403**, 785–789 (2000). https://doi.org/10.1038/35001608
28 Blaise, S., de Parseval, N., Bénit, L. & Heidmann, T. Genomewide screening for fusogenic human endogenous retrovirus envelopes identifies syncytin 2, a gene conserved on primate evolution. *Proc Natl Acad Sci U S A* **100**, 13013–13018 (2003). https://doi.org/10.1073/pnas.2132646100
29 Johnson, W. E. Origins and evolutionary consequences of ancient endogenous retroviruses. *Nat Rev Microbiol* **17**, 355–370 (2019). https://doi.org/10.1038/s41579-019-0189-2
30 Stoye, J. P. Studies of endogenous retroviruses reveal a continuing evolutionary saga. *Nat Rev Microbiol* **10**, 395–406 (2012). https://doi.org/10.1038/nrmicro2783
31 Chiappinelli, K. B. *et al.* Inhibiting DNA Methylation Causes an Interferon Response in Cancer via dsRNA Including Endogenous Retroviruses. *Cell* **162**, 974–986 (2015). https://doi.org/10.1016/j.cell.2015.07.011
32 Roulois, D. *et al.* DNA-Demethylating Agents Target Colorectal Cancer Cells by Inducing Viral Mimicry by Endogenous Transcripts. *Cell* **162**, 961–973 (2015). https://doi.org/10.1016/j.cell.2015.07.056
33 Anderson, M. S. & Su, M. A. AIRE expands: new roles in immune tolerance and beyond. *Nat Rev Immunol* **16**, 247–258 (2016). https://doi.org/10.1038/nri.2016.9
34 Klein, L., Kyewski, B., Allen, P. M. & Hogquist, K. A. Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). *Nat Rev Immunol* **14**, 377–391 (2014). https://doi.org/10.1038/nri3667
35 Arbuckle, J. H. *et al.* The latent human herpesvirus-6A genome specifically integrates in telomeres of human chromosomes in vivo and in vitro. *Proc Natl Acad Sci U S A* **107**, 5563–5568 (2010). https://doi.org/10.1073/pnas.0913586107
36 Pellett, P. E. *et al.* Chromosomally integrated human herpesvirus 6: questions and answers. *Rev Med Virol* **22**, 144–155 (2012). https://doi.org/10.1002/rmv.715
37 Wood, M. L. *et al.* Variation in human herpesvirus 6B telomeric integration, excision, and transmission between tissues and individuals. *eLife* **10**, e70452 (2021). https://doi.org/10.7554/eLife.70452
38 Sedlak, R. H. *et al.* Detection of Human Herpesvirus 6B (HHV-6B) Reactivation in Hematopoietic Cell Transplant Recipients with Inherited Chromosomally Integrated

HHV-6A by Droplet Digital PCR. *J Clin Microbiol* **54**, 1223–1227 (2016). https://doi.org/10.1128/JCM.03275-15

39 Gonzalez-Hernandez, M. J. *et al.* Expression of human endogenous retrovirus type K (HML-2) is activated by the Tat protein of HIV-1. *Journal of virology* **86**, 7790–7805 (2012). https://doi.org/10.1128/jvi.07215-11

40 van der Kuyl, A. C. HIV infection and HERV expression: a review. *Retrovirology* **9**, 6 (2012). https://doi.org/10.1186/1742-4690-9-6

41 Contreras-Galindo, R. *et al.* Characterization of human endogenous retroviral elements in the blood of HIV-1-infected individuals. *Journal of virology* **86**, 262–276 (2012). https://doi.org/10.1128/JVI.00602-11

42 Jones, R. B. *et al.* HERV-K-specific T cells eliminate diverse HIV-1/2 and SIV primary isolates. *The Journal of clinical investigation* **122**, 4473–4489 (2012). https://doi.org/10.1172/jci64560

43 SenGupta, D. *et al.* Strong human endogenous retrovirus-specific T cell responses are associated with control of HIV-1 in chronic infection. *Journal of virology* **85**, 6977–6985 (2011). https://doi.org/10.1128/JVI.00179-11

44 Shiohara, T., Inaoka, M. & Kano, Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int* **55**, 1–8 (2006). https://doi.org/10.2332/allergolint.55.1

45 Shiohara, T. & Mizukawa, Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. *Allergol Int* **68**, 301–308 (2019). https://doi.org/10.1016/j.alit.2019.03.006

46 Hama, N., Abe, R., Gibson, A. & Phillips, E. J. Drug-Induced Hypersensitivity Syndrome (DIHS)/Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS): Clinical Features and Pathogenesis. *J Allergy Clin Immunol Pract* **10**, 1155–1167.e1155 (2022). https://doi.org/10.1016/j.jaip.2022.02.004

47 Zhu, H. & Ren, V. Immunopathogenic Insights on Preferential Human Herpesvirus-6 Reactivation in Drug Rash With Eosinophilia and Systemic Symptoms: A Scoping Review. *J Cutan Med Surg* **27**, 388–398 (2023). https://doi.org/10.1177/12034754231177590

48 Milani-Nejad, N., Trinidad, J. & Kaffenberger, B. H. Viral reactivation in hospitalized patients with drug reaction with eosinophilia and systemic symptoms: A retrospective study from a tertiary medical center in the United States. *J Am Acad Dermatol* **83**, 278–279 (2020). https://doi.org/10.1016/j.jaad.2020.03.095

49 Hraiech, S., Azoulay, E. & Papazian, L. Herpesviruses in Critically Ill Patients With ARDS. *Encyclopedia of Respiratory Medicine*, 373–385 (2022). https://doi.org/10.1016/b978-0-08-102723-3.00231-6

50 Fuest, K. E. *et al.* Risk factors for Herpes simplex virus (HSV) and Cytomegalovirus (CMV) infections in critically-ill COVID-19 patients. *Multidiscip Respir Med* **17**, 815 (2022). https://doi.org/10.4081/mrm.2022.815

51 Çimendağ, H. C., Sayıner, A., Gökmen, A. N. & Avkan-Oğuz, V. Risk Factors for Cytomegalovirus Reactivation and Its Impact on Clinical Outcomes in Immunocompetent Seropositive Patients Admitted to the Intensive Care Unit: A

Single-Center Prospective Observational Study. *Infect Dis Clin Microbiol* **7**, 174–184 (2025). https://doi.org/10.36519/idcm.2025.480

52 Freeman, M. L., Sheridan, B. S., Bonneau, R. H. & Hendricks, R. L. Psychological stress compromises CD8+ T cell control of latent herpes simplex virus type 1 infections. *Journal of immunology* **179**, 322–328 (2007). https://doi.org/10.4049/jimmunol.179.1.322

53 Glaser, R., Pearl, D. K., Kiecolt-Glaser, J. K. & Malarkey, W. B. Plasma cortisol levels and reactivation of latent Epstein-Barr virus in response to examination stress. *Psychoneuroendocrinology* **19**, 765–772 (1994). https://doi.org/10.1016/0306-4530(94)90023-x

54 Sausen, D. G., Bhutta, M. S., Gallo, E. S., Dahari, H. & Borenstein, R. Stress-Induced Epstein-Barr Virus Reactivation. *Biomolecules* **11** (2021). https://doi.org/10.3390/biom11091380

55 Maguire, C. *et al.* Chronic Viral Reactivation and Associated Host Immune Response and Clinical Outcomes in Acute COVID-19 and Post-Acute Sequelae of COVID-19. *bioRxiv* (2024). https://doi.org/10.1101/2024.11.14.622799

56 Peluso, M. J. *et al.* Chronic viral coinfections differentially affect the likelihood of developing long COVID. *The Journal of clinical investigation* **133** (2023). https://doi.org/10.1172/JCI163669

57 Gold, J. E., Okyay, R. A., Licht, W. E. & Hurley, D. J. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. *Pathogens* **10** (2021). https://doi.org/10.3390/pathogens10060763

58 Saade, A., Moratelli, G., Azoulay, E. & Darmon, M. Herpesvirus reactivation during severe COVID-19 and high rate of immune defect. *Infect Dis Now* **51**, 676–679 (2021). https://doi.org/10.1016/j.idnow.2021.07.005

59 van Rijn, A. L., Roos, R., Dekker, F. W., Rotmans, J. I. & Feltkamp, M. Torque teno virus load as marker of rejection and infection in solid organ transplantation - A systematic review and meta-analysis. *Rev Med Virol* **33**, e2393 (2023). https://doi.org/10.1002/rmv.2393

60 Doberer, K., Kapps, S., Haupenthal, F. & Bond, G. Immune Monitoring Goes Viral - Torque Teno Virus for Immunologic Risk Stratification After Kidney Transplantation. *Transpl Int* **38**, 15074 (2025). https://doi.org/10.3389/ti.2025.15074

61 Timmerman, A. L. *et al.* The Impact of First-Time SARS-CoV-2 Infection on Human Anelloviruses. *Viruses* **16** (2024). https://doi.org/10.3390/v16010099