Keystone Epitope Theory: An Ecological Perspective on RNA Viruses, Tumor Immunoediting, and Vaccine Design

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Abstract.

Keystone Epitope Theory proposes that persistent, human-adapted DNA viruses focus postnatal immunity on conserved, function-linked epitopes and coordinate T-, B-, and NK-cell programs within tissue niches. Here we read fast-evolving RNA viruses and tumors through that lens. RNA viruses succeed by inflating mutable decoys and engineering peptide–HLA display so cytotoxic T-cell visibility falls while inhibitory NK tone is preserved; tumors converge on the same interoperability fault lines. We formalize "decoy versus constrained" grammar, map display engineering (e.g., HLA-E/NKG2A; HIV Nef/Vpu), and outline design rules: target epitopes with measurable fitness cost, avoid decoys that reinforce inhibitory checkpoints, and normalize display so wins are visible to both CTL and NK arms. A one-page primer with pointers to mechanistic background is provided in **Box 1**. This ecological framing links mechanism to design across HIV/HCV/influenza/SARS-CoV-2 and tumor immunoediting.
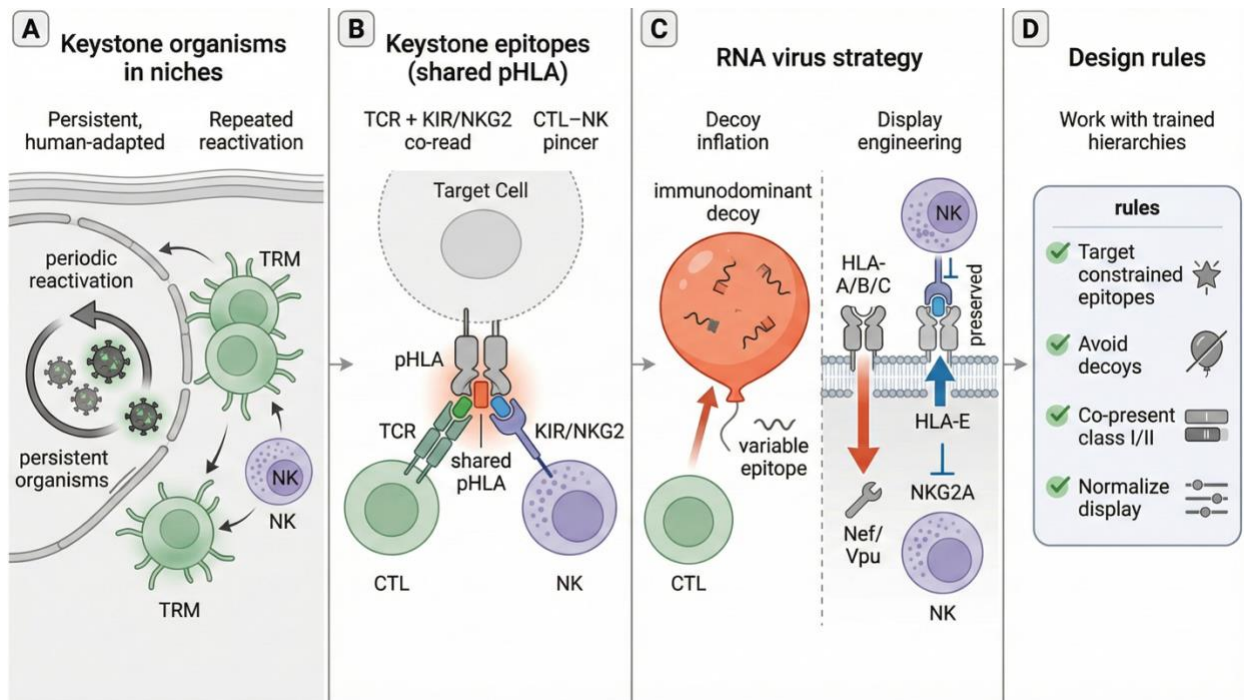
Figure 1. Graphical Abstract. Keystone Epitope Theory at a glance (global summary). Keystone organisms (persistent, human-adapted infections) shape postnatal immune hierarchies by repeatedly restimulating conserved, function-linked peptide–HLA targets within tissue niches. These "keystone epitopes" become coordination hubs that align CTL, CD4, B-cell, and NK programs on shared display surfaces. Rapidly adapting RNA viruses succeed by taking advantage of this architecture: inflating mutable decoys to misdirect within-host immunodominance while editing antigen display so CTL visibility drops but inhibitory NK tone is preserved. Tumors converge on the same fault lines via class-I/E rewiring and checkpoint reinforcement. The design implication is operational:

prioritize constrained epitopes with measurable fitness cost, avoid decoys that reinforce inhibitory wiring, and normalize display so "wins" are visible to both CTL and NK arms.

Glossary

Note: Some terms below name observed patterns (phenomena) rather than settled mechanisms. We label which is which.

- **Keystone Epitope Theory (KET)** *(model)*: A framework proposing that some long-term, host-adapted infections disproportionately shape which immune targets are prioritized over time and across tissues.

- **Keystone organism** *(model category; partly observable)*: A persistent infection (often lifelong or repeatedly reactivating) that provides recurring antigen exposure and, in KET, helps stabilize long-term immune priorities.

- **Keystone epitope** *(model category; partly observable)*: A peptide–HLA target from a keystone organism that is repeatedly encountered and relatively hard for the pathogen to change without a cost, and that tends to seed durable, high-impact T-cell memory.

- **Peptide–HLA (pHLA)** *(mechanistic unit; measurable)*: A short peptide displayed by an HLA molecule on a cell surface. CD8 T cells "see" pHLA via the T-cell receptor.

- **Immunodominance** *(phenomenon; multiple meanings)*: "Which epitopes win attention." In this paper we always specify what kind of dominance we mean (for example, within one person at a timepoint, within one person over time, across people, within a tissue, or linked to protection).

- **Immunoprevalence** *(phenomenon/measurement)*: Across a defined cohort, the fraction of people with a detectable response to a given epitope (assay threshold matters).

- **Constrained epitope** *(property; often inferable from data)*: An epitope where mutations tend to impose a fitness cost on the pathogen, limiting escape options.

- **Decoy epitope** *(functional label; needs evidence)*: A target that can attract a large response yet contributes relatively little to control, often because it is easy to escape or strategically positioned to misdirect responses.

- **Display engineering** *(mechanism class)*: Viral or tumor strategies that change what immune cells "see" (which pHLA and related ligands appear on the surface), often reducing CTL visibility while preserving inhibitory NK signaling.

- **CTL and NK cells** *(cell types)*: Cytotoxic T lymphocytes (CTLs) kill via TCR recognition of pHLA. Natural killer (NK) cells kill using germline-encoded receptors that sense HLA patterns and stress ligands.

- **KIR / NKG2A** *(mechanistic receptors)*: NK receptors that read HLA surfaces (often in peptide-influenced ways), shaping whether NK cells are inhibited or activated.

- **Tumor immunoediting** *(phenomenon with partial mechanisms)*: The process by which immune pressure shapes tumor evolution, often selecting for antigen loss, altered HLA display, and checkpoint reinforcement.

A more detailed glossary (including the full immunodominance subdefinitions) is provided in the Supplementary Materials.

1. Orientation and Scope

This review is part of a coordinated set of manuscripts on Keystone Epitope Theory. Companion papers include: (TRAIT) a quantitative trait analysis defining keystone organisms and a reactivation index [7]; (INTEROP) a systems overview of CTL and NK interoperability on shared peptide–HLA and how pathogens edit antigen display [8] and (HYPER) clinical implications of modified self (hypersensitivity, autoimmunity, transplantation) [11]. Here we focus on RNA viruses and other rapidly adaptable organisms as ecological disruptors of keystone-imprinted hierarchies, and we extend the same logic to tumor immunoediting and vaccine design. Our aim is to keep the design implications high level: what to target, what to avoid, and when to normalize display so immunogens and therapies work with, rather than against, entrenched immune priorities. For a one-page primer with section pointers, see Box 1.

Box 1. Primer to Keystone Epitope Theory (with pointers to the companion Hypersensitivity review, Ref. 9)

Keystone Epitope Theory adds a **third, postnatal focusing step** (Figure 2a) to immune education. After thymic positive/negative selection, a small set of **persistent, human-adapted organisms concentrates immune memory on constrained, function-linked epitopes** in the tissues where control must occur. This imprinting is protective because it hard-wires priorities on targets the host cannot afford to miss—yet it also defines where **modified self** can recruit entrenched memory (Figure 2b). [Ref. 9 §2.1]

These priorities are **read jointly** by cytotoxic T cells and NK cells on the **same peptide–HLA complex**. Licensing, peptide selectivity, and HLA-C levels set thresholds so that inhibitory NK tone can be maintained while CTL visibility rises—or vice versa. This CTL–NK "**tissue pincer**" is a recurring design feature in both infection and cancer. [Ref. 9 §2.2, §2.9]

Persistent DNA viruses (notably HHVs) **scaffold durable memory**: they seed tissue-resident compartments, re-stimulate at low levels to maintain recall, and keep **Class I/II epitopes** in the right anatomical niches at the right times. This **temporal–spatial layering** explains why some targets remain longitudinally immunodominant across life and why niche-matched display later matters for pathology. [Ref. 9 §2.2, §2.6]

The same architecture creates a **vulnerability window**. When a **drug-modified or post-translationally modified self-peptide approximates a keystone epitope and is displayed in the same tissue by the same risk HLA, pre-**existing memory may engage **without** the usual tolerance circuits. That is the mechanistic bridge from keystone protection to **T-cell–mediated hypersensitivity**; the clinical evidence is detailed in the companion review. [Ref. 9 §2.3; §§3.1–3.2]

Selection pressures have favored **HLA–TCR solutions** that see **conserved, functionally costly viral sites**, while still permitting **cross-reactivity** that anticipates related threats. The **allelic logic** (e.g., B57/B58) and the **structural/conformational basis** for public and private TCR cross-recognition are laid out in Ref. 9. [Ref. 9 §2.5, §2.10]

Because keystone organisms train memory **in place**, **tissue compartmentalization** matters. **TRM** at the dermal–epidermal junction, in lymphoid tissue, or along the vasculature can be **recruited directly by parenchymal display**—a key insight for patterned injury in skin, lymphoid organs, and entheses. [Ref. 9 §2.11]

Timing is pivotal. In ancestral settings, infants acquired keystone DNA viruses early; modern delays or mismatches can destabilize immunodominance hierarchies, helping to explain the rising prevalence of allergy/autoimmunity and shifting responses to acute RNA infections. **[Ref. 9 §2.4]** Related **discordant co-evolution—host immunogenetics meeting non-co-**adapted pathogen strains—adds another axis of risk. [Ref. 9 §4.1]

Keystone exposure also shapes **heterologous immunity**: persistent herpesviruses can **boost cross-protective responses** and tune regulatory and innate programs (including NK cells). These effects are protective but **context- and genotype-dependent**, reinforcing the need to read immunity as a coordinated system. [Ref. 9 §2.8, §2.9]

Taken together, the companion review provides the mechanistic substrate (what imprints, how CTL/NK co-read pHLA, and why niche and timing matter) and the clinical translation (drug hypersensitivity, organ-specific autoimmunity, transplantation, with practical rules for prediction and monitoring). The present paper builds on that foundation to analyze **RNA viruses and tumors as stress tests of the system—decoy vs. constrained epitopes, display engineering (e.g., HLA-E/NKG2A), and design rules for vaccines and immunotherapies that work with, rather than** against, entrenched hierarchies. [Ref. 9 §2.1–2.11; §3–6]

Abbreviations: KIR = Killer cell immunoglobulin-like receptor and **TRM** = tissue-resident memory
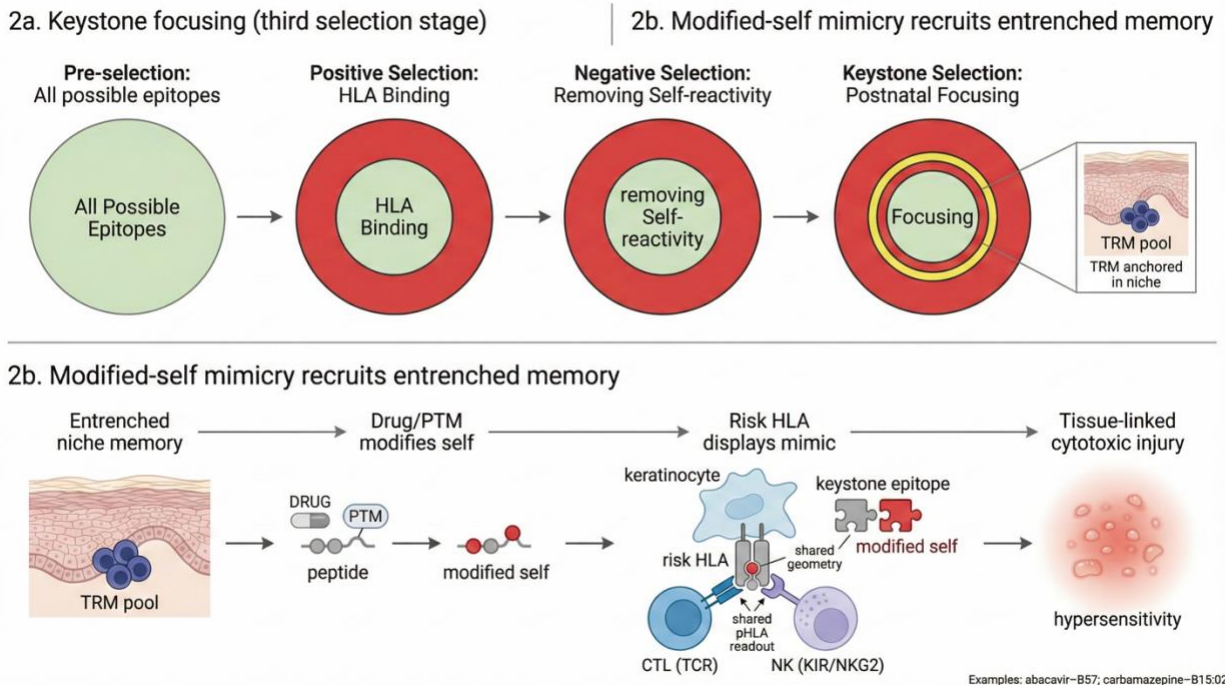
Figure 2. Shared geometry links postnatal keystone focusing to modified-self injury. (2a) Three-stage selection culminating in postnatal keystone focusing: thymic positive and negative selection define the visible, tolerated peptide–HLA space, then repeated tissue-linked exposure to persistent, human-adapted keystone organisms concentrates tissue-resident memory (TRM) and cytotoxic priorities onto conserved, function-linked epitopes. (2b) Modified-self mimicry recruits entrenched memory: a drug or post-translational modification generates a self-derived peptide that overlaps keystone epitope geometry and is displayed by risk HLA within the same tissue niche, enabling rapid CTL and NK engagement on shared peptide–HLA surfaces and producing tissue-linked cytotoxic injury (illustrated here as hypersensitivity). This mechanism provides the conceptual bridge to relate decoy logic and display control to clinical modified-self syndromes.

1.1 Introduction

Persistent partners that focus immunity on **constrained epitopes** give humans speed and reliability against familiar threats. **RNA viruses** and tumors succeed by doing the opposite: they **inflate mutable decoys** and **engineer display** so cytotoxic T cell visibility falls while **inhibitory NK tone** is preserved. In this review we formalize the **decoy-versus-constrained** grammar, show how **TCR/KIR (Killer cell immunoglobulin-like receptor) read the same pHLA** (the NK–CTL "pincer"), and map viral **display control** (Nef/Vpu; HLA-E/NKG2A; NKG2D ligands) into testable **scenarios** for HIV, HCV, influenza, and SARS-CoV-2. We minimize general background—**see Box 1 (primer) for quick reference**—and focus on mechanisms and evidence that distinguish real control from impressive but irrelevant magnitude. We conclude with **design rules**: include epitopes with measurable fitness cost; avoid decoys that reinforce inhibitory KIR; and, when necessary, normalize display so epitope-scale wins are visible to both arms. For clinical context on tolerance, tissue niches, and heterologous memory—including drug hypersensitivity and autoimmunity—see the companion **clinical review**[11]; for a population-level scaffold of keystone organisms and diagnostics, see the **trait-based map**[7]; for innate–adaptive wiring principles, see the **interoperability** overview[8].

Ecologically, Keystone Theory reads immunity through two powerful "stress tests": fast-evolving RNA viruses and tumor immunoediting. HIV continuously probes epitope geometry and Class I display, revealing where hierarchies are brittle. Tumors run the same search in miniature, evolving toward antigen loss, altered Class I/E display, and checkpoint-mediated escape. These shared fault lines make the same interoperability rules relevant to both infection and cancer, while modified-self ligands illustrate how entrenched memory can be misdirected (developed fully in the companion review on hypersensitivity, autoimmunity, and transplantation [11]). Here, we focus on adaptable pathogens and tumor immunoediting.

This keystone epitope-driven immune architecture ensures preparedness against future infections and cellular transformation, but it also creates vulnerability windows in which entrenched memory is misdirected. We explore RNA viruses as dynamic disruptors of this architecture. Unlike DNA viruses, which become entrenched in long-term immune hierarchies, RNA viruses must constantly evade or subvert keystone-shaped responses. HIV, for example, exploits immunodominance hierarchies by generating non-protective CD8$^+$ T-cell responses against decoy epitopes, subverting immune clearance. In this sense, the deeply entrenched logic of keystone imprinting functions both as a defense system and as an ecological niche that new pathogens must adapt to or circumvent.

1.2 Overview and Roadmap of the Review

This review examines how persistent DNA viruses, such as herpesviruses, establish lifelong immunodominance hierarchies that influence TCR and BCR selection, innate-adaptive coordination, and host-pathogen co-adaptation. We then examine how RNA viruses—particularly HIV, but also HCV, influenza, and SARS-CoV-2—subvert these hierarchies through immune evasion and decoying. We explore how such disruptions can lead to viral persistence, vaccine failure, or the reactivation of latent viruses. We then extend these mechanisms to tumor immunoediting, where keystone-shaped memory may misfire against tumor-associated neoepitopes. Finally, we consider how modern disruptions in early-life microbial exposure and host–pathogen co-evolution reshape immune outcomes in respiratory viral disease and cancer; implications for allergy, autoimmunity, and transplantation are developed in the companion review on hypersensitivity, autoimmunity, and transplantation [11]. Minimal mechanistic recaps point back to Hypersensitivity §§2.1–2.11 rather than re-stating them in full. For consolidated keystone features, see the Reiteration Table in Hypersensitivity §1.2/Table 1. Here we concentrate on decoy-vs-constrained rules and vaccine implications.

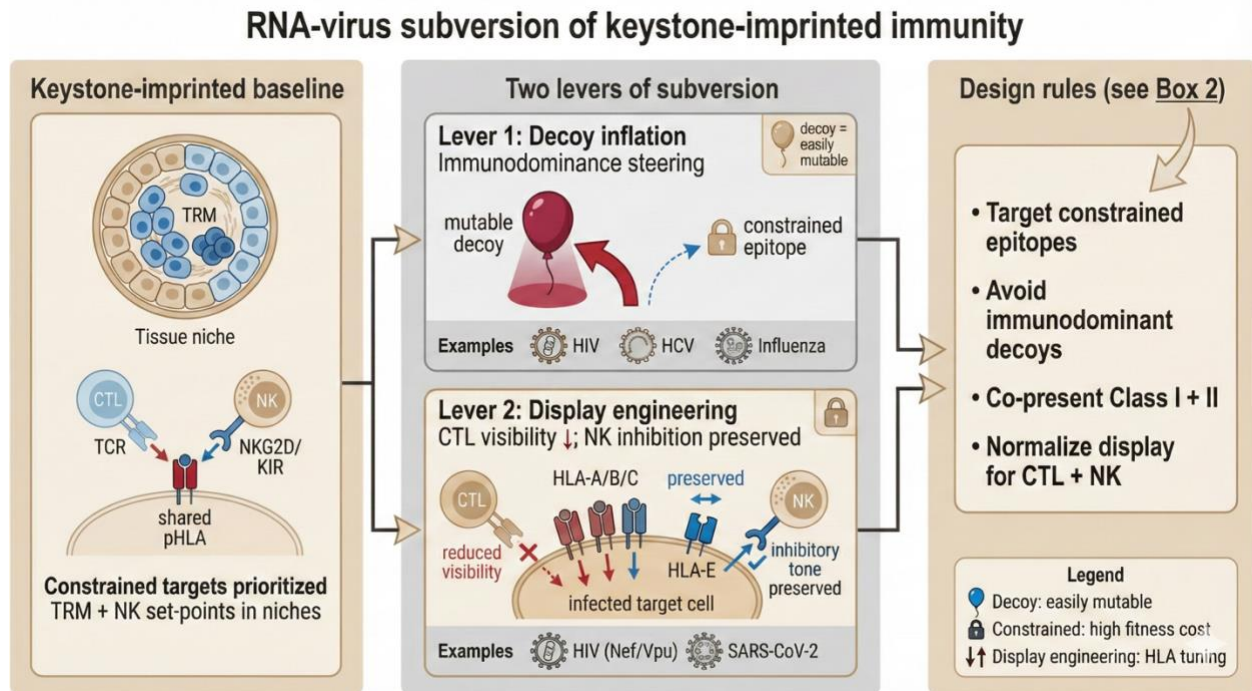The review's organizing grammar and roadmap are summarized in Figure 3.

Figure 3. Roadmap and core grammar for RNA-virus subversion of keystone-imprinted immunity. The review is organized around two coupled levers. First, within-host **immunodominance steering**: RNA viruses inflate high-visibility responses toward **mutable decoys** while constrained, function-linked sites remain under-targeted. Second, **display engineering**: viruses (and tumors) tune peptide–HLA output so CTL visibility falls while inhibitory NK tone is preserved. The figure maps HIV, HCV, influenza, and SARS-CoV-2 examples onto this grammar and shows how each lever feeds into the actionable design rules summarized in Box 2.

The shared CTL–NK 'interoperability fault line' exploited by both RNA viruses and tumors is schematized in **Figure 4**.
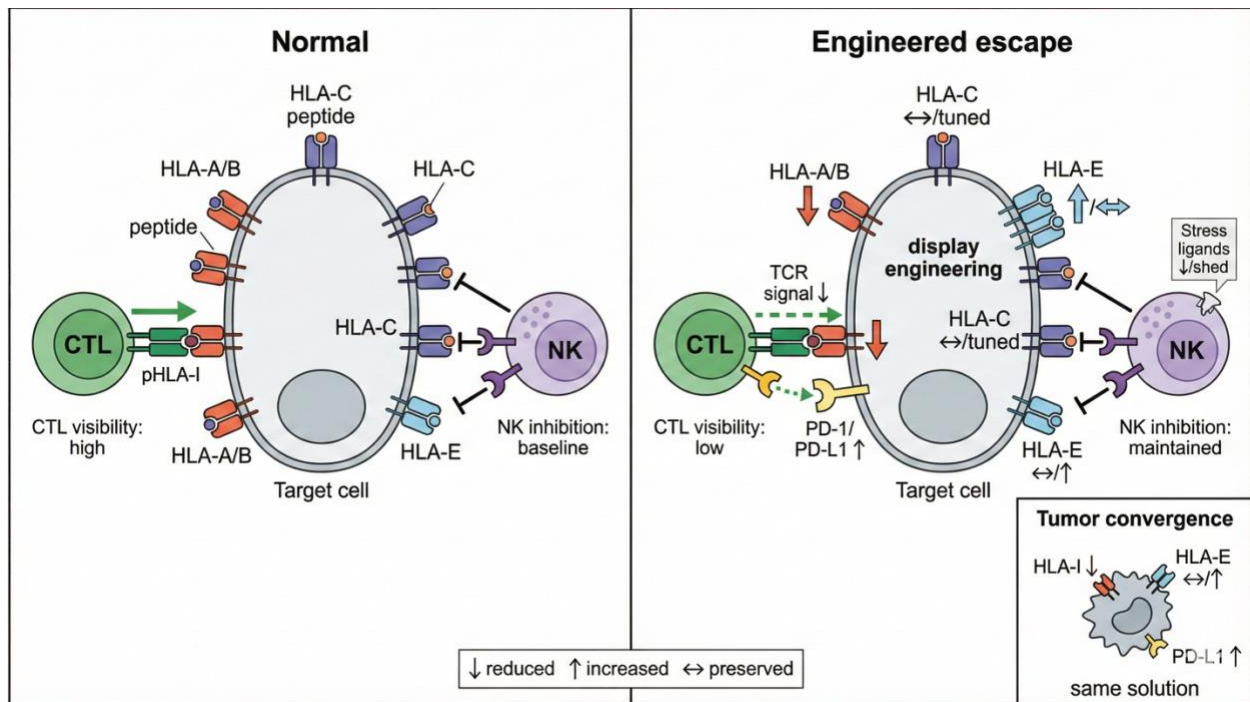
Figure 4. The interoperability fault line: how pathogens and tumors reduce CTL visibility while maintaining inhibitory NK tone. Schematic of the shared peptide–HLA surface readout by CTLs (via TCR on HLA-I) and NK cells (via inhibitory KIR and NKG2A pathways, often biased toward HLA-C and HLA-E contexts). The figure summarizes common strategies: selective reduction of HLA-A/B presentation, preservation or compensation of inhibitory ligands (for example, HLA-E axis), and checkpoint reinforcement. A parallel panel shows tumor convergence on the same solutions (class-I downregulation, inhibitory-ligand retention, checkpoint upregulation), explaining why CTL-only wins often fail without restoring NK-effective visibility.

Box 2: Example of keystone-like nonpersistent vaccines

Vaccines such as those for varicella-zoster virus (VZV) and yellow fever virus (YFV) do not establish lifelong persistence in immunocompetent hosts, they may still exhibit keystone-like properties due to their replication kinetics, tissue tropism, and ability to synchronize Class I and II epitope presentation during early infection. Both vaccines are notable for inducing durable CD8$^+$ and CD4$^+$ T cell responses [2] [3], in part because they deliver antigens in the anatomical compartments and temporal windows characteristic of natural infections. In this sense, they present keystone-like epitopes under immunological conditions that closely resemble those of a true persistent infection, resulting in unusually robust priming of long-lived effector memory. However, because they do not establish latency or provide ongoing antigenic stimulation, they cannot chronically reinforce or recalibrate immune hierarchies throughout life. Thus, while they may function as transient mimics of keystone pathogens—especially effective in their initial imprinting—they fall short of the strict definition of a keystone organism, which requires lifelong coordination of immune compartments.
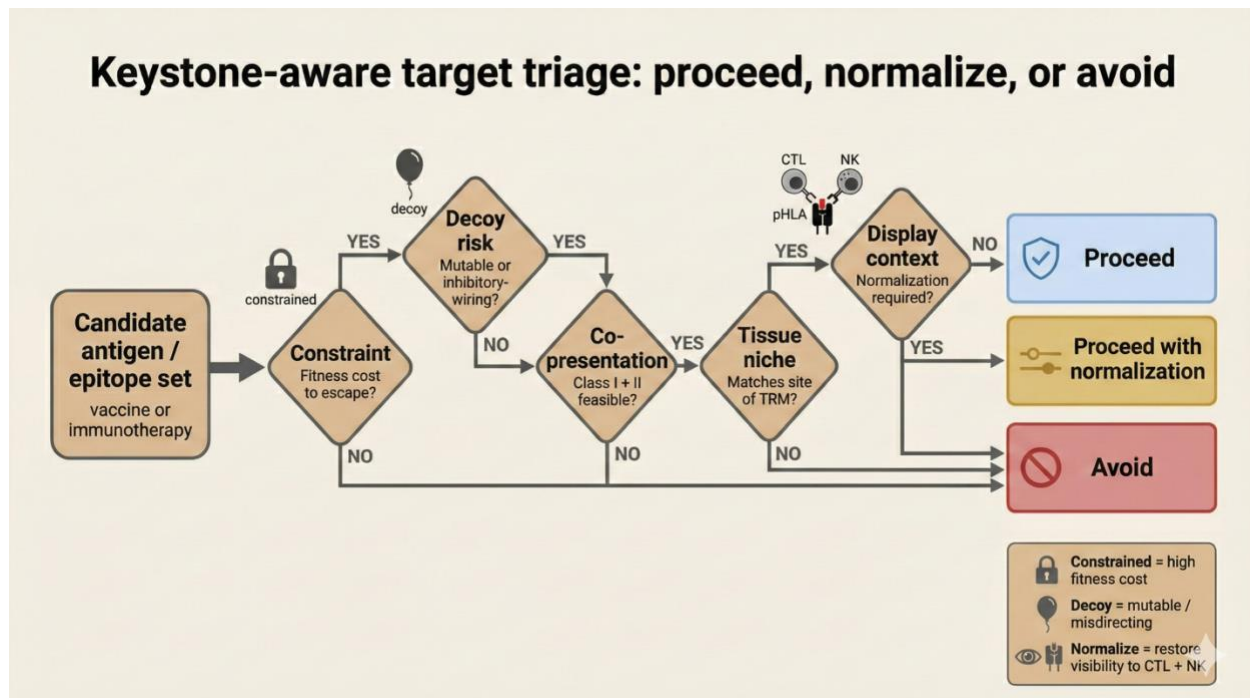
Figure 5. Practical decision tree for keystone-aware vaccine and immunotherapy design.
Starting from a candidate antigen set, the tree filters targets by (i) evidence of constraint and measurable fitness cost; (ii) decoy risk (high-visibility but easily mutable, or inhibitory-wiring reinforcing); (iii) tissue-niche relevance and class I/II co-presentation potential; and (iv) display context (whether class-I/E normalization is required for CTL and NK arms to align). Outputs are three actionable endpoints: "Proceed as immunogen," "Proceed only with display normalization," or "Avoid/replace decoy."

RNA viruses as disruptors of keystone hierarchies

With the mechanistic substrate defined elsewhere, we now ask how RNA viruses exploit it: by promoting decoys, degrading display, or reshaping thresholds (Nef/Vpu; HLA-E/NKG2A).

Before the advent of modern life, humans were typically exposed to all major species-specific keystone infections shortly after birth, ensuring early and comprehensive immune imprinting. With

reduced or delayed exposure to these keystone natural vaccinations, RNA viruses now function as an imperfect surrogate, providing repeated, intermittent short-term antigenic exposure rather than the continuous, coordinated calibration that keystone-driven immune imprinting requires. These deviations from ancestral acquisition patterns—driven by factors like improved hygiene, smaller family sizes, and reduced communal living—may disrupt early-life immune imprinting. Once established, herpesvirus infections persist chronically, continuously reinforcing antigenic hierarchies through lifelong immune imprinting and recall responses.

This evolutionary framework is further illustrated in Figure 6, which contrasts immune calibration in ancestral versus modern environments. Early-life imprinting by co-evolved keystone organisms supports compartmentalized immune readiness, while delayed or mismatched exposures in modern settings promote aberrant immunodominance and immune misfiring.

Immune Calibration in Natural vs. Modern Environments: A Co-evolutionary Perspective

Ancestral

Birth in Natural Context
Vaginal delivery, breastfeeding, early environmental exposiiore

Early-Life Keystone Infections
Early persistent infection shapes tolerance and surveillance

Tolerogenic Gut Microblome
Microbial metabolites promote mucosal tolerance

Compartnentalized Immune Calibration
Compartmentaliz-ed TRM and immune hierarchy formation

Aging with Balanced Immunity
Resilient surveillance, low autoimmunity

Modern

Birth in Sterile Environment
Cesarean delivery, tormula feeding, antibiotic exposure

Ethnic Admixture and Germline Mismatch
HLA–KIR–TCR–BCR mismatched to microbial environnment

Dysblotic Neonatal Microbiome
Fails to induce proper immune regulation

Aberrant Immunodominance Hierarchy
Mala-faptive hierarchy misguides response to real threats

Aging with Immune Misfiring Risk
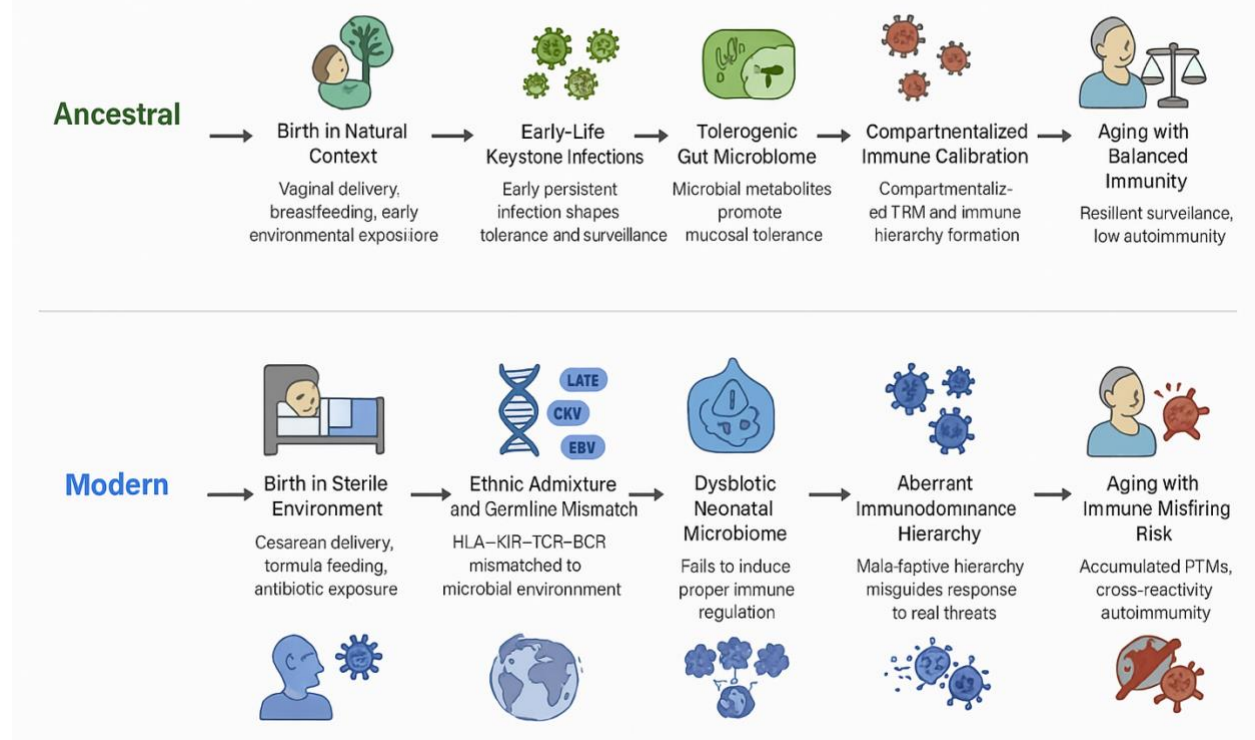Accumulated PTMs, cross-reactivity autoimmumity

Figure 6. Immune Calibration in Natural vs. Modern Environments.

The evolution of HLA-B alleles appears to reflect an adaptive response to the increasing burden of RNA viruses [15]. Evolutionarily older HLA-B alleles, such as B57 and B58, share targeting patterns with HLA-A, prioritizing conserved DNA viruses and host proteins. In contrast, later HLA-B alleles show an enhanced ability to target RNA viruses, including HIV and dengue. This shift suggests that the more recent duplication and diversification of HLA-B loci may have provided a selective advantage by improving immune recognition of RNA viruses, which can evade detection through rapid mutation and epitope decoys.

2.1 Decoy vs. constrained epitopes

(RNA Viruses as Keystone Disruptors: Evolutionary Constraints and Strategies)

The ability of keystone DNA viruses to stably present keystone epitopes is made possible by an array of highly adapted mechanisms that prevent their elimination by T cells, B cells, NK cells, and the innate immune system—either in isolation or in combination. Without these sophisticated evasion strategies, keystone viruses would not have been able to first secure their own persistence and safety within the host, a prerequisite for the symbiotic co-evolution that allows them to display keystone epitopes and ultimately enhance the survival of both the virus and its chosen host [16].

Because of their transient and highly mutable nature, RNA viruses are unreliable substitutes for keystone-driven immune calibration. Many RNA viruses evade clearance by selectively expressing immunodominant decoy epitopes, which elicit heterologous T-cell responses targeting antigenic regions where immune-driven variation is tolerated [17] [18] [15]. This strategy has been well-documented in studies demonstrating that HLA molecules preferentially target conserved regions of viral proteins, but the nature of this conservation differs depending on the virus [15]. In contrast to keystone DNA viruses, which co-evolve with their hosts and may provide keystone epitopes

that shape immune hierarchies, RNA viruses rely on an entirely different survival strategy. Rather than committing to a single host species, RNA viruses must typically 'earn a living' by constantly adapting to and switching between species. A striking feature of this long-term evolution, particularly in Flaviviridae, is the way their genomes appear pre-configured to attract immunodominant HLA-restricted responses toward more mutable regions of their proteome. This evolutionary strategy ensures that host immune pressure is consistently directed at sites where the virus retains the ability to mutate with minimal functional cost. However, once inside a new host, the virus must also adapt acutely to the specific HLA alleles it encounters, rapidly mutating within these same targeted regions to evade immune recognition. This dual-layered strategy— long-term shaping of immunodominance toward flexible regions combined with short-term, host-specific immune escape—reinforces the fundamentally disruptive role of RNA viruses in immune imprinting.

However, because vertebrate immune systems have independently evolved convergent properties—favoring MHC-restricted targeting of conserved, functionally critical regions—RNA viruses repeatedly encounter similar immune selection pressures in each new host species. Rather than posing a challenge, this predictability provides an evolutionary advantage to adaptable viruses, enabling them to consistently redirect immunodominant host responses away from conserved regions and toward more mutable parts of their genome. In other words, RNA viruses have pre-configured their genomes to exploit the common immunodominant hierarchies they are likely to encounter across multiple host species. This allows them to refine universal escape strategies, leveraging rapid antigenic drift and epitope decoying to subvert deeply entrenched immune hierarchies. The preferential targeting of non-conserved regions by HLA in flaviviruses contrasts sharply with keystone DNA viruses and represents a critical component of their immune evasion strategy.

In Keystone DNA viruses, conservation primarily reflects functional constraints, as structurally important motifs must remain unchanged to maintain viral fitness [15]. In contrast, in HIV, some conserved regions lack inherent functional constraints, yet they persist in human populations, suggesting they may be maintained because they serve as decoy targets, diverting immune responses toward non-protective regions [17].

2.2 Display engineering and threshold control (Nef/Vpu, HLA-E/NKG2A, tapasin/TAPBP)

(HIV as a Model for RNA Virus Exploitation of Keystone-Imprinted Immunodominance)

HIV functions as a live evolutionary stress test of Keystone Theory: it rapidly inflates immunodominant decoys at mutationally permissive sites, and it engineers Class-I display (e.g., Nef/Vpu) to preserve inhibitory tone (NKG2A/KIR) while eroding CTL visibility. Reading HIV through this lens makes design pitfalls and opportunities explicit. Among RNA viruses, HIV stands as the archetypal example of immune subversion through rapid evolution. Unlike DNA viruses, which evolve slowly and often co-adapt to host immunity, HIV is produced at extraordinary scale— over two billion virions daily—driven by an error-prone reverse transcriptase and a high recombination rate [19] [20]. These mechanisms enable HIV to treat each amino acid position as a quasi-independent evolutionary outcome, giving rise to a viral population capable of adapting in real time to HLA-restricted immune pressure. Yet paradoxically, this extreme adaptability makes HIV a uniquely revealing lens: its capacity to respond at a residue-specific level holds up a mirror to the selective pressures imposed by keystone imprinting. The virus maps, in reverse, the architecture of host immunity—illuminating which epitopes are prioritized, which are conserved, and how immunodominant hierarchies are shaped and subverted. At the population level, this adaptation manifests as consistent associations between specific HLA alleles and viral amino acid polymorphisms—a pattern first demonstrated in a population study of HIV adaptation to HLA-restricted responses [17]. HIV thus represents a uniquely dynamic disruptor of keystone-imprinted

immunodominance hierarchies, one that subverts immune prioritization through a combination of escape, decoying, and pre-adaptation. The following sections dissect this process, moving from individual-level immune escape to population-wide adaptation and its implications for immunotherapy and vaccine design.

2.3 Why immunodominance often goes "wrong" in RNA infections

2.3.1 HIV as an Engine of Immune Adaptation

HIV provides a striking example of how RNA viruses actively exploit and manipulate within-host immunodominance hierarchies to sustain persistence. Deep sequencing studies have shown that HIV mutations within immunodominant epitopes often persist in the population, despite immune pressure, because they do not impose a significant fitness cost on the virus [21]. Codon usage analysis suggests that HIV is pre-adapted to adapt to any HLA allele-specific selective pressure when necessary rapidly [22]. At the same time, this codon bias positions the virus to generate decoy epitopes, optimizing its ability to exploit immunodominant responses. Rather than escaping immune recognition entirely, many of these mutations redirect CD8+ T-cell responses toward ineffective, non-protective targets [18 23 24 21 25]. This dual strategy enables HIV to balance immune evasion with immune manipulation, reinforcing its persistence in genetically diverse host populations.

2.3.2 Decoy Epitopes and Immune Misdirection

A direct consequence of this immune manipulation strategy is the preferential inflation of Nef-directed responses at the expense of more protective Gag-specific responses[23]. By shifting CD8+ T-cell focus toward Nef, HIV actively reshapes the within-host

immunodominance hierarchy to sustain persistence while evading effective immune clearance.

At a population level, HIV mutations within CTL epitopes are consistently associated with specific HLA alleles, suggesting that viral adaptation is actively shaped by host immune pressure [17]. The term 'adaptation' is used when a statistical association is observed between an HLA allele and a

specific HIV amino acid residue in large-scale population studies. However, such associations do not immediately distinguish whether a mutation results from immune escape—where selection pressure eliminates immune recognition—or decoying, where immune pressure is redirected toward non-protective targets. Further functional validation is required to determine the precise mechanism of adaptation [26] [21] [25].

2.3.3 Population-Level Viral Adaptation and Pre-adaptation

Studies have shown that HIV evolves differently in distinct populations, with unique HLA-adapted polymorphisms emerging in genetically distinct host groups [27]. The balance between escape and decoy mutations is shaped by population-level HLA frequencies. In populations where a dominant HLA allele consistently targets specific epitopes, HIV is more likely to evolve escape mutations that prevent T-cell recognition entirely. Conversely, in populations with greater HLA diversity, HIV can sustain transmission by favoring decoy mutations, which divert immune responses away from functionally constrained regions of the virus, allowing it to persist without imposing a major fitness cost.

While these adaptations allow HIV to evade immune clearance in individual hosts, they also contribute to broader, population-level selection pressures. Over successive transmissions, these keystone-driven immune hierarchies become imprinted across populations, progressively shaping viral evolution in response to host genetics. Furthermore, the concept of pre-adapted HIV transmission demonstrates how keystone-driven immune pressures extend beyond a single host, progressively shaping viral evolution across transmission networks. The transmission of pre-adapted HIV variants—those already shaped by previous hosts' immune selection—weakens subsequent immune responses, leading to higher viral loads and faster CD4+ T-cell decline [28]. As protective HLA alleles become less effective due to viral adaptation, the selective advantage of these alleles erodes over time, contributing to a progressive loss of immune control at the population level [29]. Additionally, HIV adaptation to HLA-driven selection pressure is further

influenced by epistatic interactions with other host genetic factors, such as ERAP2, which modulates the peptide repertoire available for HLA-I presentation and has been associated with higher levels of viral adaptation and worsened disease outcomes [30].

2.3.4 Escape-Reversion Dynamics and Evolutionary Lock-In

Other work has demonstrated that HIV adaptation does not follow a single trajectory but involves both escape and reversion dynamics. HLA-driven HIV mutations exhibit different rates of escape and reversion, with some escape mutations persisting longer due to fitness advantages. B57-associated escape mutations, for example, rapidly revert when transmitted to non-B57 hosts, while other HLA-associated mutations remain stable over time [24]. The persistence of specific HLA-adapted polymorphisms, even in the absence of continued immune pressure, highlights the role of decoy mutations in providing a competitive advantage that sustains their prevalence. In some cases, these mutations may no longer confer a direct replicative benefit. Still, compensatory mutations elsewhere in the genome may have stabilized them, preventing reversion to the wild-type virus due to the presence of a fitness valley that the virus cannot traverse without incurring a temporary replicative cost. As a result, these polymorphisms may persist as part of a locked-in evolutionary state, continuing to misdirect immune responses while shaping viral adaptation over time.

2.3.5 Implications for HIV Vaccine and Drug Resistance

2.3.5a. Immune Pressure, Drug Resistance, and Vaccine Failure

These findings reinforce that not all escape mutations impose a fitness cost, and some are selected for their ability to misdirect immune responses. Importantly, immune-driven HIV polymorphisms may also have unintended consequences for HIV prevention strategies. For example, HLA-B18-driven escape mutations at RT codon 138 have been linked to natural resistance to rilpivirine, a key PrEP drug [31]. This highlights how immune imprinting can affect viral

persistence and therapeutic efficacy. Additionally, interactions between HLA-driven adaptation and antiretroviral therapy further complicate HIV evolution, as selection pressures from immune responses and drug resistance pathways intersect to shape viral diversity [32]. Moreover, HLA-II-associated adaptation has now been demonstrated to weaken CD4^{+} T-cell responses in HIV vaccine recipients, reducing helper T-cell support for antibody responses, which may contribute to vaccine failure. This may reflect a broader mismatch between vaccine-induced immunodominance and the keystone-based hierarchies that bias selection toward high-affinity T-cell clones and, via linked recognition, favor high-affinity B-cell responses. In the absence of persistent antigenic reinforcement, as occurs with live or chronic keystone exposures, the immune system may prioritize epitopes that are highly immunogenic yet poorly protective. Such responses may lack sufficient T follicular helper coordination to drive affinity maturation or may trigger BCR lineages with low protective potential [33]. Furthermore, early CTL immune responses during acute infection drive the emergence of viral adaptations even before full seroconversion, influencing both short-term immune control and long-term viral evolution [34].

2.3.5b Targeting Functionally Constrained Regions: Integrase as a Model

The extent of population-level adaptation is exemplified by the accumulation of escape mutations associated with previously protective HLA alleles, such as HLA-B57 and HLA-B*27, which has led to a decline in their ability to mediate immune control of HIV [35]. The success of integrase inhibitors lies in their ability to target functionally indispensable catalytic residues—sites so critical to viral replication that mutation would disrupt integrase function and compromise HIV's ability to integrate into the host genome. Medicinal chemists achieve this by designing inhibitors with exquisite structural and chemical specificity, ensuring that the drug binds only to these key residues while avoiding interactions with non-essential regions that the virus could easily mutate to develop resistance. In many ways, HLA-restricted immune responses face a similar challenge. While an effective CD8+ T-cell response must also target functionally constrained regions within viral proteins, immune recognition is inherently more vulnerable to structural escape. If the TCR's

ability to recognize a critical region of integrase depends on any residue outside of the essential functional pocket, the virus can escape by selectively mutating only those peripheral residues while preserving enzymatic function. Notably, HLA-driven escape mutations were not observed at primary integrase resistance sites—the very sites that integrase inhibitors target—highlighting the virus's ability to evade immune pressure at its most functionally constrained residues completely. Instead, the only HLA-associated polymorphisms detected occurred at non-primary antiretroviral resistance sites, further illustrating how HIV has evolved to both redirect immune pressure and exploit the structural constraints of immune recognition to avoid targeting its most vulnerable functional targets [36].

2.3.5c Neo-Epitope Formation and T-Cell Dysfunction

A longitudinal study of HIV-specific CD8+ T-cell responses confirmed that immune selection pressures lead to the emergence of neo-epitopes that induce high-avidity CD8+ T-cell responses but fail to clear the virus [26]. These responses persist throughout infection, actively contributing to immune misdirection. Rather than facilitating viral clearance, they fail to exert cytotoxicity, reinforcing that HIV exploits immunodominance hierarchies originally shaped by keystone epitopes to sustain its persistence. Additionally, early viral adaptations selected by the initial immune response can persist over time and become increasingly prevalent in circulating HIV strains, leading to an accumulation of pre-adapted variants at the population level. Furthermore, recent findings indicate that HIV adaptation to HLA-II-restricted T-cell responses, particularly in Gag, correlates with higher viral loads and more rapid disease progression [34].

The tendency of RNA viruses to mutate within regions targeted by immunodominant responses rather than conserved antigenic sites has been examined in studies comparing DNA and RNA virus evolution in response to HLA selection [15]. Keystone DNA viruses such as herpesviruses provide long-term immunodominance hierarchies that are tightly linked to host genetic selection. Interestingly, HLA targeting efficiency is similar between herpesviruses and the human proteome, supporting the concept that Keystone Epitope Theory is based on the evolutionary conservation

of functionally relevant antigenic sites [15]. However, RNA viruses do not follow this pattern—instead, their evolution is dominated by HLA-restricted immunodominant responses to highly mutable regions, leading to antigenic escape.

Whilst several studies have shown that HIV actively adapts to create decoy epitopes [18 23 24 21], single-cell transcriptomic analysis provides strong support that these decoy epitopes generate functionally ineffective CD8+ T-cell responses [25]. Such studies demonstrate that the emergence of even a single amino acid change within an HIV epitope can provoke CD8+ T-cell activation, yet these cells fail to clear infected targets effectively [25]. The altered epitope engages the TCR-HLA-peptide complex, dampening cytotoxic activity and cytokine secretion, thereby contributing to viral persistence. Instead of inducing a robust antiviral response, these CD8+ T cells exhibit a dysfunctional transcriptomic profile characterized by reduced polyfunctionality, altered signaling pathways, and impaired effector function [25]. This suggests that, HIV manipulates keystone-driven immune hierarchies to sustain ineffective CD8$^+$ T-cell responses that ultimately fail to contain the virus. Importantly, these decoy responses may also fail to recruit effective B cell help or germinal center activity. Without co-evolved CD4–B cell partnerships anchored by conserved keystone epitopes, antibody responses may remain short-lived, poorly matured, or skewed toward non-neutralizing targets—further undermining vaccine efficacy.

2.3.5d RNA Viruses as Immune Disruptors

From an evolutionary standpoint, DNA viruses (herpes, adenoviruses) act as the 'sentinel team,' maintaining long-term host adaptation, immune evasion, and mimicry, while RNA viruses (HIV, dengue) serve as disruptors, utilizing rapid antigenic variation and decoy epitopes [15]. The immune system, in response, duplicated and diversified HLA-B to target RNA viruses more effectively. However, as RNA viruses evolve at a much faster rate than human immune genes, even newly specialized HLA-B alleles are in a constant arms race with rapidly mutating RNA pathogens. This

model is strongly supported by associations between HLA-B targeting efficiency and clinical outcomes in RNA virus infections [15]. Individuals with HLA-B alleles capable of efficiently targeting conserved HIV Gag regions tend to have lower HIV viral loads [37]. Similarly, HLA targeting efficiency in dengue virus correlates with disease severity, as alleles that preferentially target non-conserved regions are linked to an increased risk of dengue hemorrhagic fever [15]. These findings suggest that HLA-B specialization for RNA viruses confers protection only when highly conserved regions are effectively targeted, reinforcing the hypothesis that RNA viruses exploit decoying strategies to subvert immune prioritization. HIV manipulates keystone-driven immune hierarchies to sustain ineffective CD8$^+$ T-cell responses that ultimately fail to contain the virus. Importantly, these decoy responses may also fail to recruit effective B cell help or germinal center activity. Without co-evolved CD4–B cell partnerships anchored by conserved keystone epitopes, antibody responses may remain short-lived, poorly matured, or skewed toward non-neutralizing targets, further undermining vaccine efficacy. More fundamentally, RNA viruses such as HIV rarely provide the persistent antigenic scaffolding needed to select and maintain high-affinity T and B cell clones directed at the virus's essential, non-adaptable structural and functional regions. This lack of evolutionary anchoring to conserved targets impairs the immune system's ability to generate durable, high-fidelity immunity through infection or vaccination.

The Keystone Epitope Theory predicts that immunodominance hierarchies shaped by keystone imprinting will prioritize functionally relevant epitopes. However, HIV subverts this process by generating immunodominant but non-protective CD8+ T-cell responses against neo-epitopes that fail to clear the infection, diverting immune pressure while preserving viral replication [26][21][25]. HIV's ability to generate immunodominant but non-protective responses illustrates how RNA viruses can exploit pre-existing hierarchies in T-cell immunity. Parallel concepts arise in other clinical contexts, including immune responses to modified self peptides as seen in drug hypersensitivity (Figure 2b), which are reviewed separately[11]. The present manuscript does not address

mechanisms underlying those phenomena or methods for defining the relevant epitopes. We speculate that including these decoy epitopes in immunogens may account, at least in part, for the failure of HIV vaccines to date. While HIV represents the most extreme example of RNA virus adaptation, other RNA viruses, such as HCV, influenza, and SARS-CoV-2, adopt distinct, sometimes more constrained strategies to engage or evade keystone-shaped immune hierarchies. These patterns generalize to HCV (escape under genotype-specific constraints), influenza (HA head decoys vs stem constraints), and SARS-CoV-2 (rapid adaptation of surface moieties).

2.4 Hepatitis C Virus: A Model of Genotype-Specific Adaptation to Keystone-Driven Immune Pressures

Hepatitis C virus (HCV) presents a compelling case of how an RNA virus adapts under keystone-driven immune pressures while following a distinct evolutionary trajectory compared to HIV. Unlike HIV, which continuously reshapes its immunodominance profile through high-frequency escape mutations, HCV exhibits constrained evolution, where certain genotypes favor immune escape while others maintain greater epitope conservation [38].

A comparative study of HCV genotypes 1 and 3 demonstrated that these strains exhibit divergent adaptation strategies, with genotype 1 showing more frequent HLA-associated immune escape, while genotype 3 displays greater conservation at immune-restricted sites [38]. This suggests that even among RNA viruses, adaptation pathways are constrained by host genetics and viral genotype, reinforcing the notion that keystone-driven immune hierarchies differ based on pathogen evolution.

Unlike HIV, which frequently reverts escape mutations in the absence of immune pressure, HCV escape mutations tend to persist, implying a fitness advantage even in hosts lacking the relevant HLA allele [39]. This suggests that while keystone epitope-driven immune imprinting establishes

strong selective pressure on RNA viruses, some viral genomes have limited plasticity to accommodate escape mutations without compromising fitness.

Furthermore, immune selection pressures are not limited to CD8+ T-cell responses. Recent studies have demonstrated that HCV undergoes CD4+ T-cell-driven immune adaptation, with HLA class II-associated polymorphisms emerging in chronic infection [40]. This reinforces the concept that keystone-driven immune imprinting shapes both cytotoxic and helper T-cell responses, structuring immune surveillance beyond CD8+ T-cell-mediated escape.

HCV evolution is further constrained by early immune responses during acute infection. Unlike HIV, which rapidly accumulates escape mutations, HCV exhibits limited plasticity in early infection, with many CD8+ T-cell escape mutations persisting into chronic infection rather than reverting [39]. This suggests that HCV must balance immune escape with viral fitness costs, reinforcing the idea that keystone-driven immune imprinting does not function uniformly across all RNA viruses.

2.4.1 HCV Adaptation in the Context of Multiple Exposures

The role of multiple exposures to HCV in shaping immune responses adds another layer to how keystone-driven immunity influences viral evolution. Studies have shown that HCV-specific CD8+ T cells from individuals with multiple exposures to different HCV genotypes maintain cross-reactivity, suggesting that immune imprinting against prior exposures can influence the ability to clear subsequent infections [41]. This contrasts with chronic single-genotype infections, where viral adaptation often results in immune escape mutations that limit cross-reactivity.

Additionally, host genetics, particularly IL28B, HLA-C, and KIR variants, play a critical role in determining both spontaneous and treatment-induced clearance of HCV [42]. The IL28B rs8099917 variant is strongly associated with spontaneous clearance, while HLA-C2 homozygosity predicts treatment failure, highlighting how host immune imprinting interacts with viral evolution. Notably, KIR-HLA interactions also influence NK cell activation and clearance outcomes, further reinforcing

that keystone-driven immune responses coordinate both adaptive and innate immunity in HCV infection [42].

Together, these findings illustrate that HCV adapts to keystone-driven immune pressures but does so in a manner distinct from HIV, an ecological contrast useful for vaccine prioritization. Rather than continuously reshaping its immunodominance profile, HCV evolution is constrained by viral fitness costs, host genetic variation, and the cumulative effects of multiple exposures, reinforcing the idea that keystone-driven immune imprinting does not function uniformly across all RNA viruses. This model of structured immune compartmentalization by keystone pathogens invites further exploration of how unrelated infections might perturb or exploit these hierarchies.

2.5 HLA Targeting Efficiency in Influenza: Insights into Keystone Epitope Selection

Not all RNA viruses evade immune surveillance by exclusively targeting variable regions. In influenza A (H1N1) infection, the efficiency with which HLA alleles target conserved viral epitopes has been shown to correlate with the magnitude of CD8+ T-cell responses and clinical outcomes [43]. HLA alleles that preferentially bind structurally constrained influenza epitopes are associated with robust interferon-gamma (IFN-γ) responses and lower mortality rates. Conversely, alleles such as HLA-A*24, which tend to bind more variable regions, are linked to increased disease severity, a pattern particularly notable in indigenous populations where these alleles are more frequent. These findings align with the Keystone Epitope Theory, reinforcing that prioritization of functionally significant epitopes underpins effective immune surveillance.

Influenza provides a unique example where HLA targeting efficiency influences immune outcomes, unlike RNA viruses such as HIV and HCV, which rely primarily on antigenic variation for immune evasion. Despite undergoing antigenic drift and shift, influenza retains conserved epitopes that function in a keystone-like manner, shaping protective immunodominance

hierarchies. However, unlike keystone DNA viruses, which maintain long-term immune imprinting through persistent exposure, influenza-driven imprinting is transient and strain-dependent. The immunodominance hierarchies shaped by HLA targeting efficiency may contribute to differential disease outcomes across populations and influence vaccine responses.

Thus, influenza highlights a constrained epitope foothold among RNA viruses, as its epitope selection is constrained by the structural and functional requirements of key proteins. In contrast, viruses such as HIV and HCV rely primarily on rapid mutation and immune evasion rather than stable epitope presentation.

2.6 SARS-CoV-2 and Keystone Epitope Theory: Cross-Reactivity and Immune Hierarchies

SARS-CoV-2 provides a distinct test case for Keystone Epitope Theory. Unlike highly mutable RNA viruses such as HIV and HCV, which continually reshape their within-host immunodominance profiles through rapid escape mutations, SARS-CoV-2 operates within a more stable immunological framework. As one of the largest known RNA viruses, its 30-kilobase genome approaches the upper limit of what can be encoded by RNA, supporting a unique replication strategy that balances genomic plasticity with partial immune recognition to facilitate efficient transmission. Unlike HIV or HCV, which rely primarily on mutation-driven antigenic drift, SARS-CoV-2 exploits pre-existing immune hierarchies shaped by prior exposure to coronaviruses or herpesviruses, navigating rather than escaping immune memory. At the level of innate–adaptive interoperability, sarbecoviruses down-modulate NKG2D ligands (e.g., via ORF6 and Nsp1), blunting NK degranulation; restoring those signals rescues NK responses—consistent with display-focused tactics that dampen early pincer responses without fully hiding from T-cell memory [44]. For curated evidence that herpesvirus imprinting can be protective or cross-protective—including maternal effects—see Box 3.

Rather than evading immunity through constant antigenic drift, SARS-CoV-2 engages or sidesteps pre-existing immune hierarchies shaped by prior exposure to common coronaviruses or latent DNA viruses.

In doing so, SARS-CoV-2 does not contradict Keystone Epitope Theory, it refines it. This virus reveals how keystone-imprinted memory may be reactivated, redirected, or mislocalized in ways that impact disease severity, viral persistence, and vaccine responsiveness. The following subsections examine five dimensions in which SARS-CoV-2 reshapes or exploits keystone-guided immune memory: cross-reactive T-cell engagement, altered epitope hierarchy, herpesvirus reactivation, compartmental evasion, and challenges for vaccine targeting.

2.6.1 Pre-Existing Cross-Reactive Memory and Keystone Priming

Unlike persistent DNA viruses or highly mutable RNA viruses, SARS-CoV-2 does not rely primarily on lifelong latency or rapid antigenic variation. Instead, it engages immune memory pre-structured by earlier coronavirus exposures—offering a natural test of Keystone Epitope Theory in the setting of a novel acute infection. Studies have demonstrated that 20-50% of unexposed individuals have detectable T-cell reactivity against SARS-CoV-2 [45]. This pre-existing cross-reactivity is largely driven by prior exposure to common cold coronaviruses (HCoVs), which share homologous T-cell epitopes with SARS-CoV-2. These findings support the concept that keystone-driven immune imprinting plays a key role in shaping immune responses to emerging pathogens, even before direct exposure.

Further studies have mapped between 30-40 immunodominant T-cell epitopes per individual, showing that SARS-CoV-2 immunodominance is dictated by the affinity of epitopes for specific HLA molecules rather than sequence homology alone [46]. This suggests that pre-existing immune hierarchies, shaped by both prior coronavirus exposures and HLA-restricted antigen presentation, determine which SARS-CoV-2 epitopes are preferentially recognized and targeted.

The impact of prior coronavirus infections on SARS-CoV-2 immunity extends beyond immunodominance. A comprehensive analysis of common cold coronaviruses identified 165 CD4+ T-cell epitopes, many of which are also recognized in SARS-CoV-2 infection [47]. Notably, 89% of cross-reactivity was predicted by sequence conservation of >67%, reinforcing the concept that T-cell memory is structured rather than stochastic and follows the principles of keystone imprinting. These data reinforce a central tenet of Keystone Epitope Theory: that early viral exposures can shape durable, hierarchical immune memory that influences responses to later-emerging pathogens—even across genera.

2.6.2 Rewiring Immunodominance: Beyond Sequence Homology

Beyond cross-reactivity, SARS-CoV-2 challenges another assumption: that sequence similarity alone dictates T-cell targeting. Instead, epitope hierarchy is shaped by HLA-binding affinity, recombination, and immunogen structure. Unlike HIV and HCV, which evade immune recognition primarily through antigenic drift, SARS-CoV-2 employs recombination-based strategies that generate novel sub-genomic RNA transcripts while maintaining partial immune recognition [48]. These findings illustrate that while SARS-CoV-2 exhibits substantial immune cross-reactivity with prior coronavirus exposures, it follows a distinct evolutionary trajectory from highly mutable RNA viruses. Rather than relying primarily on continuous antigenic variation, SARS-CoV-2 leverages genomic plasticity to optimize viral fitness while maintaining immune recognition profiles that facilitate transmission.

The interplay between keystone-driven immune imprinting, T-cell cross-reactivity, and viral recombination highlights the need for a nuanced approach to vaccine design, ensuring that immunodominant epitopes effectively engage both naïve and memory T-cell populations.

Insights into HLA targeting efficiency have direct implications for vaccine design and immunogen selection. The distinction between conserved epitope targeting in DNA viruses and the decoying

strategies of RNA viruses suggests that effective vaccines must prioritize stable, functionally constrained regions rather than immunodominant but mutable targets [15]. This may help explain the historical difficulty in developing protective vaccines for RNA viruses such as HIV, where immune responses are often misdirected toward non-protective regions that rapidly mutate. A deeper understanding of HLA targeting efficiency could enable rational vaccine design that optimizes antigen selection to reinforce keystone-driven immune imprinting rather than being subverted by viral escape mechanisms. These findings, while highlighting the breadth of T cell cross-reactivity with SARS-CoV-2, also invite a deeper analysis of how keystone-shaped memory may be functionally redirected or bypassed altogether during acute infection. This reveals that keystone imprinting involves not just exposure and memory, but also the quality and HLA compatibility of epitope presentation—refining our understanding of how immunodominance hierarchies are structured.

2.6.3 Latent Herpesvirus Reactivation and Immune Disruption

The destabilization of pre-existing memory during acute infection is further illustrated by reactivation of latent herpesviruses—offering a window into how keystone memory is recalibrated under stress. Emerging evidence further supports the dynamic interplay between SARS-CoV-2 infection and keystone-virus–driven immune hierarchies. In the IMPACC cohort, reactivation of latent herpesviruses, particularly EBV and CMV, was observed in a substantial proportion of hospitalized COVID-19 patients, with transcriptomic evidence of viral reactivation in blood, airway, and lung samples [49]. Reactivation of EBV occurred early in the disease course, while CMV and HSV1 reactivation peaked later, correlating with increased levels of IL-6, CXCL10, and other inflammatory mediators [49]. These findings support the concept of transient epitope-triggered activation (TETA) of latent DNA viruses in response to SARS-CoV-2–driven immune perturbation.

In parallel, SARS-CoV-2–specific T cells have been identified in both exposed and unexposed individuals, and in some cases exhibit cross-reactivity with CMV antigens [50]. A particularly compelling study by Pothast et al. showed that cross-reactive CD8^{+} T cells specific for a CMV pp65 epitope (IPSINVHHY) also recognize a SARS-CoV-2 spike peptide (FVSNGTHWF), both presented by HLA-B*35:01, despite low sequence similarity. These T cells were detectable in multiple CMV-seropositive individuals and COVID-19 patients, were encoded by a public TCR, and could reduce SARS-CoV-2 replication in vitro, although their phenotype during acute infection was not strongly activated, consistent with a limited role in later-stage disease [51]. These findings suggest that keystone-shaped memory can be reengaged or disrupted by heterologous infection, revealing the dynamic and conditional nature of memory maintenance.

Additional studies have demonstrated cross-reactivity between SARS-CoV-2 and EBV-derived epitopes in HLA-B*07:02[+] individuals [52], and between SARS-CoV-2 and seasonal betacoronaviruses [53]. Moreover, pre-existing T cells in unexposed individuals have been shown to target conserved nonstructural proteins (e.g., NSP7, NSP13), consistent with prior imprinting from persistent or endemic betacoronaviruses [54]. These observations suggest that keystone pathogen–shaped immune memory may be broadly redirected during SARS-CoV-2 infection, although direct epitope-level cross-reactivity with other latent herpesviruses such as HHV-6 or HSV remains unconfirmed. While cross-reactive T cells may offer early protection, their functional quality, tissue localization, and durability vary. Keystone Epitope Theory predicts that such cells may be drawn to early, immunodominant but non-protective decoy epitopes, temporarily delaying more effective subdominant responses.

2.6.4 Compartmental Misdirection and IFN Evasion

Perhaps the most striking way SARS-CoV-2 reshapes immunity is not by changing epitopes, but by avoiding the compartments where keystone-trained surveillance resides. This model must also

be viewed in light of SARS-CoV-2's broader evolutionary strategy, which centers on the early evasion of interferon-mediated innate immune responses. SARS-CoV-2 suppresses type I and III IFN signaling via multiple nonstructural proteins, resulting in delayed viral recognition, impaired T cell priming, and increased viral replication [55]. Resident memory T cells (TRMs) in the upper and lower respiratory tract are uniquely positioned to trigger rapid IFN release upon detecting infected cells, an outcome SARS-CoV-2 appears to evade. It is plausible that SARS-CoV-2 and other endemic coronaviruses have evolved to avoid re-stimulating TRMs or innate-like T cells at mucosal barriers and instead shape immune recall toward systemic compartments and decoy antigens. Consistent with this, current vaccines generate strong circulating memory but typically fail to induce TRMs [55]. This compartmental misdirection may be a hallmark of persistent viral fitness strategies, allowing transient re-engagement of keystone-shaped immunity while evading the IFN-mediated alarms that would otherwise abort early replication and transmission. This immune diversion tactic not only enables efficient SARS-CoV-2 transmission but also destabilizes previously imprinted memory networks, setting the stage for latent virus reactivation in tissues where keystone surveillance was once robust.

Through a combination of stealth compartmental entry, delayed innate activation, and partial epitope mimicry, SARS-CoV-2 avoids acute clearance and perturbs the equilibrium of chronic keystone infections. Indeed, recent studies reveal that acute infection can transiently interfer with immunological control of herpesvirus latency, illuminating the interplay between keystone-shaped memory and heterologous immune perturbation. This insight refines Keystone Theory by showing that the success of memory responses depends not only on epitope specificity, but on anatomical accessibility—highlighting that even well-imprinted memory may fail if mislocalized.

2.7 Heterologous Immune Perturbation and Latent Virus Reactivation

Animal models support a dynamic view of latency maintenance in which latent DNA viruses such as MHV-68 require continuous immune surveillance to suppress reactivation. Barton et al. showed that CD8$^+$ T cells and IFN-γ are required to control MHV-68 latency, and that latently infected mice display sustained macrophage activation and protection from unrelated bacterial infections, suggesting that latency may elevate basal, innate, and possibly adaptive immune readiness [9]. Reese et al. demonstrated that helminth infection reactivates MHV-68 via IL-4–induced STAT6 signaling, which counteracts IFN-γ–mediated suppression of the viral lytic switch, establishing a "two-signal" model for reactivation involving concurrent Th2-skewing and reduced IFN-γ tone [56]. In humans, Daud et al. showed that *Plasmodium falciparum* infection during pregnancy was associated with increased EBV viral load and reactivation, reinforcing the concept that heterologous immune stimulation can transiently breach viral latency control [57]. Importantly, such transient loss of latency control should not be seen as a pathological breakdown, but rather as a functional feature of the system, an evolved mechanism through which the immune system leverages low-level reactivation of persistent viruses to amplify and recalibrate immune responses to new threats. In this model, the latent virus serves both as sentinel and amplifier, allowing keystone-shaped memory to be adaptively re-engaged across diverse immune contexts. Gordon et al. provided indirect but compelling evidence that CMV-specific CD8$^+$ T cells expand during unrelated viral challenge, for example, vaccinia infection, even in the absence of cognate antigen recognition [58]. While this might suggest cross-reactive recruitment of keystone-shaped memory T cells to early, non-protective viral epitopes, the study more directly supports a second model: that these inflationary CD8$^+$ T cells are activated through TCR-independent cytokine signals, such as IL-12 and IL-18, serving as pre-armed reinforcements that are summoned to inflamed sites without needing to detect antigen. In this view, their presence during heterologous infection reflects a systemic mobilization of keystone-trained effectors to defend against perceived breach, regardless of specificity. These two models, direct TCR-mediated cross-reactive recognition vs.

cytokine-driven bystander activation, remain mechanistically distinct but are not mutually exclusive. Crucially, whether these responses are mediated directly through immune receptors such as TCRs or BCRs, or indirectly via cytokine-induced bystander pathways, their engagement still reflects the host's ability to harness keystone-imprinted memory in defense of new threats. This functional readiness, whether receptor-specific or non-specific, underscores the adaptive benefit to the host of keystone-driven immune imprinting.

We next examine how tumors exploit the same interoperability fault lines—antigen visibility, class-I/-E rewiring, and checkpoint gating—to divert keystone-trained memory. Practical display rules and interoperability hooks (HLA-E/NKG2A; decoy vs constrained) are summarized in **Box 2**.

3 Tumor immunoediting through the keystone lens

A growing body of evidence suggests that T-cell receptors (TCRs) primed by persistent herpesvirus infections, such as Epstein–Barr virus (EBV) and cytomegalovirus (CMV), can cross-recognize tumor-associated antigens through molecular mimicry. This cross-reactivity allows virus-specific TCRs to engage structurally similar epitopes presented by tumor cells, thereby contributing to spontaneous or immunotherapy-augmented anti-tumor immunity [59] [60]. Such herpesvirus-primed TCRs may serve as an endogenous pool of high-affinity T cells that could be leveraged in TCR gene transfer or adoptive cell therapies targeting solid tumors [61]. Tumors also co-opt the HLA-E/NKG2A axis that gates both CD8 and NK effector programs; single-cell and clinical analyses in bladder cancer show that NKG2A blockade restores cytotoxicity—particularly when tumors retain HLA-E and DNAM-1 ligands—underscoring how display-level wiring can be therapeutically reversed [62].

However, this same mimicry-based surveillance opens the door to immune subversion. Tumors, much like HIV, may evolve to express "decoy" epitopes—antigenic motifs that resemble

immunodominant viral epitopes but are non-protective or even functionally suppressive [63]. These "neutral cancer epitopes" may soak up herpesvirus-primed TCR responses without yielding effective tumor cell killing, while "bad cancer epitopes" may promote dysfunctional or tolerogenic T cell states. Such dynamics could explain cases where T-cell infiltration occurs without clinical response and support the notion that not all immunodominant tumor epitopes are therapeutically useful. In this context, herpesvirus-primed TCRs can act as a double-edged sword—powerful when appropriately directed, but vulnerable to hijacking by tumors that mimic their viral targets [64].

A companion clinical review develops the altered-self consequences in detail.[11]. For

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Box 3. Evidence of Human Herpes Virus Protection or Cross-Protection

1 Cross-Strain Protection Within the Herpesvirus Family
Several studies have documented strain-level cross-protection within the herpesvirus family. Prior oral infection with HSV-1 has been shown to reduce the severity of subsequent genital HSV-2 infection in murine models [1]. Epidemiological studies similarly suggest that early acquisition of HSV-1 may reduce susceptibility to HSV-2 later in life [4]. These findings illustrate how initial herpesvirus exposures can preconfigure immune hierarchies in a manner that blunts subsequent disease severity, potentially through shared antigenic determinants or cross-reactive T-cell responses.

2 Maternal Immunity and Intergenerational Protection
Maternal immunity to herpesviruses may confer indirect cross-protective benefits to offspring. In murine models, maternal immunization with HSV antigens reduced both mortality and neurological morbidity in neonates challenged with HSV infection [5]. These protective effects were attributed to passive transfer of maternal antibodies and priming of neonatal innate responses, demonstrating how keystone imprinting can extend its protective effects across generations.

3 Vaccine Studies Demonstrating Cross-Protection
Experimental vaccines against HSV-2 that target conserved glycoproteins such as gD have conferred protection against both HSV-1 and HSV-2 in guinea pig models [6]. These results suggest that shared viral antigens can be leveraged to elicit broadly protective immune responses, and that cross-protection can be induced even without full viral replication or persistence—though less durably than natural keystone infections.

4 Immune Competition and Epitope Hierarchy
Herpesvirus imprinting can reshape immune hierarchies, influencing responses to later, unrelated infections. In murine models, latent infection with murine γ-herpesvirus 68 or murine cytomegalovirus increases resistance to subsequent Listeria monocytogenes and Yersinia pestis challenge through sustained interferon-γ production and systemic macrophage activation, indicating that pre-existing herpesvirus-driven immunity can bias effector hierarchies toward more rapid pathogen control [9]. In aged mice, lifelong CMV infection broadens the T-cell receptor repertoire mobilized against third-party Listeria infection, consistent with a reshaping of epitope-level hierarchies that improves coverage of non-herpes antigens [10]. In humans, CMV- and EBV-specific CD8 T cells become activated and proliferate during acute hepatitis B, contributing substantially to the activated CD8 pool and demonstrating that herpesvirus-specific memory clones can be recruited into heterologous antiviral responses [12] [13] Together, these findings support the concept that prior herpesvirus infection can re-weight epitope prioritization and effector set points during later infections, potentially limiting establishment or severity of some pathogens through cross-reactive recognition, cytokine-driven bystander activation, or altered antigen presentation pathways, although these mechanisms remain incompletely defined.

5 Genetic Architecture Supporting Cross-Protection
Host genetics may also influence the degree of cross-protection following herpesvirus infection. For example, individuals carrying the activating NK receptor allele KIR3DS1 have been shown to experience milder herpesvirus outcomes and slower progression of HIV disease [14]. This suggests that herpesvirus-driven selective pressures may have shaped immune receptor genotypes that also enhance resilience to other pathogens.

NKG2A/HLA-E wiring parallels and how tumor display engineering mirrors viral strategies, see the Interoperability [8] review and Hypersensitivity [11] §2.9.

4 Conclusion and Design Rules

Keystone imprinting offers a solution to antigen prioritization by anchoring memory on conserved, functionally consequential epitopes and by coordinating cytotoxic T, helper T, B-cell, and NK programs within the right tissue niches. The same architecture defines the terrain that fast-evolving RNA viruses and tumors probe for weaknesses: they divert responses toward mutable or non-productive targets and rewire antigen display to preserve inhibitory tone while reducing cytotoxic visibility. A parallel vulnerability arises when modified-self repertoires approximate these hard-wired motifs; entrenched memory can be re-engaged despite intact regulation, a theme developed fully in the companion review on hypersensitivity, autoimmunity, and transplantation.

The practical message here is deliberately simple: target constrained epitopes, avoid decoys, and normalize display so true wins are visible to both CTL and NK arms. Read together with the quantitative trait map of keystone organisms and the systems overview of T–NK interoperability, this ecological perspective on RNA viruses and tumor immunoediting provides a coherent route from mechanism to design. The larger lesson is conceptual: treat co-evolved partners as structural components of the human immune ecosystem—partners that calibrate immune priorities over a lifetime. Designing vaccines and immunotherapies that work with (not against) these entrenched hierarchies moves us from fighting isolated battles to engineering durable balance.

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Supplementary Materials

Glossary and conceptual clarifications (with anti-glossary notes)

How to read this glossary: Several terms below describe **observed patterns** (repeatable empirical regularities) that can arise from multiple mechanisms. Other terms label **mechanisms** or **methods**. Each entry states whether it is primarily a phenomenon, a mechanism, a method, or a model construct.

Keystone Epitope Theory (KET)
- **Type:** *Model/framework.*
- **Definition:** KET proposes that a subset of persistent, human-adapted infections disproportionately shapes immune "priority setting" by repeatedly restimulating specific peptide–HLA targets in tissue niches, thereby stabilizing aspects of long-term immune hierarchy.
- **Mechanistic status:** The biology of persistence, memory boosting, and tissue compartmentalization is well-established. The claim of **disproportionate organizing influence** by a subset of organisms/epitopes is a testable hypothesis, not a settled mechanism.

Anti-glossary note: "Theory" here is not a claim of certainty. It is a structured set of predictions intended to be falsifiable.

Keystone organism
- **Type:** *Proposed operational category; grounded in observable persistence/latency but graded.*
- **Working definition:** A persistent, human-adapted infection that (i) establishes long-term latency or chronic low-level replication, (ii) repeatedly restimulates antigen-specific memory in defined tissue niches, and (iii) tends to present conserved, function-linked epitopes that occupy stable positions in immune priority patterns.
- **Mechanistic status:** Persistence and reactivation are mechanistically understood in many systems; the "keystone" claim is that some persistent organisms have **outsized** effects on immune architecture.

Does not mean: Every persistent infection; every herpesvirus in every host; uniformly beneficial effects; or a binary yes/no class.

Keystone epitope
- **Type:** *Proposed operational category (model) with measurable components.*
- **Working definition:** A peptide–HLA target that is (i) repeatedly presented due to persistence/reactivation, (ii) constrained (escape is limited or costly), and (iii) associated with durable, high-quality T-cell responses and, in some contexts, coordinated humoral responses via linked recognition.
- **Mechanistic status:** "Repeated exposure" and "constraint" can be measured. The claim that such epitopes more often seed unusually durable, regulation-resistant, compartment-spanning memory is a KET prediction.

Does not mean: Any "important-looking" peptide; all peptides from a keystone organism; or any epitope that is merely magnitude-dominant in one assay.

Keystone imprinting (KET usage)
- **Type:** *Proposed phenomenon (pattern) plus candidate mechanisms.*

- **Working definition:** Durable biasing of immune priorities established by early and repeated exposure to keystone organisms, expressed as predictable "target preferences" across time, and sometimes across tissues and heterologous challenges.
- **Mechanistic status:** The phenomenon (durable bias) is plausible and testable; mechanisms may include preferential boosting of certain memory clonotypes, tissue-resident memory seeding, and repeated antigen availability in specific niches.

Does not mean: Automatically equivalent to original antigenic sin (OAS). OAS is a narrower phenomenon (variant-strain skewing within a viral family).

Immunodominance and related terms
Immunodominance (term of art; this paper always specifies which meaning)
- **Type:** *Phenomenon/measurement label, not a mechanism.*
- **Definition:** "Immunodominance" is used inconsistently across immunology. In this manuscript it is never used without a modifier, because multiple distinct phenomena are often conflated. Dominance can refer to **display**, **response magnitude**, **time dynamics**, **population frequency**, **tissue compartment**, or **clinical control**.
- **Mechanistic status:** The mechanisms that generate dominance patterns can include antigen abundance, processing/presentation kinetics, HLA binding/stability, precursor frequency, competition, trafficking, inflammation, and escape. No single mechanism explains all cases.

1) Presentation-dominance (immunopeptidome-dominance)
- **Type:** *Phenomenon/measurement.*
- **Definition:** A peptide is "dominant in display" if it is abundant and/or stable on a given HLA molecule (typically measured by HLA peptidomics).
- **Mechanistic status:** Partly mechanistic: driven by antigen abundance, processing, TAP/ERAP trimming, HLA binding affinity, and complex stability. **Crucial caveat:** display-dominance does not guarantee a dominant T-cell response.

2) Episode-specific immunodominance (within-host, cross-sectional)
- **Type:** *Phenomenon/measurement.*
- **Definition:** At a defined timepoint in one host, epitopes are rank-ordered by response magnitude and/or function (frequency, cytokines, killing).
- **Mechanistic status:** Partial. Mechanisms can include precursor frequency, antigen kinetics, competition, and inflammation.

3) Longitudinal immunodominance (within-host, temporal)
- **Type:** *Phenomenon (pattern over time).*
- **Definition:** The within-host hierarchy changes over time (for example, escape-driven collapse of an initial dominant response with "fill-in" by subdominant responses).
- **Mechanistic status:** Partial. Mechanisms include antigen persistence, exhaustion, escape, altered processing, and compartmental reseeding.

4) Population-level immunodominance
- **House rule in this manuscript:** We use **immunoprevalence** for the "how many people respond" component to reduce confusion.
- **Type:** *Phenomenon/measurement.*
- **Definition:** Across individuals (often HLA-stratified), epitopes differ in how frequently they are recognized, and sometimes in median magnitude.

5) Compartmental immunodominance
- **Type:** *Phenomenon/measurement.*
- **Definition:** Dominance defined within a specific anatomical compartment (for example, TRM-rich tissue vs blood), which may not match blood-based rankings.
- **Mechanistic status:** Partial. Mechanisms include local antigen availability, residency, trafficking constraints, and local regulation.

6) Control-dominance (protective dominance)
- **Type:** *Inference from outcomes (phenomenon linked to phenotype).*
- **Definition:** An epitope/response contributes disproportionately to pathogen control or clinical outcome, regardless of whether it is magnitude-dominant or immunoprevalent.
- **Mechanistic status:** Case-dependent; requires outcome-linked evidence.

Immunodominance hierarchy
- **Type:** *Descriptor/measurement construct.*
- **Definition:** An ordered list of targets plus the metric and level used (presentation-, episode-, longitudinal-, immunoprevalence-, compartmental-, or control-dominance).
- **Mechanistic status:** None implied. A hierarchy is a way of summarizing data; mechanisms must be argued separately.

Immunoprevalence
- **Type:** *Measurement descriptor.*
- **Definition:** The proportion of subjects in a defined cohort who mount a detectable response to an epitope (threshold and assay must be stated).

Anti-glossary note (for immediate placement under "Immunodominance"): "Immunodominant" does **not** automatically mean: most protective; highest HLA-binding affinity; highest peptide abundance; universal across tissues; stable over time; or present in most people. Dominance is conditional on HLA, presentation context, tissue niche, and time.

Decoy vs constrained framing
Constrained epitope
- **Type:** *Measurable property.*
- **Working definition:** An epitope where substitutions incur measurable fitness costs (replication, transmission, structural integrity), limiting escape or making escape costly.
- **Mechanistic status:** Often strong when supported by fitness/escape data; "conserved" alone is insufficient.

Decoy epitope
- **Type:** *Functional label (phenotype).*
- **Working definition:** An epitope that elicits strong or sustained responses yet contributes little to control (or is associated with predictable escape), often because it is mutationally permissive, poorly positioned temporally or anatomically, or linked to low-impact effector differentiation.
- **Mechanistic status:** Case-dependent; requires evidence (for example, escape kinetics, outcome association, or demonstrated misdirection).

Does not mean: Any variable epitope, or any dominant response that fails in some contexts.

Display and interoperability
Display engineering
- **Type:** *Mechanism class with measurable correlates.*
- **Working definition:** Viral or tumor strategies that alter the pattern of peptide–HLA output and/or co-ligands so CTL visibility decreases while inhibitory NK signaling is preserved or enhanced (examples in this review include manipulation of class I versus HLA-E contexts and checkpoint reinforcement).
- **Phenomenon (correlates):** Shifted HLA peptidomes, altered class I surface levels, altered HLA-E axis engagement, altered stress-ligand display.

Does not mean: Simple antigenic variation alone.

Interoperability fault line
- **Type:** *Conceptual model term (pattern) anchored in mechanisms.*
- **Working definition:** The shared vulnerability point where pathogens/tumors can reduce CTL effectiveness by lowering class I presentation of relevant pHLA while keeping NK

cells inhibited (often via preserving inhibitory ligands such as HLA-E contexts), yielding "CTL-only wins" that do not clear infection/tumor.

CTL visibility / inhibitory NK tone
- **Type:** *Phenomenon descriptors (with mechanistic drivers).*
- **CTL visibility:** How easily CTLs detect infected/malignant cells via relevant pHLA on HLA-I.
- **Inhibitory NK tone:** The net inhibitory signaling on NK cells via inhibitory receptors (for example, KIR and NKG2A pathways), which can prevent NK killing despite cellular stress.

NK–CTL "pincer"
- **Type:** *Conceptual model term (mechanistically motivated).*
- **Working definition:** The idea that CTLs and NK cells interrogate overlapping HLA surfaces with different receptor systems (TCR for CTLs; germline receptors such as KIR/NKG2A for NK), creating two coordinated cytotoxic pressures that can be jointly manipulated by altered display.

Core molecules and cells
Peptide–HLA (pHLA)
- **Type:** *Mechanistic unit; measurable.*
- **Definition:** The cell-surface complex of a peptide bound to an HLA molecule. It is the recognition unit for CD8 T cells and can influence NK receptor binding in some contexts.

TCR (T-cell receptor)
- **Type:** *Mechanistic receptor.*
- **Definition:** Somatically rearranged receptor on T cells that recognizes specific pHLA complexes.

KIR (killer cell immunoglobulin-like receptors)
- **Type:** *Mechanistic receptors.*
- **Definition:** NK receptors that bind HLA class I molecules; some interactions are peptide-influenced, tuning inhibition or activation depending on receptor type and context.

NKG2A and HLA-E
- **Type:** *Mechanistic checkpoint axis.*
- **Definition:** NKG2A is an inhibitory receptor (typically with CD94) that recognizes HLA-E presenting specific leader-like peptides, contributing to NK inhibition and calibration.

TRM (tissue-resident memory T cells)
- **Type:** *Cell-state category (phenomenon with mechanisms).*
- **Definition:** Memory T cells that reside long-term in tissues rather than recirculating.
- **Mechanistic status:** Residency programs are increasingly well-characterized; the claim that keystone exposures preferentially seed or maintain TRM patterns in specific niches is a KET prediction.

Tumor concepts
Tumor immunoediting
- **Type:** *Phenomenon (process inferred from evolution under immune pressure).*
- **Definition:** Tumors evolve under immune selection, often selecting for antigen loss, altered antigen processing/presentation, altered HLA expression, and checkpoint reinforcement.
- **Mechanistic status:** Multiple mechanisms are known; the precise mix varies by tumor and context.

Immune checkpoint
- **Type:** *Mechanism class.*

- **Definition:** Inhibitory pathways that restrain immune activation (in this review, the emphasis includes checkpoint reinforcement that preserves inhibitory signaling in the face of stress).

Cross-reactivity and modified self
Modified self
- **Type:** *Mechanistic phenomenon (presentation change).*
- **Definition:** A self-derived peptide that becomes newly immunogenic because a drug or post-translational modification changes peptide processing or the peptide–HLA repertoire, potentially recruiting pre-existing memory if structural similarity exists.

Anti-glossary (global "does not mean" clarifications)
- **"Immunodominant"** does not mean "most protective." It means "dominant by a stated metric,".
- **"Integrate into immune hierarchies"** does not mean viral DNA integration into the host genome. It refers to durable positioning within immune memory priorities.
- **Verbs like "exploit," "engineer," "optimize," or "designed"** do not imply intent or agency. They are shorthand for selection effects and opportunistic outcomes.
- **"Linkage"** (genetic distance on a chromosome) is not the same as **"linkage disequilibrium"** (statistical non-random allele association). We use LD explicitly when that is intended.