Keystone Theory: Implications for Effective T and Natural Killer Cell Interoperability

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Abstract

Cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells form complementary arms of human immunity, yet their interoperability depends on shared peptide–HLA surfaces and finely tuned checkpoints. *Keystone Epitope Theory* proposes that persistent pathogens and host coevolution have shaped these interfaces, aligning TCR and KIR/NKG2 readouts to sustain coordinated control. Here we synthesise structural, genetic, and functional evidence into twelve *Keystone Propositions* (KP1–KP12) that capture triad integration, quantitative tuning, postnatal imprinting, and viral subversion. We then apply this framework to HIV, presenting fourteen canonical scenarios (S1–S14) that map how constrained epitopes, decoy misdirection, and whole-cell display engineering shape outcomes. This systems overview links peptide geometry, licensing set-points, and immunoregulatory wiring to translational design, providing a decision tree for when CTL and NK arms align, when they are diverted, and how interventions can restore balance. We conclude with a design grammar for vaccines and immunotherapies: avoid decoys, prioritise constrained epitopes, co-present class I and II, respect licensing and imprinting, and normalise display when necessary.

Keywords: Keystone Epitope Theory, cytotoxic T lymphocyte, natural killer cell, peptide-HLA, immune licensing, KIR, NKG2A, immune checkpoints, viral escape, HIV, constrained epitopes, decoy epitopes, vaccine design, immunotherapy, immune interoperability

Orientation and Scope

This review is part of a coordinated set of manuscripts developing *Keystone Epitope Theory*. A foundational quantitative trait analysis defines keystone organisms and introduces a reactivation index as a systems biomarker [1]; a clinical companion addresses the downstream consequences of modified self, including hypersensitivity, autoimmunity, and transplantation [2]; and an ecological companion extends the framework to RNA viruses and tumors, formalising "decoy versus constrained" grammar and principles of display engineering for vaccine design [3].

Here we provide the systems overview. Our focus is on how cytotoxic T cells (CTLs) and natural killer (NK) cells interoperate on shared peptide–HLA targets, how licensing and checkpoint wiring calibrate thresholds, and how pathogens exploit these axes by editing antigen display. We formalise twelve Keystone Propositions (KP1–KP12) that link structural geometry, quantitative tuning, postnatal imprinting, and viral subversion. We then apply these propositions to HIV, presenting a taxonomy of fourteen scenarios (S1–S14) that illustrate classic pincers, decoy misdirection, and whole-cell display control.

The aim is to provide a mechanistic scaffold: to show how a single pHLA surface can simultaneously govern CTL and NK outcomes, how viruses exploit this shared geometry, and how these rules can be translated into actionable design grammar for vaccines and immunotherapies.

Introduction

From Keystone Organisms to Peptide Geometry-and Back to Translational Impact

A small group of persistent, human-adapted pathogens-herpesviruses like CMV, EBV, HSV, as well as Mtb and others-do more than evade immunity: they structure it. These *keystone organisms* calibrate immune architecture across tissues and life stages by persisting within defined niches, interacting with multiple immune arms, and imprinting durable memory [1]. Their reactivation patterns under immunosuppression reflect not isolated vulnerability, but collapse of coordinated immune systems [4–6].

This review presents a unifying model-*Keystone Epitope Theory*-that connects the macro-scale influence of keystone organisms to the micro-scale geometry of peptide presentation and receptor recognition. It outlines how these dynamics shape immune imprinting, viral escape, autoimmune risk, and vaccine failure, and proposes a framework of twelve core mechanisms, or *Keystone Propositions (KPs)*, that define this interaction space.

Ultimately, this theory loops back to practice. It explains why immune magnitude can fail to deliver control, why tissue-specific mimicry arises, and how effective immunogens must engage coordinated arms of immunity while bypassing viral traps. From ecological partners to molecular targets to diagnostic and therapeutic design, the theory aims to realign our understanding of host-pathogen coevolution with translational goals in immunology.

From Microbial Ecology to Molecular Rules

Keystone organisms exert their influence by guiding postnatal immune imprinting. These early or chronic exposures shape hierarchical preferences for specific epitopes and seed tissue-resident memory in targeted compartments [6]. Yet the molecular mechanisms that underpin this system-wide coordination remain under-characterized.

At the center of immune recognition lies a shared surface: peptide-HLA (pHLA) complexes. These structures are simultaneously sensed by T cell receptors (TCRs) on cytotoxic $CD8^+$ T cells and by killer-cell immunoglobulin-like receptors (KIRs) or NKG2 family receptors on NK cells. The outcome-killing, tolerance, or evasion-depends not just on whether the immune system responds, but *how* it reads these surfaces.

The twelve propositions that follow outline this logic, progressing from structural determinants to imprinting and diversification, and finally to viral subversion and translational consequences.

KP1–KP4: Joint Recognition and Constrained Targets

The first group of Keystone Propositions (KP1–KP4) centers on how CTLs and NK cells converge on shared surfaces and how the structure and constraint of those surfaces governs immunity. At the core, both cell types sense peptide–HLA (pHLA) complexes: CTLs via the TCR, and NK cells via KIRs or NKG2 receptors (KP1) [7, 8]. These receptors do not operate in isolation, activation thresholds are tuned by quantitative features such as HLA-C expression (KP2) [9, 10], peptide binding stability (KP2) [11], and accessory factors like tapasin and TAPBP, which assist in peptide loading (KP2) [12, 13]. Viruses exploit this same interface by remodeling class I display and checkpoint axes, for example via Nef- or Vpu-mediated changes in HLA-A/B/C abundance and peptide supply that preserve inhibitory signaling through HLA-E/NKG2A or KIR and skew the pincer (KP3) [14–17].

Functionally, control is strongest when CTLs target *constrained epitopes* (KP4), regions where escape mutations diminish viral fitness and often require compensatory changes. These epitopes act as structural anchors of long-term containment and are preferentially selected across individuals and populations [18–20].

KP5-KP7: Imprinting, Coevolution, and Regulatory Circuits

The next cluster (KP5-KP7) captures how durable immune hierarchies form and persist. Keystone exposures during early life imprint long-term preferences for specific class I and II epitopes, seeding tissue-resident memory and reinforcing learned immune hierarchies across compartments (KP5) [6]. This bias is not arbitrary: coevolution between host and pathogen shapes the repertoire of available HLA alleles and pathogen epitopes over millennia (KP6) [21, 22], resulting in entrenched host-pathogen pairings.

These hierarchies are further sculpted by non-classical regulatory axes-such as HLA-E/NKG2A and LILRB2/ILT4-that shape thresholds for tolerance and effector engagement (KP7) [17, 23]. These mechanisms provide immune redundancy, but also create specific windows of vulnerability under perturbation.

KP8-KP10: Peptide Dependence, Licensing, and Population Variation

The third group (KP8-KP10) highlights how the same pHLA surface can generate divergent outcomes across contexts. NK cells exhibit *peptide-dependent tuning* (KP8), where subtle changes in peptide sequence can switch an inhibitory interaction to activating-or vice versa-via specific KIRs [7, 24]. This peptide sensitivity is individualized through NK *licensing*, a developmental process in which NK cells are "educated" to recognize self-HLA and calibrate their responsiveness accordingly (KP9) [8, 25, 26].

At the population level, these dynamics vary dramatically. Geographic differences in HLA and KIR allele frequencies, combined with regional pathogen pressures, create divergent immune outcomes to identical viral mutations (KP10) [21, 27, 28]. What escapes control in one host may remain visible in another.

KP11-KP12: Viral Subversion of Immune Priorities

The final pair (KP11-KP12) describes how viruses exploit the architecture of immune hierarchies. This reflects *decoy epitope misdirection*: viruses evolve immunodominant but non-protective epitopes that preferentially engage inhibitory KIRs, diverting CTLs toward ineffective targets while maintaining NK suppression (KP11) [20, 29–32].

This also involves *display engineering*, in which viral proteins such as Nef and Vpu modulate antigen presentation. These proteins downregulate HLA-A and HLA-B to escape CTL detection while preserving or enhancing expression of HLA-C and HLA-E, which maintain NK cell tolerance (KP12) [14, 15, 24]. Together, these strategies allow viruses to exploit postnatal imprinting for their own benefit, disconnecting immune magnitude from control and challenging vaccine design.

Why Coordination Matters

Taken together, KP1-KP12 define a systems-level model of immune engagement, where the geometry of peptide display, the regulation of recognition thresholds, and the evolutionary history of both host and pathogen jointly determine outcome. They explain why high immune magnitude can coexist with poor control, why mimicry risk concentrates in tissue niches imprinted by keystone organisms, and why successful vaccines must do more than trigger memory-they must coordinate arms, avoid decoys, and respect the architecture of trained immunity.

From Theory to Mechanism: The Keystone Propositions

Together, KP1-KP12 define a multidimensional decision space, where immune magnitude, specificity, and coordination must align to yield control. Each proposition is grounded in structural, genetic, or functional evidence, and comes with explicit assays, examples, and design implications.

In the section that follows, we present each proposition as a mechanistic module. In the section after that, we apply them to a concrete setting-HIV infection-where the interplay of CTL and NK cells across constrained and decoy epitopes provides a rich testbed for prediction, falsification, and translational insight.

Box 1. Primer on Immune Components and Terms

Table 1 *

Term	Definition	Role in Immune Response
$CD8^+$ cytotoxic T cell (CTL)	T cell subtype that recognizes peptide antigens presented on HLA class I molecules via TCR	Kills infected or malignant cells displaying foreign or abnormal peptides; key effector against viruses and tumors
$CD4^+$ helper T cell	T cell subtype that recognizes peptides presented on HLA class II molecules	Coordinates immune responses by providing help to CTLs, B cells, and macrophages; essential for long-term immunity
NK cell (Natural Killer)	Innate lymphocyte that senses abnormal or missing-self via inhibitory and activating receptors (e.g., KIR, NKG2)	Eliminates cells with reduced HLA-I or abnormal surface markers; acts independently of antigen specificity
TCR (T cell receptor)	Antigen receptor on T cells that recognizes peptides bound to HLA molecules	Enables $CD8^+$ and $CD4^+$ T cells to detect infected or transformed cells
KIR (Killer-cell Immunoglobulin-like Receptor)	Family of receptors on NK cells that recognize specific motifs on HLA class I molecules	Modulate NK cell activation or inhibition; responses are tuned by prior education and peptide context
HLA class I (A, B, C)	Molecules that present intracellular peptides to $CD8^+$ T cells; also sensed by NK cells	Enable cytotoxic surveillance of viral or tumor-derived peptides; also regulate NK cell inhibition
HLA class II	Molecules that present extracellular-derived peptides to $CD4^+$ T cells	Support adaptive immunity by activating helper T cells during infection and inflammation
HLA-E, HLA-F	Non-classical HLA class I molecules sensed by NK cell receptors like NKG2A or KIR3DS1	Modulate tolerance and activation in NK cells; often exploited by viruses for immune evasion
Peptide-HLA (pHLA) complex	Molecular surface formed by a peptide bound in the groove of an HLA molecule	Determines recognition by TCRs and NK receptors; structural constraints affect immunogenicity
Tissue-resident memory T cell (T_{RM})	Long-lived T cell subset that resides permanently in tissues	Provides rapid local protection; shaped by early-life infection and compartment-specific cues
Immunodominance	Hierarchical pattern of immune responses to multiple potential epitopes	Determines which viral or tumor peptides are preferentially targeted by T cells
Constrained epitope	Peptide where escape mutations impose a significant fitness cost to the pathogen	Often targeted in protective immunity; ideal for vaccine design
Decoy epitope	Peptide that elicits strong but non-protective responses	Diverts immune targeting away from conserved or functionally relevant epitopes
Immune magnitude vs control	Observation that strong immune responses do not always lead to pathogen clearance	Highlights importance of targeting, coordination, and evasion dynamics in immunity

Twelve Rules for Immune Engagement

To operationalize Keystone Epitope Theory, we outline twelve core propositions (KP1-KP12) that explain how peptide display, receptor logic, quantitative tuning, imprinting, and evasion coalesce to determine outcomes. Each KP lists a concise definition, a mechanistic synopsis, and a concrete example (linked to the S1-S14 scenario taxonomy).

2.1 KP1 - Triad integration: CTL and NK readouts of a shared pHLA surface

Cytotoxic T cells and NK cells often interrogate the same peptide-HLA (pHLA) complex, but from different angles. Small changes in peptide pose or HLA groove chemistry can tilt recognition on both arms simultaneously-tightening or loosening the immune "pincer."

(a) **Definition.** Triad integration refers to the shared use of the same pHLA surface by CTL TCRs and NK receptors (KIRs or CD94/NKG2), meaning that one geometric change can coordinate or uncouple adaptive and innate cytotoxicity [7, 8, 17, 25].

(b) **Mechanism.** Polymorphic residues in the HLA groove (e.g., positions 67, 70, 97, 156) set peptide conformation and stability, tuning both TCR recognition and KIR binding [7]. For the HLA-Bw4/KIR3DL1 axis, C-terminal peptide features and Bw4-80I/80T polymorphisms modulate inhibitory signaling, with stronger education and effector potential when binding is tight [8]. For the HLA-E/CD94-NKG2 axis, signal peptides from HLA-A/B/C/G determine which VL9 variants are loaded, shifting the balance between inhibitory NKG2A and activating NKG2C recognition [25]. Rare activating KIR allotypes (e.g., KIR3DS1*014) illustrate how subtle sequence differences can reprogram binding specificity [33].

(c) **Evidence.** Mutational scans of HLA-B*57:01 show that residue substitutions (M67, S70, V97, L156) differentially alter TCR and KIR readouts of the same epitope [7]. Functional studies confirm that stronger KIR3DL1-Bw4 binding and higher receptor/ligand density predict better cytotoxicity against HIV-infected targets [8]. For HLA-E, only a subset of signal peptide variants generate VL9 complexes that efficiently engage CD94/NKG2 receptors, explaining inter-allelic differences in inhibitory tone [25]. Inhibitory KIR2DL2-HLA-C interactions can be destabilized by peptide substitutions, releasing NK activity in HIV infection [24]. Tumor and viral systems further illustrate how elevated HLA-E restrains both CTLs and NK cells via NKG2A, and how blockade restores cytotoxicity [17].

(d) **Examples.** (i) HLA-B*57:01-restricted Gag epitopes (TW10, KF11) highlight how escape variants alter both TCR visibility and KIR3DL1 binding. (ii) KIR3DL1/Bw4-80I partnerships calibrate NK education and predict stronger killing of autologous HIV-infected $CD4^+$ T cells [8]. (iii) HLA-C*12:02 or C*14:03 with KIR2DL2 shows reduced inhibition due to unstable peptide presentation, correlating with lower viraemia in Japanese cohorts [24]. (iv) Elevated HLA-E in tumors engages NKG2A and restrains CTL/NK function; anti-NKG2A blockade restores effector responses [17].

(e) **Implications.** Any intervention that stabilizes favorable pHLA geometry without reinforcing inhibitory readouts can align CTL and NK activity. Vaccine design and checkpoint strategies must therefore be tested against *both* TCR and NK receptor readouts of the same peptide-HLA surface.

2.2 KP2 - Quantitative ligand-receptor tuning calibrates thresholds

Immunity is not only about having the "right" epitope-it is about how much, how long, and in what context it is displayed. Small quantitative shifts in class I expression, peptide stability, and receptor dosage can tip outcomes from protection to progression.

(a) **Definition.** Quantitative traits of class I presentation and receptor content-such as HLA-C surface abundance, peptide-HLA stability, tapasin/TAPBP dependence, and KIR copy number-set the activation thresholds for CTLs and NK cells [8–10, 12, 13, 34].

(b) **Mechanism.**

- **HLA-C expression.** Genetically encoded variation in HLA-C expression alters both CTL visibility and NK education. Higher expression increases pHLA density, strengthening CTL pressure but also inhibitory KIR ligation [9, 10, 35].
- **Peptide stability.** Epitope half-life at the surface predicts immunodominance. Protective alleles are preferentially stabilized by networked, structurally constrained epitopes [11].
- **Tapasin/TAPBP.** Tapasin independence broadens the peptide repertoire of certain HLA allotypes, while higher TAPBP expression selectively rescues presentation in tapasin-dependent contexts and improves malaria outcomes [12, 13].
- **KIR gene dose/density.** The number and surface density of KIR3DL1/3DS1 molecules and Bw4 ligands tune NK licensing strength, with stronger binding yielding more responsive NK cells [8, 34].
- **Leader peptides and HLA-E.** Signal peptide polymorphisms from HLA-A/B/C shape HLA-E expression and thus NKG2A education, shifting the balance of inhibitory tone [25, 26].

(c) **Evidence.** (i) Multi-ancestry cohorts confirm that high-expression HLA-C allotypes lower HIV set-point viral load and drive stronger C-restricted CTL responses [9, 10]. (ii) TAP-deficient systems show that immunodominant HIV epitopes are superior stabilizers, linking peptide half-life to immunodominance [11]. (iii) Tapasin-independent alleles present broader repertoires and correlate with better HIV control [12]. (iv) Elevated TAPBP expression reduces malaria burden in carriers of tapasin-dependent allotypes [13]. (v) KIR3DS1/3DL1 copy number variation associates with lower HIV viral load; binding strength and receptor/ligand density predict NK education in vitro [8, 34]. (vi) Elevated HLA-A expression enhances HLA-E presentation and NKG2A inhibitory tone, worsening HIV control [26].

(d) **Examples.** *S3 vs S4*: In one case, CTL diversion to a decoy epitope is partially offset if inhibitory KIR engagement is not reinforced; in another, viral peptides enhance inhibitory binding, blunting both CTL and NK arms [29, 30]. *Quantitative rescue*: Higher TAPBP expression aids carriers of dependent alleles, illustrating how small boosts in peptide loading machinery shift infection outcomes [13].

(e) **Implications.** Thresholds are tunable. Interventions that modestly raise HLA-C expression, bias toward kinetically stable epitopes, enhance TAPBP in susceptible contexts, or adjust KIR gene dose can flip the balance of control without altering epitope identity. Vaccine and therapeutic design should explicitly stratify by quantitative HLA tiers, tapasin dependence, and receptor-ligand gene content.

2.3 KP3 - Viral subversion of HLA class I display and checkpoints

Viruses do not just hide-they edit the cell surface. By selectively reshaping class I and stress ligands, they evade CTL detection while preserving or even enhancing inhibitory signaling for NK cells, creating a tilted playing field for immune surveillance.

(a) **Definition.** Viral accessory proteins and mimics remodel class I HLA and checkpoint ligands in ways that suppress CTL clearance and blunt NK activation, often in allele- or strain-specific patterns [14–17].

(b) **Mechanism.**
- **Nef and Vpu.** HIV-1 Nef preferentially downregulates HLA-A and -B, sparing HLA-C; Vpu can also reduce HLA-C in a host- and strain-tuned manner. Together, these changes fragment CTL surveillance while retaining inhibitory KIR ligands [14, 15].
- **HLA-E detours.** Signal peptides from HLA-A/B/C-or viral mimics like CMV UL40-stabilize HLA-E, increasing inhibitory CD94/NKG2A signaling even when classical class I is downregulated [17, 25].
- **Stress checkpoints.** Sarbecoviruses (e.g., SARS-CoV-2) attenuate or shed NKG2D ligands (MICA/B), cutting off an activating route for NK cells [16].

(c) **Evidence.** (i) In primary HIV-1 infection, Vpu deletion restores HLA-C levels and enhances CTL suppression of viral replication [14]. (ii) HIV-1 downregulation of HLA-C diminishes inhibitory KIR2DL1/2DL3 binding, leaving NK responsiveness strain-dependent [15]. (iii) HLA-E/CD94-NKG2A forms a functional checkpoint in cancer and infection; blockade re-engages effector cytotoxicity [17]. (iv) SARS-CoV-2 ORF6 induces MICA/B shedding, detectable as elevated serum MIC-A/B in patients, and blockade of shedding restores NK killing in vitro [16].

(d) **Examples.** *S2*: HIV preserves inhibitory KIR engagement after CTL escape, subverting the NK "rescue." *S12*: Sarbecoviruses down-modulate NKG2D ligands, blunting NK activity. *S14*: Elevated HLA-E engages NKG2A and restrains cytotoxicity until checkpoint blockade intervenes.

(e) **Implications.** Viral display engineering shows how whole-cell surface editing can undermine epitope-level gains. Restoring balanced class I display (countering Vpu/Nef), preventing NKG2D ligand shedding, or transiently blocking the HLA-E/NKG2A checkpoint are therapeutic avenues to re-establish a functional CTL-NK pincer.

2.4 KP4 - Constrained epitopes: fitness costs and compensated escape

Not all viral targets are equal. Some epitopes sit in "load-bearing" regions of the viral machine, where mutations exact heavy replication costs. Pushing the virus into these corners forces escape along narrow, costly, and sometimes reversible paths.

(a) **Definition.** Constrained epitopes are regions of viral proteins where immune-driven mutations reduce replication capacity or require complex compensatory pathways. These epitopes are often structurally central, highly networked, or functionally indispensable [18, 19, 36].

(b) **Mechanism.** Escape mutations in constrained sites perturb structural interactions (e.g., capsid interfaces), impairing viral assembly or function. Such changes often revert in transmission to hosts lacking the selecting HLA, or are buffered by second-site compensations that restore partial fitness [18, 20]. Sustained pressure at multiple constrained sites further limits viable routes, "cornering" the virus [36].

(c) **Evidence.** (i) Early HIV cohorts show rapid escape at B*57-restricted Gag sites, with frequent reversion on transmission, consistent with fitness costs [20]. (ii) Network and topological analyses identify capsid "sectors" enriched for controller-targeted epitopes, where multi-mutant combinations are rarely tolerated [18, 19]. (iii) Structural studies confirm that residues with high connectivity are preferentially targeted by protective HLA alleles [36]. (iv) Closely related alleles (e.g., B*27:05 vs B*27:02) impose different hierarchies, showing how subtle binding-groove differences steer which constrained epitopes are pressured [37].

(d) **Examples.** *S1*: The B*57-restricted Gag epitope TW10 (TSTLQEQIGW) escapes via T242N, reducing replication and requiring compensations such as H219Q or I223V in the cyclophilin A loop [38, 39]. *S6*: Compensation routes restore replication after high-cost escape, illustrating predictable multi-step paths. Controllers preferentially target "sector 3" residues in Gag, where higher-order constraints prevent accumulation of multiple mutations [18].

(e) **Implications.** By deliberately focusing immunity on constrained epitopes, immunogens can force pathogens into high-cost escape, reduce viable routes, and prolong control. Designs should prioritize epitopes with measurable replication penalties and limited compensation, ideally spanning multiple sites within structurally networked regions.

2.5 KP5 - Imprinting: thymic biases and lifelong focusing

The immune system never starts from scratch. Thymic selection sketches the TCR repertoire, and persistent pathogens etch in the details-shaping durable hierarchies of response that persist across tissues and decades.

(a) **Definition.** Imprinting encompasses both thymic selection, which biases the breadth and cross-reactivity of naïve TCRs, and postnatal reinforcement by chronic or latent infections, which fix long-term hierarchies of immunodominance and memory [5, 6, 40].

(b) **Mechanism.**

- **Thymic foundation.** HLA alleles presenting narrower self-peptidomes (e.g., B*57) select for TCRs with higher cross-reactivity, biasing responses toward conserved viral epitopes [40].

- **Postnatal reinforcement.** Latent-lytic cycling by herpesviruses or other persistent pathogens repeatedly recalls memory, aligning class I and II responses and seeding durable tissue-resident memory (TRM) [5].
- **Allele-specific focusing.** Closely related HLA subtypes impose distinct immunodominance hierarchies (e.g., B*27:05 vs B*27:02), fixing divergent escape footprints [37].
- **Mimicry risk.** Repeated boosting of the same antigens can enforce cross-reactivity to self-like proteins (e.g., EBNA-1 and CRYAB) [6].

(c) **Evidence.** (i) Modeling shows that thymic selection under B*57 narrows self-peptidomes and enriches for cross-reactive TCRs [40]. (ii) EBV infection imprints EBNA-1-specific antibody repertoires that persist and acquire cross-reactivity to host proteins [6]. (iii) HSV reactivation in CLL patients drives coordinated B and T cell surges across compartments, coinciding with tumor regression, illustrating systemic recall [5]. (iv) Comparative studies of B*27:05 and B*27:02 show allele-dependent dominance of Gag vs Nef responses, leading to different escape patterns [37].

(d) **Examples.** *EBV*: EBNA-1 responses persist long after acute infection, with antibodies that broaden in function and cross-react with CRYAB [6]. *HSV*: Reactivation triggers systemic B and T cell activation, demonstrating how imprinting synchronizes tissue and systemic immunity [5]. *HIV*: B*27:05 vs B*27:02 impose distinct target preferences (Gag KK10 vs Nef VW9), each leaving characteristic footprints [37].

(e) **Implications.** Imprinting clarifies why immune hierarchies become entrenched and sometimes exploitable by pathogens. Vaccines that co-present class I and II epitopes from structurally constrained regions, and that seed the right tissue niches, may align with these durable biases rather than compete with them.

2.6 KP6 - Host-pathogen coevolution

Across centuries and continents, pathogens have sculpted human immune genes, and hosts in turn have left signatures in viral genomes. These reciprocal pressures are written in the geography of HLA and KIR alleles, the footprints of escape mutations, and the clines of pathogen lineages.

(a) **Definition.** Host-pathogen coevolution describes reciprocal adaptation between immune genes (HLA, KIR) and viral/bacterial lineages. It manifests as balancing selection in hosts, escape and compensation in pathogens, and population-specific architectures of receptor-ligand pairs [21, 22, 28].

(b) **Mechanism.**
- **Balancing selection.** Diversity at HLA-B and HLA-C broadens peptide coverage, while frequent recombination at the KIR locus generates novel inhibitory/activating haplotypes [22, 41].
- **Ligand-receptor tuning.** Polymorphisms at positions 67, 70, and 97 of HLA-B strongly shape peptide binding and KIR engagement, influencing set-point viral load [42].

- **Escape and reversion.** HIV adapts to protective HLA alleles with rapid escape, often reverting in transmission if fitness costs are high [18, 20].
- **Population matching.** HLA-KIR pairs and pathogen lineages co-segregate geographically: e.g., HLA-B*27 alleles and tuberculosis Beijing strains, or KIR3DS1 and Bw4 clines tracking human migration [21, 28].

(c) **Evidence.** (i) Large-scale surveys show inverse correlations between activating KIR3DS1 and its Bw4-80I ligand across populations, consistent with reciprocal selection [21]. (ii) HLA-B heterozygosity and divergent allele combinations broaden the HIV peptide repertoire and associate with lower viral load [22]. (iii) Comparative studies show that B*27:05 and B*27:02, though closely related, direct immune pressure to different proteins (Gag vs Nef), each leaving distinct escape patterns [37]. (iv) In South Africa, HLA-C*16:01 with KIR2DL3 is linked to higher viraemia, illustrating how ancestry-specific licensing landscapes affect outcomes [27]. (v) Beyond viruses, HLA class I alleles track with local *M. tuberculosis* lineages, reflecting bacterial-host co-adaptation [28].

(d) **Examples.** *S5*: Nef- and Vpu-mediated editing intersects with host KIR/HLA backgrounds, showing how viral adaptation exploits local licensing biases. *S6*: Constrained escape followed by compensation reflects epitope-specific coevolution. Population-level HIV adaptation maps (North America, sub-Saharan Africa) illustrate how circulating strains accumulate HLA-associated polymorphisms over decades [29, 30].

(e) **Implications.** Coevolution means no receptor-ligand interaction is context-free. Immunogen design and clinical trials must account for ancestry, allele frequencies, and circulating strain backgrounds, or risk misaligning with entrenched host-pathogen dynamics.

2.7 KP7 - Immunoregulatory wiring: checkpoints and contextual control

Even when peptide geometry is favorable, the immune outcome is decided by circuitry. Inhibitory and activating pathways overlay pHLA recognition, setting the context for effector success, exhaustion, or dysregulation.

(a) **Definition.** Immunoregulatory wiring refers to the network of checkpoint axes-HLA-E/CD94-NKG2A on NK and CD8 T cells, myeloid ILT4/LILRB2 engagement of HLA-B, and NKp44 sensing of HLA-DP-that modulate cytotoxic tone across tissues and chronicity [17, 26, 43, 44].

(b) **Mechanism.**
- **HLA-E/NKG2A.** Signal peptides from HLA-A/B/C govern HLA-E display, tuning inhibitory NKG2A thresholds. Elevated HLA-A expression enhances HLA-E presentation, raising inhibitory tone and impairing HIV control [25, 26].
- **PD-1 and stem-like CD8 T cells.** In chronic infection and cancer, PD-1 marks a self-renewing CD8 subset that can be reinvigorated under checkpoint blockade [45].

- **ILT4/LILRB2.** Engagement of HLA-B by myeloid ILT4 dampens antigen presentation and costimulation, biasing toward tolerance [43].
- **NKp44/HLA-DP.** Certain HLA-DP allotypes expressed on proliferating CD8 T cells are recognized by NKp44, restraining expansion and preventing hyper-clonality, particularly in HCMV-imprinted settings [44].

(c) **Evidence.** (i) Signal peptide variation determines which HLA-E-VL9 complexes engage CD94/NKG2A or NKG2C, shaping inhibitory versus activating outcomes [25]. (ii) High HLA-A expression increases HLA-E/NKG2A inhibition, correlating with poorer HIV control [26]. (iii) PD-1^+ $TCF1^+$ stem-like CD8 T cells fuel responses after checkpoint blockade in cancer and chronic infection [45]. (iv) Functional studies confirm HLA-B*35-Px allotypes enhance ILT4 binding, suppressing dendritic priming [43]. (v) NKp44-HLA-DP engagement selectively prunes effector clones; individuals lacking NKp44-binding DP haplotypes accumulate hyper-expanded CD8 populations [44].

(d) **Examples.** *S10/S14*: In tumors and chronic infection, elevated HLA-E restrains CTLs and NK cells via NKG2A, a brake released by anti-NKG2A therapy [17]. *ILT4 bias*: HLA-B*35-Px drives stronger ILT4 engagement, dampening priming in dendritic cells [43]. *NKp44-HLA-DP editing*: Proliferating CD8 T cells with NKp44-binding DP haplotypes are selectively curtailed in vivo, especially after HCMV imprinting [44].

(e) **Implications.** Immunoregulatory wiring explains why magnitude does not always equal protection. Therapies that block or reroute checkpoints (e.g., NKG2A, PD-1, ILT4) must be tailored to the tissue and HLA background. Vaccine and immunotherapy designs should anticipate how wiring layers might suppress otherwise effective epitope targeting.

2.8 KP8 - Peptide-synchronized pincer

The same peptide-HLA (pHLA) complex can serve two masters. CTLs read one face via the TCR, while NK receptors sense another. Subtle changes in peptide length, stability, or conformation can flip the "pincer" from cooperative clearance to viral escape.

(a) **Definition.** Peptide-synchronized pincers occur when features of a pHLA complex-identity, length, pose, or stability-simultaneously shape CTL recognition and NK receptor engagement, coordinating or uncoupling the two arms [7, 24, 46].

(b) **Mechanism.**
- **HLA-C ligands.** Viral substitutions can destabilize pHLA-C, reducing surface density of KIR2DL2/3 ligands even when KIR affinity is unchanged, thereby relieving NK inhibition while impairing CTL recognition [24].
- **HLA-B ligands.** The C-terminal face of peptide and HLA-B groove polymorphisms jointly tune KIR3DL1 binding; mutations that ablate TCR recognition may simultaneously weaken inhibitory KIR ligation [7].
- **Peptide length competition.** Processing variants of the B*27:05-restricted KK10 epitope show that truncated peptides can outcompete immunogenic

forms for HLA binding, reducing TCR visibility and altering KIR3DL1 inhibition [46].

- **Activating KIRs.** Rare activating allotypes such as KIR3DS1*014 can directly bind Bw4, showing how small sequence shifts enable activating routes on the same peptide face [33].
- **Density dependence.** Receptor/ligand densities and binding strength calibrate NK education and responsiveness, intersecting with peptide effects [8].

(c) **Evidence.** (i) In Japanese HIV cohorts, CTL escape in Pol epitopes reduces pHLA-C stabilization, weakening KIR2DL2 engagement and unleashing NK activity [24]. (ii) Structural studies of HLA-B*57 and B*27 show that peptide substitutions at anchor or solvent-exposed residues alter both TCR docking and KIR3DL1 binding [7]. (iii) KK10 length variants demonstrate peptide competition: shorter forms outcompete immunogenic 10-mers and change KIR binding, blunting both CTL and NK responses [46]. (iv) Binding and functional assays confirm that receptor-ligand density and affinity predict NK education and cytotoxicity against autologous HIV-infected targets [8].

(d) **Examples.** *S1*: Classic pincer where CTL target constrained epitopes and NK inhibition is limited. *S2*: Viral adaptations preserve inhibitory KIR binding while blunting CTL recognition. *S7*: Peptide antagonism-mutants weaken inhibitory KIR engagement without global HLA loss, restoring NK activity [24]. *S11*: Activating-KIR pathways such as KIR3DS1*014 binding Bw4 demonstrate rare but potent alternative routes [33].

(e) **Implications.** Epitope choice can inadvertently strengthen inhibitory NK readouts or destabilize pHLA in ways that disable both arms. Immunogens should prioritize peptides that preserve CTL recognition without reinforcing inhibitory KIR engagement, and may exploit peptide antagonism to tip the balance toward coordinated CTL-NK clearance.

2.9 KP9 - Licensing set-points: NK education by self-HLA

NK cells strike with different intensity depending on how they were "schooled." Licensing-education by self-HLA ligands-sets baseline responsiveness long before pathogen encounter, shaping whether an NK cell pauses or attacks.

(a) **Definition.** NK licensing (or education) is the process by which inhibitory receptor engagement of self-HLA class I establishes functional competence and calibrates activation thresholds. Licensing strength depends on ligand presence, density, and peptide context, especially HLA-Bw4-KIR3DL1, HLA-C1/C2-KIR2DL, and HLA-E-CD94/NKG2A axes [8, 9, 25, 26].

(b) **Mechanism.**

- **KIR3DL1/Bw4.** Stronger binding and higher receptor/ligand densities yield more potent licensing and cytotoxicity against both HLA-null and infected targets [8].

- **HLA-C ligands.** Expression levels vary by allele and tune inhibitory tone through KIR2DL1/2DL2/2DL3, with high-expression allotypes conferring stronger education [9, 35].
- **HLA-E/NKG2A.** Licensing via NKG2A is set by signal peptide variants from HLA-A/B/C and by HLA-A expression levels, which determine how much VL9 is supplied to HLA-E [25, 26].
- **Peptide dependence.** CTL escape mutations that destabilize HLA-C presentation can reduce KIR binding and unmask NK activation [24].
- **Ancestry context.** Certain HLA-KIR pairs, such as HLA-C*16:01 with KIR2DL3, track with worse outcomes in African cohorts, underscoring population-specific licensing baselines [27].

(c) **Evidence.** (i) Functional assays show that KIR3DL1-Bw4 education scales with both affinity and density, predicting cytotoxicity against HIV-infected CD4 T cells [8]. (ii) HLA-C expression tiers correlate with viral load and with stronger C-restricted CTL responses [9]. (iii) Elevated HLA-A expression increases HLA-E presentation, biasing licensing toward NKG2A and impairing HIV control [26]. (iv) Signal peptide polymorphisms dictate which VL9 peptides stabilize HLA-E, setting the inhibitory tone for NKG2A^{+} NK subsets [25]. (v) Escape-driven destabilization of C*12:02 epitopes reduces KIR2DL2 binding, restoring NK activity and lowering viraemia [24]. (vi) Cohort data from South Africa link C*16:01+KIR2DL3 to higher viral loads and faster progression [27].

(d) **Examples.** *S8*: Licensing school-signal peptide variants alter HLA-E tone, biasing toward NKG2A or KIR pathways. *High-gain licensing*: KIR3DL1$^{\text{high}}$ with Bw4-80I produces strongly educated NK cells and superior HIV suppression. *Peptide tuning*: Escape in Pol epitopes reduces C*12:02 stabilization, weakening KIR2DL2 engagement and unleashing NK activity.

(e) **Implications.** NK responsiveness is not fixed but set by inherited HLA/KIR combinations and peptide context. Clinical trials and immunogen studies should stratify by licensing covariates-HLA expression tier, -21M/T status, and KIR gene content-and anticipate that viral escape can shift the licensing balance toward or away from effective NK rescue.

2.10 KP10 - Eco-geographic licensing and ancestry context

The NK "curriculum" is not universal. Human migration, admixture, and local pathogen pressures have left distinct signatures on KIR and HLA class I, shaping licensing baselines that differ by ancestry and geography.

(a) **Definition.** Eco-geographic licensing refers to the shaping of NK education by population-specific distributions of KIR gene content and HLA class I ligands. These long-term adaptations reflect balancing selection, adaptive admixture, and local pathogen landscapes [21, 41, 47].

(b) **Mechanism.**

- **KIR locus diversity.** Rapid recombination and gene conversion at the KIR locus generate diverse haplotypes (A vs B, hybrid alleles, CNVs), shifting inhibitory versus activating receptor content across populations [41].
- **HLA ligand distributions.** Frequencies of C1/C2 and Bw4/Bw6 motifs vary geographically, showing clines consistent with balancing selection and co-adaptation with KIR repertoires [21].
- **Adaptive admixture.** Alleles like HLA-B*46:01 and B*58:01 rose to high frequency in East Asia via admixture, enriching strong KIR ligands in response to local pathogen burdens [47].
- **Clinical consequence.** Misalignment between host ancestry and circulating pathogen strains can alter licensing set-points, influencing infection risk and disease progression [27].

(c) **Evidence.** (i) Global surveys show negative correlations between activating KIR3DS1 and Bw4-80I ligands, with both frequencies showing geographic clines radiating from East Africa [21]. (ii) Phased haplotyping in thousands of individuals reveals over 30 distinct KIR gene-content haplotypes, documenting rapid diversification across ancestries [41]. (iii) East Asian populations show enrichment for KIR-binding HLA-B alleles (e.g., B*46:01, B*58:01) through adaptive admixture, illustrating pathogen-driven selection [47]. (iv) In South Africa, the HLA-C*16:01+KIR2DL3 pair is associated with higher viraemia and faster HIV progression, underscoring eco-geographic specificity [27].

(d) **Examples.** *S5*: Display engineering by HIV interacts differently with host backgrounds, depending on local licensing biases. *Ancestry contrasts*: B*27:05 vs B*27:02 impose divergent immunodominance hierarchies, illustrating how fine-grained allele differences and population frequency shape coevolutionary outcomes [37]. *Population clines*: Negative correlations between KIR3DS1 and Bw4-80I across 30 global populations highlight reciprocal adaptation [21].

(e) **Implications.** NK set-points are eco-geographically tuned. Vaccine design, immunogen testing, and checkpoint strategies must be interpreted in ancestry context-what protects in one population may not in another. Trials should stratify by KIR/HLA background and replicate across populations to avoid miscalibration.

2.11 KP11 - Decoy epitope misdirection; dual-arm diversion

Not all strong immune responses are protective. Viruses can steer CTLs toward mutable, low-cost epitopes-decoys-that dominate immunodominance hierarchies yet provide little control. Some of these same peptides also preserve inhibitory KIR binding, diverting both arms of immunity.

(a) **Definition.** Decoy epitopes are immunodominant viral sites that mutate freely without fitness penalty. They misdirect CTL responses away from constrained targets, while in some contexts maintaining or enhancing inhibitory NK receptor engagement [20, 24, 30, 48].

(b) **Mechanism.**

- **CTL diversion.** Immunodominant responses against mutable epitopes (often Env or Nef) rapidly drive escape, but these mutations persist because they cost the virus little [20].
- **NK reinforcement.** Certain decoy peptides stabilize inhibitory KIR binding (e.g., KIR2DL2 with HLA-C*12:02 or C*14:03), blunting NK rescue even as CTLs chase escape [24].
- **Population spread.** Over decades, such decoy-driven escape variants accumulate in circulating viral strains, reflecting sustained misdirection at the population level [29, 30].
- **Two-for-one diversion.** In some cases, CTL diversion and NK inhibition converge, creating dual-arm blunting of clearance [48].

(c) **Evidence.** (i) Longitudinal HIV cohorts show rapid escape at immunodominant sites, often without viral fitness cost, indicating ineffective targeting [20]. (ii) Population analyses document increasing background frequencies of HLA-associated viral polymorphisms, including those restricted by protective alleles, consistent with decoy-driven spread [29, 30]. (iii) Functional assays reveal peptide variants that maintain inhibitory KIR binding while abrogating CTL recognition, illustrating dual misdirection [24]. (iv) Vaccine trials highlight that alleles favoring Gag targeting (protective) differ from those skewing toward Env (susceptibility), showing how immunodominance bias alters outcomes [32].

(d) **Examples.** *S3*: Decoys where CTL diversion occurs but NK inhibition is not reinforced, allowing partial compensation. *S4*: Two-for-one diversion where CTLs chase a mutable epitope and NK cells remain inhibited. *Population preadaptation*: The steady accumulation of decoy-site polymorphisms in circulating HIV demonstrates diversion at epidemic scale [29, 30].

(e) **Implications.** Magnitude can be misleading. Effective designs should avoid epitopes with rapid, low-cost escape and focus instead on constrained sites (KP4). Surveillance should monitor the slow creep of decoy adaptations in circulating strains, and vaccines should weight quality (fitness cost, cross-reactivity, protection) over magnitude of response.

2.12 KP12 - Class I and peptidome engineering: inhibition-preserving display control

Viruses rarely gamble on a single epitope. Instead, they rewire the entire display case-downregulating some HLA molecules, reshaping the peptide repertoire, and preserving inhibitory ligands-so that even if CTLs win a battle, the system-level architecture still favors the pathogen.

(a) **Definition.** Class I and peptidome engineering refers to viral strategies that globally remodel HLA class I expression and peptide presentation. The goal is to diminish CTL visibility while preserving or reinstating inhibitory NK signaling [13–17].

(b) **Mechanism.**

- **Differential downregulation.** HIV Nef removes HLA-A and HLA-B, sparing HLA-C; Vpu further tunes HLA-C levels in an allele- and strain-dependent manner [14, 15].
- **HLA-E checkpoints.** Leader peptides and viral mimics (e.g., CMV UL40) stabilize HLA-E, enhancing NKG2A-mediated inhibition even as classical class I is lost [17, 25].
- **Peptide-loading bias.** Host TAPBP and tapasin dependence shape which peptides are loaded; higher TAPBP expression aids tapasin-dependent alleles, improving outcomes such as malaria control [13].
- **Stress ligand evasion.** Sarbecoviruses downregulate or shed NKG2D ligands (MICA/B), reducing NK triggering [16].
- **ADCC blunting.** By reducing Env exposure on infected cells, HIV further limits CD16-mediated NK antibody-dependent cellular cytotoxicity [14, 15].

(c) **Evidence.** (i) Vpu deletion in HIV restores HLA-C surface levels and enhances CTL suppression of replication [14]. (ii) HIV downregulation of HLA-C alters KIR2DL binding, modulating NK responses in a strain-dependent manner [15]. (iii) Protective KIR2DL2-HLA-C combinations rely on display-level effects: CTL escape mutations that destabilize pHLA-C reduce inhibitory ligation and restore NK activity [24]. (iv) In COVID-19, soluble MICA/B increases due to viral shedding, correlating with impaired NK responses; blocking shedding restores NK cytotoxicity [16]. (v) Elevated HLA-E sustains NKG2A checkpoints; blockade reinvigorates CTL and NK activity in tumors and chronic infection [17]. (vi) TAPBP expression stratifies disease outcomes in malaria, but only among carriers of tapasin-dependent alleles [13].

(d) **Examples.** *S5*: Display engineering by Nef and Vpu fractures CTL visibility while maintaining inhibitory tone. *S12*: Sarbecoviruses shed NKG2D ligands to disarm NK activation. *S14*: Elevated HLA-E engages NKG2A, dampening effector function until checkpoint blockade releases the brake.

(e) **Implications.** Epitope-level wins are fragile if the global display environment remains subverted. Therapies must address both levels: restoring balanced class I expression, blocking NKG2D ligand shedding, and transiently relieving HLA-E/NKG2A inhibition. Immunogen designs should be paired with strategies that normalize the peptidome, ensuring CTL and NK arms converge on effective clearance.

HIV as a Mechanistic Probe of Triad Integration and Viral Evasion

HIV infection offers a uniquely well-mapped landscape to probe the rules of Keystone Epitope Theory. Decades of cohort studies, longitudinal sequencing, and functional assays have exposed how CTL pressure and NK checkpoints converge on shared peptide-HLA surfaces, how escape and compensation trajectories unfold, and how viral proteins edit class I display. Unlike many pathogens, HIV leaves an indelible record of immune selection in the form of population-level escape polymorphisms,

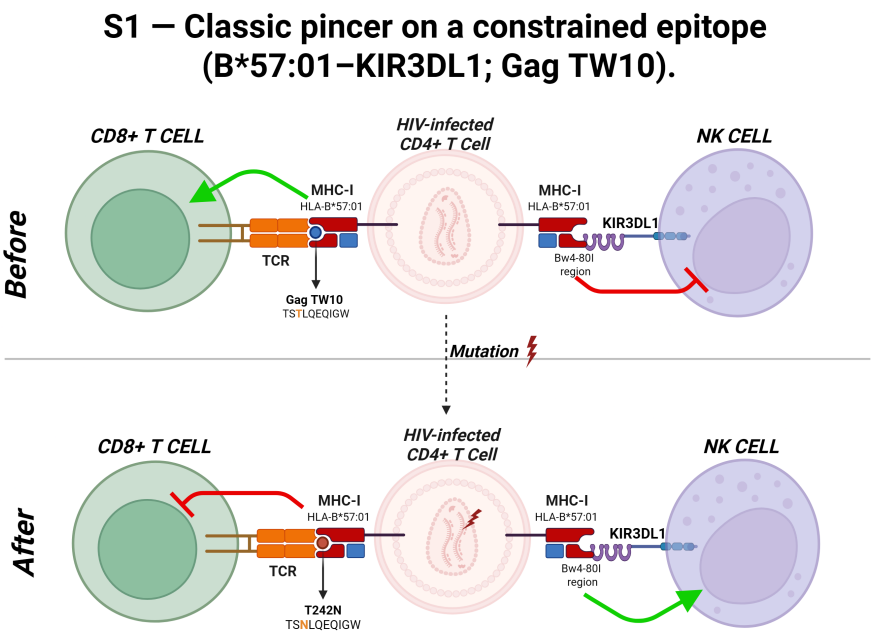

Fig. 1 S1 - Classic pincer on a constrained epitope (B*57:01-KIR3DL1; Gag TW10). The same peptide-HLA surface coordinates CTL targeting and NK checkpoints (KP1). In the *BEFORE* state, an HIV-infected CD4$^+$ T cell displays the B*57:01-restricted, contact-dense Gag TW10 epitope; CTLs recognize and kill effectively, while licensed KIR3DL1$^+$ NK cells remain inhibited by strong Bw4 engagement (KP9). In the *AFTER* state, canonical TW10 escape (for example T242N) lowers CTL recognition yet remains fitness-costly in the constrained Gag sector (KP4); modest changes in peptide context and reduced effective Bw4 input can relieve inhibition at the licensed set-point and permit NK compensation (KP8, KP9). Together these effects illustrate triad integration on one interface and why protective B*57:01 responses cluster on structurally constrained epitopes (KP1, KP4). Paper-to-mechanism links: early escape and rapid reversion at TW10 support fitness costs and constraint (KP4) [20]; sector and network analyses explain why multi-site change is rarely tolerated in p24 (KP4) [18, 19]; KIR3DL1-Bw4 binding strength and receptor-ligand density calibrate licensing and predict killing of HIV-infected autologous targets (KP9) [8]; immunodominance logic across B27 variants generalizes the selection hierarchy that motivates early TW10 pressure (supporting KP4) [37].

allowing within-host dynamics to be read across epidemics. We therefore present a scenario taxonomy (S1-S14) in which each branch captures a distinct outcome of CTL-NK interplay: from classic pincers on constrained epitopes, to two-for-one decoys, to engineered detours through HLA-E, HLA-F, and NKG2D. Together these scenarios provide a decision tree for interpreting immune outcomes and a scaffold for translating Keystone Propositions into testable predictions.

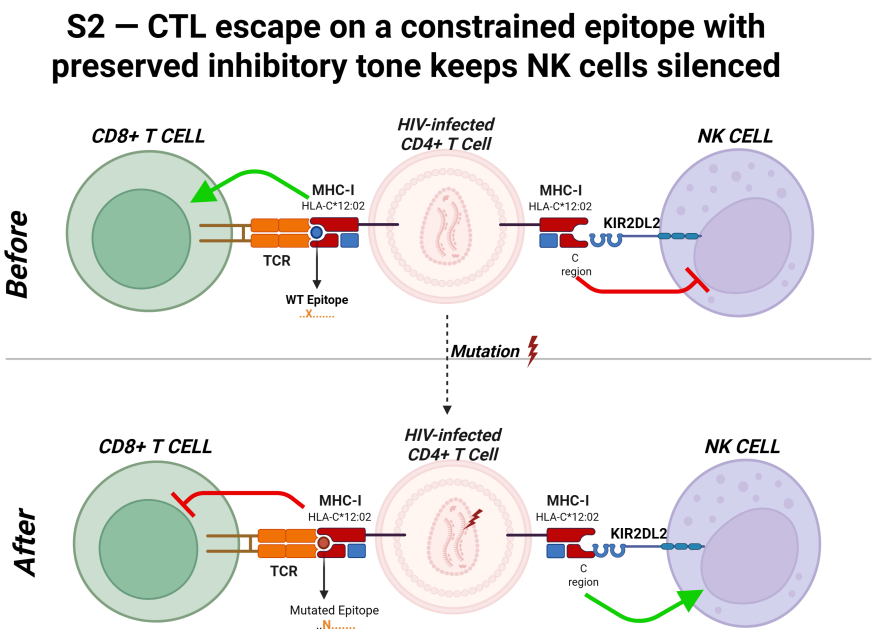

Fig. 2 S2 - CTL escape on a constrained epitope with preserved inhibitory tone keeps NK cells silenced. A constrained CTL target mutates to evade the TCR, yet the infected cell maintains inhibitory input to NK cells through classical KIR-HLA engagement or by detouring inhibition to the HLA-E-NKG2A axis, so innate rescue does not occur (KP1, KP3, KP8, KP9, KP10). *BEFORE*: the index peptide-HLA is presented to an effective CTL, while self-HLA on the same cell engages inhibitory KIR calibrated by prior licensing, restraining NK cells at their set-point [8]. *AFTER*: a single amino-acid substitution abrogates TCR recognition but preserves inhibitory occupancy in one of two ways: (i) classical C1-KIR2DL2/3 or Bw4-KIR3DL1 remains engaged if peptide-HLA stability and KIR-contact geometry are retained, so educated NK cells remain inhibited at their licensing threshold [8]; or (ii) HLA-E loading with host VL9 signal peptides sustains strong CD94/NKG2A signaling, the strength of which is set by the host's HLA-A/B/C signal-peptide repertoire and HLA-E allotype, including non-additive competition among VL9 donors and the distinctive behavior of the HLA-B -21M variant [25]. The KIR2DL2-HLA-C*12:02/*14:03 system exemplifies the complementary branch: when CTL-selected substitutions reduce peptide-HLA-C stability without increasing KIR binding, NK inhibition can fall and NK control can rise; S2 depicts the preserved-inhibition outcome where inhibitory tone is maintained despite CTL escape [24]. Checkpoint logic for the detour branch is supported by tumor settings in which HLA-E on targets inhibits NKG2A$^+$ effectors and NKG2A blockade restores TCR-independent cytotoxicity, underscoring an alternative inhibitory axis that can dominate when classical HLA presentation is altered [17].

S1 - Constrained B*57:01 Gag TW10 escape shifts control from CTL to NK via KIR3DL1 licensing

Original interpretation. Protective HLA-B*57:01 restricts responses to the Gag TW10 epitope, a site embedded in a constrained structural sector. Escape at this site

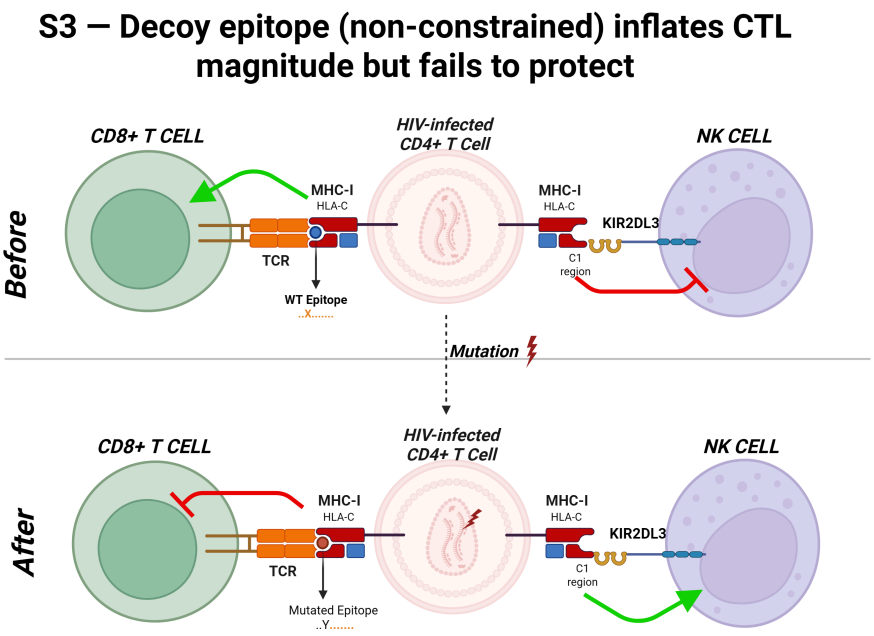

Fig. 3 S3 - Decoy epitope (non-constrained) inflates CTL magnitude but fails to protect. An immunodominant yet non-constrained peptide presented by HLA-C draws strong CTL responses but offers little durable control. The virus escapes rapidly at low fitness cost, while inhibitory NK tone via C1-KIR2DL3 remains largely unchanged, so innate rescue does not occur (KP1, KP4, KP8, KP9). *BEFORE*: a high-frequency HLA-C-restricted peptide is robustly displayed, producing a large CTL response; NK cells remain inhibited at their licensing set-point through C1-KIR2DL3. Longitudinal acute-infection data show that dominance at mutable targets often tracks rapid escape and that in proteins like Nef the correlation between recognition and escape can be poor [20]. *AFTER*: a single substitution within the decoy peptide abrogates TCR recognition with minimal fitness penalty, yielding fast and durable escape; inhibitory engagement of KIR on NK cells is preserved, so NK activity does not compensate. Population studies show these HLA-associated polymorphisms can spread over time in individuals lacking the selecting allele, biasing future hosts toward preadapted, non-protective targets [30]. Mechanistic and subtype-comparative work further shows that some differential escapes are driven by epitope-HLA binding context rather than fitness constraints, marking such regions as poor immunogens consistent with the decoy concept [31].

(for example, T242N) reduces CTL recognition but imposes fitness costs, leading to partial reversion or compensatory mutations upon transmission [18–20, 37].

Keystone reinterpretation. This scenario exemplifies triad integration (KP1) and constrained-epitope logic (KP4). The same B*57:01-TW10 surface is read by CTLs via the TCR and by NK cells via KIR3DL1 (Bw4-80I). Escape diminishes CTL control yet reduces effective KIR3DL1 inhibitory tone, permitting NK compensation when licensing thresholds are surpassed (KP8, KP9). Network analyses confirm TW10 resides in a highly connected sector where multi-mutation escape is rare, reinforcing

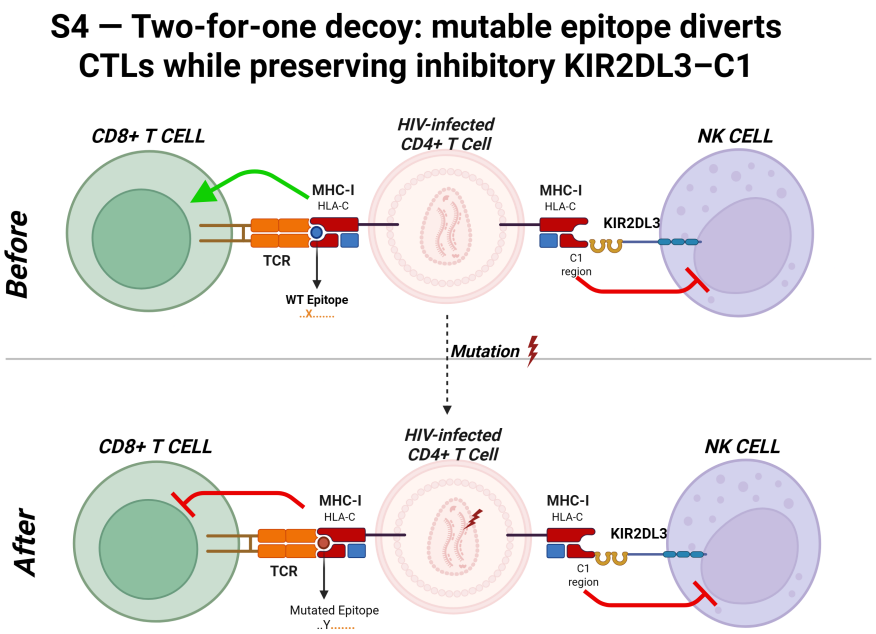

Fig. 4 S4 - Two-for-one decoy: mutable epitope diverts CTLs while preserving inhibitory KIR2DL3-C1. *Concept.* A non-constrained HLA-C-presented epitope attracts strong CTL magnitude yet escapes at low fitness cost. The escape variant remains adequately displayed by HLA-C and continues to engage inhibitory KIR2DL3, so licensed NK cells stay inhibited and do not compensate (KP1, KP4, KP8, KP9). *BEFORE*: ancestral peptide-HLA-C (C1) elicits CTL killing, while C1-KIR2DL3 maintains an inhibitory NK baseline at the licensing set-point (CTL ✓, NK ×, VL ↔). *AFTER*: a single substitution in the decoy epitope abolishes TCR recognition with minimal fitness penalty, yet preserves HLA-C stability and inhibitory C1-KIR2DL3 engagement; CTL fails, NK stays inhibited, and VL rises (CTL ×, NK ×, VL ↑). *Population context.* Across the North American epidemic, background frequencies of HLA-associated polymorphisms are modestly higher in modern than historic sequences, and modern Nef clones show stronger HLA class I downregulation than historic clones, consistent with gradual diversification and tuned display control that can reinforce decoy outcomes [29]. *Genetic-context nuance.* Roughly one-third of mapped HLA-associated polymorphisms are differentially selected between subtypes A1 and D, driven either by epitope-HLA binding differences or by distinct mutational barriers, highlighting how some epitopes function as decoys in one backbone while others are constrained targets (vaccine-relevant distinction) [31].

its constrained status [18, 19]. These dynamics are schematized in Fig. 1, where CTL recognition is lost but NK cells regain activity as inhibitory input is reduced.

Testable predictions.

- CTL escape mutations at TW10 (T242N) will show rapid selection in acute infection and rapid reversion upon transmission, evidencing fitness cost (KP4) [20].
- KIR3DL1^{+} NK cells from Bw4-80I carriers will exhibit heightened degranulation after TW10 escape, correlating with receptor density and ligand density (KP9) [8].

- Functional assays should reveal reduced inhibitory KIR3DL1-Bw4 engagement post-escape, shifting NK activity upward (KP8) [8].
- Viral load trajectories will remain stable or decline depending on the balance between CTL loss, NK compensation, and the intrinsic cost of escape (KP1, KP4).

S2 - CTL escape with preserved inhibitory KIR or HLA-E detour keeps NK silenced

Original interpretation. Escape at a constrained CTL epitope can abrogate TCR recognition without enabling NK rescue. In this case, inhibitory tone is preserved either through classical KIR-HLA engagement (for example, B*57:01-KIR3DL1 or C*03:04-KIR2DL3) or by detouring inhibition to the HLA-E-NKG2A axis [8, 24]. The result is a net subversion of immune control, with viral load trending upward.

Keystone reinterpretation. This scenario illustrates triad integration (KP1) where CTL escape alters one arm but does not relieve the other. Preservation of inhibitory input through classical KIR-HLA interactions maintains NK suppression even after CTL failure, aligning with KP8 (peptide-dependent KIR engagement) and KP9 (licensing set-points). Alternatively, viral and host signal peptides can stabilize HLA-E, reinforcing NKG2A-mediated inhibition (KP3 checkpoint coupling). Host variation at HLA signal-peptide positions (-21M/T) and HLA-A expression levels modulates this HLA-E detour, placing the outcome within eco-geographic licensing frameworks (KP10) [17, 25]. Together, these outcomes are depicted in Fig. 2, where CTL loss is paired with preserved NK inhibition.

Testable predictions.

- Escape at constrained epitopes will diminish CTL recognition but preserve inhibitory KIR binding in specific contexts, maintaining NK suppression (KP8, KP9) [8].
- Functional assays will show that KIR2DL2/3 binding remains stable after certain Pol epitope escapes, sustaining NK inhibition and associating with higher viraemia [24].
- HLA-E peptidomics and reporter assays will reveal non-additive competition among signal-peptide variants, predicting when NKG2A detours dominate (KP3, KP10) [25].
- Inhibition through NKG2A can be released by checkpoint blockade, restoring cytotoxicity in both NK and CD8 compartments, as shown in tumor models and chronic infection (KP3) [17].

S3 - Non-constrained decoy epitope inflates CTL magnitude but fails to protect

Original interpretation. Some immunodominant HIV epitopes are highly mutable and impose little or no viral fitness cost when they escape. CTLs expand vigorously against these sites, but the responses fail to provide durable protection, and viraemia persists [20].

Keystone reinterpretation. This scenario represents a classic decoy (KP11) where immunodominance misdirects CTLs toward non-constrained targets. The HLA-C-restricted decoy epitopes considered here escape rapidly, yet continue to engage inhibitory KIR (such as C1-KIR2DL3), leaving NK suppression intact (KP1, KP8, KP9). Because these epitopes are not structurally constrained (KP4), they revert slowly if at all after transmission, enabling accumulation of preadapted polymorphisms in the circulating population [30, 31]. Over time, this creates a background of viruses that bias incoming hosts toward ineffective responses. The dynamics are depicted in Fig. 3, which contrasts a robust but non-protective CTL response in the *BEFORE* state with durable CTL failure and persistent NK inhibition in the *AFTER* state.

Testable predictions.

- Longitudinal cohort studies will show rapid CTL escape at immunodominant but non-constrained sites, with minimal reversion after transmission, consistent with low fitness cost (KP4) [20].
- Functional assays should demonstrate that inhibitory KIR2DL3 binding is maintained despite peptide substitutions, preserving NK inhibition (KP8, KP9) [31].
- Population-level sequencing will reveal an increased prevalence of HLA-associated polymorphisms in modern compared with historic isolates, reflecting the spread of decoy-driven escapes (KP5-KP7) [30].
- Vaccines that focus responses on these epitopes will elicit magnitude without protection, underscoring the need to prioritize constrained targets instead (KP4, KP11).

S4 - Two-for-one decoy: mutable epitope diverts CTLs while preserving inhibitory KIR2DL3-C1

Original interpretation. Certain immunodominant HIV epitopes act as "two-for-one" decoys. They not only draw strong CTL responses but also maintain inhibitory NK tone, so that both adaptive and innate cytotoxicity are blunted [29, 31].

Keystone reinterpretation. This scenario illustrates dual misdirection (KP11). A non-constrained epitope presented by HLA-C undergoes rapid escape with little fitness cost (KP4), while continued HLA-C engagement of KIR2DL3 maintains NK inhibition (KP8, KP9). Over epidemic time, population analyses show accumulation of HLA-associated polymorphisms at these sites, reflecting how circulating viruses reinforce decoy outcomes [29]. Subtype-specific comparisons further show that whether a site functions as a decoy or a constrained target depends on epitope-HLA binding context, emphasizing the importance of genetic background [31]. Fig. 4 schematizes this two-for-one diversion: CTL pressure fails and NK cells remain silenced.

Testable predictions.

- CTL escape mutations at decoy sites will accumulate and persist in the population, with little pressure for reversion, consistent with low fitness cost (KP4) [29].
- Subtype-specific mapping will show differential selection at decoy epitopes, depending on local HLA binding properties (KP8) [31].

- Functional studies should demonstrate stable or enhanced KIR2DL3 binding despite peptide changes, keeping NK cells inhibited (KP8, KP9).
- Hosts carrying preadapted viruses will mount strong CTL responses against these epitopes yet experience poor control, validating decoy misdirection (KP11).

S5 - Display engineering blunts both arms: Nef removes HLA-A/B and Vpu tunes HLA-C

Original interpretation. HIV employs accessory proteins to remodel antigen display: Nef selectively downregulates HLA-A and -B, and Vpu reduces HLA-C surface levels. This dual strategy weakens CTL surveillance and modulates NK checkpoints [14, 15, 24].

Keystone reinterpretation. S5 represents global display engineering (KP12), where the virus edits entire HLA classes rather than a single epitope. Nef-driven loss of A/B reduces CTL visibility, while Vpu-driven HLA-C downregulation undermines HLA-C-restricted CTLs and reshapes inhibitory KIR ligation (KP1, KP3). The outcome depends on the magnitude of HLA-C reduction and the licensing background of the host: modest downregulation maintains NK inhibition, while stronger downregulation can relieve inhibition and permit partial NK rescue (KP8, KP9). Fig. 5 depicts this systematic blunting of both CTL and NK arms.

Testable predictions.

- Vpu disruption will restore HLA-C levels and improve suppression by HLA-C-restricted CTLs (KP3) [14].
- NK responses will vary depending on the extent of HLA-C downmodulation: strains with stronger Vpu effects will permit greater NK activity (KP8, KP9) [15].
- Population studies will reveal strain-specific differences in HLA-C downregulation that correlate with viraemia (KP10).
- Peptide destabilization of HLA-C (for example, Pol epitopes on C*12:02 or C*14:03) will reduce inhibitory KIR engagement, providing a parallel mechanism for NK activation (KP8) [24].

S6 - Compensation after costly escape restores viral fitness and re-establishes inhibitory balance

Original interpretation. In constrained epitopes such as B*57:01-restricted Gag, CTL escape mutations carry steep fitness costs. Over time, compensatory substitutions can restore replication, stabilizing viral load while CTL pressure remains ineffective [18, 19].

Keystone reinterpretation. This scenario captures an evolutionary arc shaped by constrained topology (KP4). The initial escape relieves CTL pressure but impairs viral fitness, transiently reducing inhibitory tone to NK cells. Compensation then restores both viral fitness and inhibitory engagement at the B*57:01-KIR3DL1 interface, silencing NK rescue (KP1, KP3, KP8, KP9). Thus, what begins as a protective

configuration (S1) evolves into a stable escape equilibrium with restored NK inhibition. Fig. 6 illustrates this two-step trajectory, with transient NK relief followed by reinstated inhibition.

Testable predictions.

- Sequence analyses will reveal early costly escapes in constrained Gag epitopes, followed by secondary compensations within linked sectors (KP4) [18].
- Compensation will correlate with restoration of viral replication capacity and increased prevalence of tolerated multi-mutation states (KP4).
- Functional studies should show that compensatory changes reinstate KIR3DL1-Bw4 engagement, returning licensed NK cells to an inhibited state (KP1, KP9).
- Longitudinal viraemia will first dip or stabilize after escape, then rebound as compensation restores viral fitness (KP3).

S7 - Peptide antagonism at HLA-C lowers KIR2DL2 inhibition and enables NK control

Original interpretation. HIV epitopes presented by HLA-C can vary in their ability to stabilize peptide-HLA complexes. Some substitutions reduce surface stability without changing KIR affinity, lowering inhibitory tone and enabling NK control even in the presence of CTL escape [24].

Keystone reinterpretation. This scenario illustrates peptide-dependent checkpoint tuning (KP8). Mixtures of self and viral peptides on HLA-C recalibrate inhibitory KIR2DL2/3 ligation, shifting NK thresholds without bulk HLA-C loss. In C*14:03, reduced peptide stabilization lowers pHLA density and releases NK activity despite unchanged affinity. Similarly, escape in the C*12:02 Pol-IY10 epitope (V9A) weakens peptide-HLA binding, tipping the balance toward NK rescue (KP1, KP3, KP4, KP9). Comparable principles extend to HLA-B, where residue-level changes (for example, at position 97) partition TCR versus KIR engagement [7]. These dynamics are summarized in Fig. 7, contrasting intact inhibitory tone in the *BEFORE* panel with NK compensation in the *AFTER* panel.

Testable predictions.

- Protective associations will emerge in cohorts carrying C*12:02 or C*14:03 in combination with KIR2DL2, correlating with lower viral load [24].
- Biophysical assays will show reduced peptide stabilization on C*14:03 relative to C*14:02, with similar KIR affinity but lower ligand density [24].
- Functional NK assays will demonstrate increased suppression of HIV replication when inhibitory ligand density is reduced (KP8, KP9).
- Structural studies at HLA-B will confirm residue-specific partitioning of peptide effects on TCR recognition versus KIR binding, supporting generalization across loci [7].

S8 - Licensing school sets the baseline: HLA-B -21M biases NKG2A tone, HLA-A expression tunes it, and KIR3DL1-Bw4 calibrates the alternative school

Original interpretation. Host genetics preconfigures NK education through two competing schools: one dominated by KIR3DL1-Bw4, the other by HLA-E-NKG2A. Signal-peptide polymorphisms at HLA-B (-21M/T) and HLA-A expression shape the balance between these schools [8, 25, 26].

Keystone reinterpretation. This scenario demonstrates how licensing set-points (KP9) and eco-geographic context (KP10) preconfigure responses before infection. In -21T backgrounds with average HLA-A expression, NK cells are predominantly KIR-educated, so HIV-driven HLA-B downregulation produces missing-self and NK activation. In contrast, -21M backgrounds with higher HLA-A expression elevate HLA-E surface levels, biasing education toward NKG2A and raising inhibitory tone (KP1, KP3). Population variation in -21M frequencies and HLA-A expression explains heterogeneity in HIV outcomes across ancestries. These dynamics are depicted in Fig. 8, contrasting the KIR- versus NKG2A-school outcomes.

Testable predictions.

- Cohort studies will confirm that higher HLA-A expression correlates with higher viraemia, especially in -21M/M donors (KP9) [26].
- Reporter assays will show non-additive competition among signal-peptide variants for HLA-E loading, modulating NKG2A tone [25].
- Functional assays will demonstrate stronger NK degranulation in -21T donors with Bw4 ligands than in matched -21M donors, consistent with KIR-school dominance [8].
- Ancestry-linked frequencies of -21M haplotypes will predict population differences in reliance on NKG2A versus KIR education (KP10) [25].

S9 - Activating-KIR (KIR3DS1) rescue depends on ligand display vs viral avoidance

Original interpretation. Some cohorts link KIR3DS1 to improved HIV outcomes, but the effect depends on whether activating ligands are displayed or avoided. Rare allotypes such as KIR3DS1*014 can directly bind Bw4 and trigger NK activation, while other allotypes cannot [33].

Keystone reinterpretation. This scenario highlights triad integration (KP1) and peptide-sensitive KIR engagement (KP8). The inhibitory axis is B*57:01-KIR3DL1, which calibrates NK licensing (KP9). Upon infection, HIV downregulates HLA-Bw4, creating missing-self. If activating ligands (for example, HLA-F open conformers or permissive Bw4-peptide contexts) engage KIR3DS1, NK rescue is robust. If not, NK responses remain partial, reflecting viral avoidance (KP3). Population variation in KIR3DS1 alleles (for example, enrichment of KIR3DS1*014 in specific ancestries) influences how often the engage branch occurs (KP10). These branches are depicted in Fig. 9.

Testable predictions.

- Functional NK assays will show strong lysis of HIV-infected autologous cells by KIR3DS1 homozygotes in Bw4-80I backgrounds, consistent with activating input [8].
- Reporter cells expressing KIR3DS1*014 (W138G) will bind Bw4 tetramers and signal robustly, whereas common allotypes will not [33].
- Population surveys will reveal ancestry-linked enrichment of permissive KIR3DS1 allotypes, predicting cohort differences in engage versus avoid outcomes (KP10) [33].
- Viraemia will decline only when both missing-self and activating-KIR engagement converge, whereas missing-self alone yields incomplete rescue.

S10 - HLA-E detours rebalance cytotoxic control via NKG2A

Original interpretation. HLA-E can act as a checkpoint, either suppressing NK cells through CD94/NKG2A or, in some contexts, presenting viral peptides to unconventional CD8 T cells. Polymorphisms in HLA signal peptides and quantitative HLA-A expression levels tune this balance [17, 25].

Keystone reinterpretation. This scenario exemplifies display-to-checkpoint coupling (KP3) and triad integration (KP1). Host signal-peptide variants compete for HLA-E loading, producing non-additive levels of NKG2A engagement (KP8). Where strong VL9 donors and HLA-E*01:03 dominate, inhibitory tone through NKG2A is reinforced, suppressing cytotoxic responses. Alternatively, NKG2A blockade or poor-recognition VL9 variants lower the checkpoint, permitting innate-like CD8 or NK effector responses. These dynamics map directly to licensing set-points (KP9) and population variation (KP10), since -21M versus -21T haplotypes stratify individuals into NKG2A versus KIR "schools." Fig. 10 depicts these alternative routes, with inhibitory dominance or therapeutic detour depending on peptide supply.

Testable predictions.

- Functional assays will confirm that only a subset of signal peptides stabilize HLA-E and engage NKG2A, and that VL9 competition is non-additive [25].
- Clinical blockade of NKG2A (for example, monalizumab) will restore cytotoxicity in settings where HLA-E is abundant [17].
- HLA-E peptidomics will show that -21M haplotypes yield stronger NKG2A inhibition, predicting poorer viral control (KP10) [25].
- Individuals with high HLA-A expression will exhibit steeper inhibitory tone and higher viraemia over time, consistent with NKG2A-dominant schooling [26].

S11 - Danger flag: HLA-F open conformers engage KIR3DS1 activation

Original interpretation. Beyond classical epitopes, HIV-infected cells can express non-classical ligands such as HLA-F open conformers, which act as danger flags by engaging the activating NK receptor KIR3DS1. This offers an alternative route to cytotoxicity when CTL responses falter [33].

Keystone reinterpretation. This scenario underscores how activating KIRs provide rare but potent alternative arms (KP1, KP3, KP8). Residue-level studies show that glycine at position 138 in KIR3DS1 enables Bw4 binding and functional signaling, whereas tryptophan abrogates it. Additional gating residues at D1 and D2 define whether open conformers of HLA-F or Bw4 ligands can be productively engaged. Thus, activating-KIR rescue depends on highly specific receptor-ligand geometry, often restricted to rare allotypes such as KIR3DS1*014. Population variation in these alleles (KP10) influences how often the danger-flag detour is realized. Fig. 11 illustrates this switch: in the *BEFORE* state, NKs are restrained, while in the *AFTER* state, HLA-F open conformers trigger KIR3DS1 and unleash NK killing.

Testable predictions.

- Reporter assays will show that KIR3DS1*014, but not common allotypes, binds Bw4 tetramers and signals through NFAT pathways [33].
- Functional studies will confirm stronger lysis of autologous infected cells by NK cells from KIR3DS1 homozygotes in Bw4-80I backgrounds [8].
- Population-level surveys will reveal that activating KIR3DS1 alleles are rare and geographically structured, predicting ancestry-linked outcome differences [33].
- HLA-F open conformer expression will correlate with enhanced NK degranulation in ex vivo assays, confirming its role as a danger flag.

S12 - NKG2D tug-of-war: ligand induction versus viral shedding

Original interpretation. Infection induces stress ligands such as MICA/B and ULBPs that activate NK cells via NKG2D. HIV and other viruses counter this by promoting ligand shedding, reducing surface expression and releasing soluble forms that desensitize NKG2D [16].

Keystone reinterpretation. This scenario highlights induced-self dynamics (KP1, KP2) and display engineering (KP3, KP7). In early infection, upregulated MICA/B ligands engage NKG2D, strengthening NK control. Over time, viral proteins such as ORF6 drive proteolytic shedding, blunting surface engagement and raising soluble ligands that downregulate NKG2D on NK and CD8 cells. In tissues where HLA-E persists, inhibitory tone via NKG2A compounds this escape [17]. Fig. 12 depicts this tug-of-war: the *BEFORE* state favors NK activation, while the *AFTER* state reflects shedding-driven suppression and checkpoint reinforcement.

Testable predictions.

- Patient sera will contain soluble MIC-A/B during chronic infection, correlating with impaired NK responses [16].
- Blocking MICA/B shedding with antibodies will restore NK recognition and cytotoxicity (KP3) [16].
- NKG2A blockade will synergize with anti-shedding strategies to restore cytotoxicity in tissues where HLA-E remains (KP7) [17].
- Time-course studies will show strong NK responses in acute infection (ligand induction) but weakened responses in chronic infection (ligand shedding).

S13 - Vpu-driven HLA-C downregulation reshapes NK checkpoints and weakens HLA-C-restricted CTL

Original interpretation. HIV-1 Vpu selectively downregulates HLA-C, reducing the effectiveness of HLA-C-restricted CTLs and retuning inhibitory input to NK cells. This complements Nef-mediated downregulation of HLA-A and -B, creating a comprehensive program of class I editing [14, 15].

Keystone reinterpretation. This scenario exemplifies display engineering (KP12). By lowering HLA-C surface density, Vpu diminishes both CTL recognition and inhibitory KIR2DL1/2DL3 ligation (KP1, KP3). The outcome depends on host licensing (KP9): in strongly licensed NK subsets, residual inhibition persists even when HLA-C is reduced; in other settings, stronger Vpu activity may unmask NK reactivity, yielding strain-dependent outcomes (KP8, KP10). These dynamics are summarized in Fig. 13, where intact HLA-C in the *BEFORE* state gives way to reduced display and altered CTL/NK balance in the *AFTER* state.

Testable predictions.

- Vpu-deficient viruses will restore HLA-C expression and allow stronger suppression by HLA-C-restricted CTLs [14].
- KIR2DL binding assays will confirm reduced engagement of infected targets when HLA-C is downregulated, correlating with Vpu strength (KP8) [15].
- Functional comparisons between licensed and unlicensed NK subsets will show muted rescue in licensed subsets despite reduced HLA-C, consistent with fixed licensing thresholds (KP9) [15].
- Cohort studies will demonstrate that baseline HLA-C expression levels and C1/C2 group status stratify individual outcomes, reflecting eco-geographic licensing (KP10).

S14 - Layered checkpoints: PD-1 stem-like pool and HLA-E-NKG2A detour shape late cytotoxic control

Original interpretation. Chronic HIV infection induces multiple layers of inhibition: PD-1 restrains a TCF-1$^+$ stem-like CD8 pool, while HLA-E-NKG2A provides a downstream checkpoint that limits both NK and CD8 responses when classical HLA is reduced [17, 45].

Keystone reinterpretation. This scenario illustrates immunoregulatory wiring (KP7) in combination with triad integration (KP1). The upstream PD-1 gate controls expansion of a stem-like CD8 reservoir that fuels long-term immunity, while the downstream HLA-E-NKG2A axis suppresses cytotoxicity in tissues where HLA-A/B/C is diminished (KP2, KP3, KP8). Blockade strategies therefore bifurcate outcomes: PD-1 release expands the effector pool if classical display remains, whereas NKG2A blockade restores cytotoxicity in HLA-ABC-low, HLA-E$^+$ environments. Population data linking KLRC1 (NKG2A) expression to outcomes further connect this axis to eco-geographic variation (KP10). These layered checkpoints are illustrated in Fig. 14, showing PD-1 release and NKG2A detour as distinct branches of late cytotoxic control.

Testable predictions.

- Sorted PD-1$^+$ TCF-1$^+$ CD8 T cells will proliferate and differentiate upon PD-1 blockade, expanding effector-like progeny [45].
- NKG2A acquisition on CD8 T cells will coincide with tissue residency markers, and NKG2A blockade will restore degranulation against HLA-E$^+$ targets [17].
- Transcriptomic profiling will reveal layered checkpoint programs, with PD-1 preceding NKG2A during CD8 differentiation [17, 45].
- Clinical cohorts will show that KLRC1 expression predicts improved outcomes after PD-L1 blockade in CD8-high tumors, supporting the generalizable checkpoint logic (KP7, KP10).

Beyond HIV

The principles of Keystone Epitope Theory extend well beyond HIV. Other persistent pathogens, tumours, and population-level variation all exploit the same axes of peptide display, checkpoint wiring, and licensing set-points. Together, they provide both the postnatal context in which acute infections unfold and the translational lessons that immunogen design must respect.

Herpesvirus imprinting (CMV, EBV, HSV).

Episodes of CMV, EBV, and HSV reactivation leave durable marks on CTL and NK architecture. They establish tissue-resident memory niches, bias checkpoint set-points, and reinforce immunodominance hierarchies that subsequent pathogens—including fast-evolving RNA viruses—exploit [5, 6]. This imprinting explains why late-life reactivation events often coincide with systemic vulnerability: collapse of the keystone architecture, not failure of a single epitope response.

Cancer checkpoints (HLA-E/NKG2A, ILT4/LILRB2).

Tumours harness the same inhibitory wiring as viruses. Elevated HLA-E engages NKG2A to suppress cytotoxicity, a brake that can be released by therapeutic blockade [17]. Myeloid engagement of HLA-B by ILT4/LILRB2 dampens inflammasome activation and pyroptosis, further tilting the system toward tolerance [23]. These parallels underscore how viral and tumour evasion operate on convergent control points.

Population genetics & heterogeneity.

HLA class I and II polymorphism contributes to striking heterogeneity in disease outcomes. Heterozygote advantage persists in HIV cohorts [22], while allele-specific focusing shapes immunodominance hierarchies [49]. Rapid recombination at the KIR locus and geographic clines in HLA-Bw4, C1/C2, and HLA-E signal peptides reinforce eco-geographic diversity [21, 41]. Together, these patterns explain why identical viral variants yield divergent outcomes across ancestries.

Design learning from HIV.

The design lessons are general: prioritise epitopes embedded in constrained networks, avoid decoys that reinforce inhibitory tone, and pair class I with class II epitopes to

align help and clearance. HIV cohorts have already provided proof that constrained-epitope prioritisation improves predictive value for protection, whereas decoy targeting correlates with poor outcomes [32, 50].

Clinical and translational implications

Keystone Epitope Theory can be operationalised into a design grammar for vaccines and immunotherapies. The critical insight is that magnitude alone is not sufficient—epitopes must be chosen and presented in ways that align CTL and NK arms while bypassing viral traps.

Design grammar (integrating KP11 & KP12).

(i) **Avoid decoys**: exclude highly mutable, KIR-reinforcing peptides; require demonstrable fitness costs or constraint. (ii) **Emphasise constrained epitopes**: focus on epitopes embedded in networked regions where escape is costly and compensatory routes are limited [18, 19]. (iii) **Co-present class I/II**: align CD4 help with CTL/NK targeting to strengthen coordination. (iv) **Avoid strengthening inhibitory KIR**: screen candidate epitopes against KIR binding to ensure they do not reinforce inhibition, integrating KP8 assays [7, 24]. (v) **Respect licensing set-points**: stratify designs by HLA-C expression, KIR genotype, HLA signal-peptide status, HLA-A expression, and CMV/EBV serostatus [8, 9, 25, 26]. (vi) **Normalise display**: counteract viral editing of class I (e.g., Nef/Vpu), and consider transient checkpoint interventions (anti-NKG2A, anti-PD-1) so epitope-level wins persist in vivo [14, 15, 17].

Operationalisation.

This grammar can be implemented through paired CTL–NK screening of immunogens, a keystone protein atlas stratified by tissue and niche to guide delivery and TRM seeding, and systems-level monitoring using a *Keystone Reactivation Index* (KRI) based on niche-specific surveillance. Functional endpoints should extend beyond immune magnitude to include *KIR–pHLA binding*, *subset-resolved NK function*, *true CTL killing*, and *viral load trajectories*.

Outlook

KP11 and KP12 highlight the two most adversarial levers in host–pathogen conflict: epitope-scale misdirection and whole-cell display control. Integrated with KP1–KP10, they provide a falsifiable roadmap for the next generation of assays and interventions.

(i) *Paired TCR/KIR binding and function* to the same pHLA will distinguish decoy from constrained epitopes, resolving whether an immunogen risks dual-arm diversion [7, 24]. (ii) *CRISPR-engineered Nef/Vpu panels* with quantitative class I surface profiling and immunopeptidomics will define the landscape of viral display engineering [13–15]. (iii) *Licensing-aware checkpoint studies* will test NKG2A blockade in the context of host signal-peptide and HLA-A backgrounds, revealing when inhibitory tone can be safely relieved [17, 25, 26]. (iv) *Ancestry-stratified epitope trials* will clarify

whether constrained-epitope prioritisation holds across populations, or whether local licensing ecologies impose divergent outcomes [21, 27].

The overarching goal is to build with, rather than against, the immune architecture that evolution has already tuned. By aligning design with Keystone Propositions and validating predictions across pathogens, tissues, and populations, the field can move from descriptive immunology toward a predictive, testable framework for durable immune protection.

Appendix A Narrative for Litrature Review

A.1 Identification and characterization of antigen-specific CD8+ T cells using surface-trapped TNF-α and single-cell sequencing [51]

- **Core question/approach:** Develop a workflow to isolate viable antigen-specific CD8+ T cells via surface-trapped TNF-α after short peptide stimulation, then perform single-cell RNA/TCR-seq and re-express paired TCRs for functional validation.
- **Key findings:** Responders defined as TNF+/CD69+ CD8+ cells at least 2x above control after 8 h; 1e6 PBMC per pool; ELISPOT LOQ 50 SFC per 10^5 CD8+. Discovery of HIV Gag EL9 (EVIPMFSAL) with HLA-A*68:02 restriction; EL9 elicited nearly 2-fold higher IFN-γ than 15mer SA15 (Fig.4A-H).
- **Mechanistic link:** *Direct* - peptide-HLA-TCR mapping with functional readouts and HLA restriction assignment demonstrates how epitope geometry and HLA pocket chemistry guide TCR recognition (Fig.4H).
- **Keystone assessment:** Supports - KP4 (constrained epitopes); KP5 (imprinting). Platform pinpoints conserved epitope geometry and captures TCR repertoires likely shaped by thymic selection and exposure.
- **Evidence type & confidence:** Molecular/structural - Moderate. Multimodal method with clear functional validation, though human n is limited and TNF-capture frequencies can be below ICS.
- **Contradictions/nuance:** TNF-capture yields lower apparent responder frequencies than ICS yet suffices for sorting; generalizability requires larger human cohorts.

A.2 Differential Immunodominance Hierarchy of CD8+ T-Cell Responses in HLA-B*27:05 and -B*27:02-Mediated Control of HIV-1 Infection [37]

- **Core question/approach:** Compare immunodominance hierarchies between HLA-B*27:05 and HLA-B*27:02 carriers and map dominant CD8+ T-cell epitopes.
- **Key findings:** Dominant B*27-restricted responses more frequent in B*27:05 than B*27:02 (24/41 vs 8/33, p=0.006), with B*27:05 focusing on Gag KK10/KY9 and B*27:02 skewing to Nef VW9 (Fig.1-3; Table 1).
- **Mechanistic link:** *Direct* - peptide-HLA-TCR targeting differs by B*27 subtype, yielding distinct immunodominance hierarchies aligned with protection (Fig.1-3). *Circumstantial* - immunodominant but less protective Nef VW9 focus in B*27:02 suggests decoy misdirection; NK/KIR not assessed.
- **Keystone assessment:** Supports - KP4 (constrained epitopes); KP5 (imprinting); KP11 (decoy immunodominance). Protective B*27:05 concentrates responses on constrained Gag sites, whereas B*27:02 skews to Nef, consistent with immunodominant yet less protective targeting.
- **Evidence type & confidence:** Clinical cohort - Moderate. Clear allele-specific functional mapping with cohort context, though fitness costs are inferred rather than directly measured.

- **Contradictions/nuance:** Allele and subtype specificity may shift hierarchies across populations; NK components not interrogated here.

A.3 HIV-1 adaptation to NK-cell-mediated immune pressure [48]

- **Core question/approach:** Identify viral sequence footprints of NK pressure stratified by KIR genotype and validate with NK functional assays.
- **Key findings:** KIR2DL2 carriage associated with specific polymorphisms, including Vpu positions 71 and 74, after controlling for HLA. NK degranulation (CD107a) increased from ∼4.1%±2.0 to ∼39.3%±6.7 against variant versus index in KIR2DL2/3+ donors, p¡0.0001 (Fig.1-2).
- **Mechanistic link:** *Inferred* - KIR-HLA axis selects viral variants that reduce NK inhibition or alter activation thresholds; functional data confirm shifts in NK activity but do not map peptide-level KIR engagement directly.
- **Keystone assessment:** Supports - KP3 (viral subversion); KP6 (coevolution); KP1 (triad). Viral polymorphisms track host KIR genotype and impact NK function, indicating reciprocal adaptation.
- **Evidence type & confidence:** Population genetics - High. Cohort-level sequence associations plus orthogonal functional assays strengthen inference; functional validation sample size is limited.
- **Contradictions/nuance:** HLA covariation remains a potential confounder; specific peptide dependencies underlying KIR engagement are not resolved here.

A.4 Influence of HLA-C Expression Level on HIV Control [9]

- **Core question/approach:** Test whether quantitative variation in HLA-C expression relates to set-point viral load, disease progression, and immune correlates.
- **Key findings:** Higher HLA-C expression associated with lower viral load in European Americans (n=2527, p¡1e-7) and African Americans (n=1209, p=8e-6) and with slower progression to CD4¡200 per +100 MFI (HR 0.67, 95% CI 0.58-0.78; n=1069). Increased CTL responses and escape at HLA-C sites observed (Fig.1-3; Table 1).
- **Mechanistic link:** *Inferred* - ligand abundance tunes CTL visibility and likely NK education thresholds, integrating quantitative presentation with effector activation.
- **Keystone assessment:** Supports - KP2 (quantitative tuning); KP9 (licensing set-point). Expression level acts as a quantitative dial for surveillance and escape.
- **Evidence type & confidence:** Clinical cohort - High. Large multi-ancestry cohorts with convergent immunologic correlates; NK phenotypes not directly assayed.
- **Contradictions/nuance:** Expression was proxied rather than directly measured for each allotype; heterogeneity across HLA-C alleles and environments may modulate effect sizes.

A.5 HIV-1 Vpu Mediates HLA-C Downregulation [14]

- **Core question/approach:** Define whether and how Vpu downregulates HLA-C across primary HIV-1 clones and map responsible vpu regions and residues; assess CTL consequences.
- **Key findings:** Most primary clones downregulated HLA-C (Fig.1B, **p¡0.005; ****p¡0.0001). The effect mapped to a 149 bp vpu segment and specific residues (Fig.2-3). Clones with weaker HLA-C downregulation showed less suppression of CTL activity (Fig.6).
- **Mechanistic link:** *Direct* - Vpu reduces HLA-C surface expression, decreasing CTL antigen presentation and exerting class I display control across isolates; likely shifts NK inhibition-activation balance (Figs.1-3,6).
- **Keystone assessment:** Supports - KP3 (viral subversion); KP1 (triad integration); KP8 (NK-CTL pincer); KP12 (class I display control). Downregulation of a keystone ligand rebalances CTL and NK arms, consistent with system-level display tuning.
- **Evidence type & confidence:** Functional virology - High. Multiple isolates, precise mapping, and functional CTL readouts.
- **Contradictions/nuance:** Magnitude varies with viral strain and host HLA-C allotype; not all vpu variants exert equal effects.

A.6 HIV peptidome-wide association study reveals patient-specific epitope repertoires associated with HIV control [52]

- **Core question/approach:** Use peptidome-wide association to link predicted, disease-associated HLA-bound epitopes to HIV set-point viral load in a large cohort.
- **Key findings:** Disease-associated predicted epitopes at HLA-B explained roughly 12.2% of spVL variance; env alone explained about 6.4%; 132 HLA-B epitopes implicated (Fig.2; n=6311).
- **Mechanistic link:** *Inferred* - quantitative epitope repertoire shapes CTL control, highlighting conserved, contact-dense epitopes as key drivers.
- **Keystone assessment:** Supports - KP4 (constrained epitopes); KP2 (quantitative tuning). Epitope-level signals outperform allele counts, pointing to conserved targets under constraint.
- **Evidence type & confidence:** Population genetics - High. Large n and coherent epitope-level modeling; functional validation is limited within the study.
- **Contradictions/nuance:** Dependence on binding predictions and cohort composition; direct NK-linked effects are not probed here.

A.7 HLA Heterozygote Advantage against HIV-1 Is Driven by Quantitative and Qualitative Differences in HLA Allele-Specific Peptide Presentation [22]

- **Core question/approach:** Test whether heterozygote advantage arises from increased peptide breadth and complementarity of presented repertoires, using computational prediction and cohort data.

- **Key findings:** Heterozygosity at HLA-B and HLA-C associated with lower spVL (p=1.3e-6 and 2.8e-6). Broader and more divergent peptide repertoires correlated with better control (Kendall tau magnitudes around -0.12 for peptide breadth and -0.08 for allele divergence; Figs.3-4).
- **Mechanistic link:** *Inferred* - quantitative breadth and qualitative divergence of peptide presentation in heterozygotes enhance CTL coverage of constrained epitopes.
- **Keystone assessment:** Supports - KP2 (quantitative tuning); KP6 (coevolution). Complementary allele repertoires yield broader, more efficient CTL surveillance.
- **Evidence type & confidence:** Population genetics - High. Robust multi-locus modeling with clear statistical signals; NK education effects are not modeled directly.
- **Contradictions/nuance:** Reliant on in silico binding predictions and cohort assumptions; generalization to non-HIV pathogens requires caution.

A.8 HLA-C downregulation by HIV-1 adapts to host HLA genotype [53]

- **Core question/approach:** Does HIV-1 tune Vpu-mediated HLA-C downregulation to host HLA-C genotypes, reshaping NK versus CTL pressure? Quantified HLA-C surface loss by primary env/Vpu variants, mapped genotype correlations, and probed Vpu-HLA-C interaction by co-immunoprecipitation.
- **Key findings:** Among 195 replication-competent env clones, using a 6-fold threshold 69 were ""strong"" HLA-C downmodulators and 117 were weak; across individuals r=0.27, p=0.0005; across eight HLA-C alleles r=0.68, p=0.03; population HLA-C frequencies correlated negatively with downmodulation (r=-0.57, p=0.01). Vpu was necessary, and co-IP implicated the HLA-C transmembrane region. Key panels: Fig.3A-B, Fig.5A-D, Fig.6-8.
- **Mechanistic link:** Direct - Vpu engages HLA-C and downregulates it in an allele- and subtype-dependent manner, reducing inhibitory KIR ligands while altering CTL visibility (Fig.5-8); strain-variable class I tuning by Vpu consistent with KP12 display control (Fig.3A-B; Fig.6-8).
- **Keystone assessment:** Supports - KP3 (viral subversion), KP2 (quantitative), KP6 (coevolution), KP9 (licensing), KP12 (class I tuning by Vpu). Rationale: variant- and allele-tuned HLA-C control indicates class I display tuning that rebalances NK licensing and CTL recognition.
- **Evidence type & confidence:** Functional virology; *High* confidence given large panels and direct biochemical and phenotypic readouts.
- **Contradictions/nuance:** Cell-type dependence (primary cells vs 293T), heterogeneity among isolates, and allele or subtype specificity temper generalization.

A.9 HLA-C Downmodulation by HIV-1 Vpu [54]

- **Core question/approach:** Short perspective articulating the implications of Vpu-driven HLA-C downmodulation for CTL escape and NK evasion.
- **Key findings:** Summarizes the mechanism and tradeoffs, without new quantitative data.

- **Mechanistic link:** Circumstantial - reiterates the direct Vpu-HLA-C axis and its dual impact on NK inhibition and CTL recognition, framing class I tuning by Vpu.
- **Keystone assessment:** Indirect - KP3 (viral subversion), KP12 (class I tuning by Vpu). Rationale: positions Vpu as a class I display controller that rebalances the two arms.
- **Evidence type & confidence:** Review/perspective; *Low* confidence for quantitative inference because no primary N or effect sizes are presented.
- **Contradictions/nuance:** Commentary scope; defers to primary datasets for allelic and cellular context.

A.10 HLA/KIR restraint of HIV: Surviving the fittest [55]

- **Core question/approach:** Review integrates immunogenetics and functional work to explain how HLA-KIR diversity shapes HIV pathogenesis.
- **Key findings:** Summarizes associations of KIR3DL1 with Bw4 subtypes and their effects on progression, highlighting selection signals and population structure; specific Ns or CIs are not newly reported here.
- **Mechanistic link:** Circumstantial - positions HLA pocket chemistry, peptide presentation, and KIR binding within a triad that calibrates NK education and CTL pressure.
- **Keystone assessment:** Indirect - KP1 (triad), KP6 (coevolution), KP9 (licensing), KP10 (eco-geography). Rationale: synthesizes convergent lines showing co-tuned NK and CTL pressures.
- **Evidence type & confidence:** Review/perspective; *Low* confidence for quantitative inference due to no new effect sizes.
- **Contradictions/nuance:** Emphasizes allele- and ancestry-specific effects; mechanistic granularity varies across referenced studies.

A.11 HLA tapasin independence broadens peptide repertoire and is associated with HIV control [12]

- **Core question/approach:** Do HLA allotypes with reduced tapasin dependence present broader peptide repertoires and correspond to superior HIV control at the population level?
- **Key findings:** Tapasin-independent allotypes displayed broader peptide repertoires, and cohort analyses linked this property to improved viral control; principal results are shown in Fig.1-3 with p-values (e.g., p¡0.01-0.0001) and regression tables.
- **Mechanistic link:** Inferred - quantitative tuning of peptide loading (tapasin independence) changes pHLA stability or abundance seen by TCRs and KIRs; the paper notes that viral evasion targets peptide-loading machinery.
- **Keystone assessment:** Supports - KP2 (quantitative), KP6 (coevolution), KP3 (viral subversion). Rationale: broader presentation correlates with better control and aligns with known viral pressure on antigen loading.
- **Evidence type & confidence:** Population genetics; *Moderate* confidence, given cross-cohort associations plus molecular phenotyping but limited within-paper mechanistic dissection.

- **Contradictions/nuance:** Some protective alleles (e.g., B*57) are tapasin-dependent, indicating non-monotonic relationships and context from epitope topology.

A.12 HLA-DP on Epithelial Cells Enables Tissue Damage by NKp44+ Natural Killer Cells in Ulcerative Colitis [56]

- **Core question/approach:** Does epithelial HLA-DP drive NKp44-mediated cytotoxicity in UC, and can this be reversed by checkpoint blockade?
- **Key findings:** Transcriptomic meta-analysis (13,927 UC vs 26,764 controls) shows HLA-DP upregulation; organoid-NK co-cultures reveal NKp44-dependent killing that is mitigated by NKp44 blockade; representative MFI and viability changes appear in main and supplementary figures.
- **Mechanistic link:** Direct - epithelial class II (HLA-DP) ligates NKp44, wiring an immunoregulatory axis that promotes tissue damage; blockade rescues epithelial survival.
- **Keystone assessment:** Supports - KP7 (immunoregulatory wiring to dysregulation). Rationale: demonstrates a checkpoint-like circuit producing pathology.
- **Evidence type & confidence:** Clinical cohort; *High* confidence from convergent in situ and functional organoid assays.
- **Contradictions/nuance:** Disease-specific context; HLA-DP polymorphism and peptide dependence not fully parsed.

A.13 Inhibitory killer cell immunoglobulin-like receptors strengthen CD8+ T cell-mediated control of HIV-1, HCV and HTLV-1 [57]

- **Core question/approach:** Do iKIR genotypes augment protective HLA effects on viral control across diverse infections?
- **Key findings:** HIV-1 cohort (n=217): coefficient=-0.42±0.14, p=0.004 (Fig.6C; Table S3); HCV: HR=0.44, 95% CI 0.22-0.87, p=0.02 (Fig.7C; Table S4); HTLV-1: OR=0.22, 95% CI 0.08-0.60, p=0.006 (Fig.2E; Table S2). Effects require the combination of protective HLA and cognate iKIR.
- **Mechanistic link:** Inferred - inhibitory KIR raise or calibrate activation thresholds so that conserved, protective CTL responses exert greater impact.
- **Keystone assessment:** Supports - KP1 (triad), KP2 (quantitative), KP9 (licensing). Rationale: cross-viral, genotype-phenotype links that integrate NK licensing with CTL efficacy.
- **Evidence type & confidence:** Clinical cohort; *High* confidence from multi-cohort replication with consistent directions and statistics.
- **Contradictions/nuance:** Dependence on joint genotype (HLA plus iKIR); magnitude varies across viruses and cohorts.

A.14 KIR3DL1 and HLA-B density and binding calibrate NK education and response to HIV [8]

- **Core question/approach:** How do KIR3DL1-HLA-Bw4 binding strength and surface densities of receptor or ligand calibrate NK education and killing of HIV-infected autologous cells?
- **Key findings:** Binding-reactivity correlations (r^2 ≈0.33-0.41, p≤0.005; Fig.4A-C); high KIR3DL1 density compensates for weak affinity (Fig.5-6); Bw4 surface density predicts education (r^2 ≈0.45-0.52, p¡0.0001; Fig.7D-F); HIV reduces Bw4 MFI ∼60% with ∼15.5±9.3% infection; educated KIR3DL1$^+$ NK preferentially kill infected autologous CD4 T cells (Fig.8E).
- **Mechanistic link:** Direct - quantitative KIR3DL1-HLA-Bw4 interactions and expression levels set licensing thresholds mapping to cytotoxic responses against HIV-infected targets; infection reduces HLA-Bw4 density, evidencing class I display control under infection (Fig.7-8).
- **Keystone assessment:** Supports - KP2 (quantitative), KP9 (licensing), KP3 (viral subversion), KP12 (class I display control). Rationale: demonstrates how density and affinity tune education and documents infection-driven Bw4 reduction that interfaces with viral class I control.
- **Evidence type & confidence:** Functional virology; *High* confidence based on multiple orthogonal assays and clear effect sizes.
- **Contradictions/nuance:** B*27 shows weak KIR3DL1 binding yet high Bw4 density and strong education; subtype-specific context shapes outcomes.

A.15 Reduced Viral Replication Capacity of Human Immunodeficiency Virus Type 1 Subtype C Caused by Cytotoxic T-Lymphocyte Escape Mutations in Gag Is Associated with HLA-B*57 and HLA-B*58:01 [39]

- **Core question/approach:** Functional virology linking B*57/B*58:01-restricted Gag escape to viral replication capacity (RRC) in subtype C, with cohort context for HLA associations.
- **Key findings:** Single mutants T242N, A146P, A163G reduced RRC to 0.86, 0.91, and 0.89, respectively; the triple A146P+T242N+A163G dropped RRC to 0.62 (WT=1.0). Protective B*57/B*58:01 were enriched among viruses with lower RRC. Fig. 2A-2B, p. 2460-2468.
- **Mechanistic link:** Direct - HLA-B*57/B*58:01-restricted TCR pressure on the TW10 p24 epitope forces mutations that reduce peptide-MHC-TCR fitness, producing quantitative decrements in replication (stepwise with combinations).
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP2 (quantitative). Rationale: measurable fitness penalties for escape at conserved Gag positions align with constrained-epitope theory.
- **Evidence type & confidence:** Functional virology, High confidence given direct RRC measurements and clear effect sizes.
- **Contradictions/nuance:** Effects shown in subtype C; some single mutants cause modest RRC loss, so context and compensatory pathways matter.

A.16 Escape and Compensation from Early HLA-B57-Mediated Cytotoxic T-Lymphocyte Pressure on Human Immunodeficiency Virus Type 1 Gag Proteins [38]

- **Core question/approach:** Define how CTL escape (TW10 T242N) and compensatory capsid mutations shape replication, cyclophilin A dependence, and viremia.
- **Key findings:** Compensation (H219Q/I223V/M228I) restored replication and associated with higher plasma viremia (donors r=0.34, p=0.13; recipients r=0.59, p=0.02); correlations are shown in Fig. 2. Reduced cyclophilin A dependence accompanied compensation. p. 12608-12618.
- **Mechanistic link:** Direct - TCR-driven escape undermines capsid fitness and cyclophilin usage; secondary mutations re-optimize capsid while sustaining CTL escape, shifting quantitative set-points of replication and viremia.
- **Keystone assessment:** Supports - KP4 (cost at conserved sites), KP2 (quantitative tuning). Rationale: fitness-compensation cycles mirror constrained topology.
- **Evidence type & confidence:** Functional virology, Moderate confidence due to differing effect sizes across donor and recipient groups.
- **Contradictions/nuance:** Compensation pathways are heterogeneous; statistics are stronger in recipients than donors; no direct KIR data.

A.17 Marked Epitope- and Allele-Specific Differences in Rates of Mutation in Human Immunodeficiency Virus Type 1 Gag Proteins [20]

- **Core question/approach:** Longitudinal sequencing of early infection (N=98 seroconverters) to quantify escape and reversion within HLA-restricted Gag epitopes.
- **Key findings:** About 80% of published CTL epitopes evolved in early infection, with rapid reversion observed in B*57-restricted epitopes; among the 10 fastest-evolving epitopes, 5 were restricted by control-associated alleles; early immune pressure concentrated in Gag. Fig. 1-2; p. 9216-9227.
- **Mechanistic link:** Circumstantial - allele and epitope-specific escape and reversion patterns imply peptide-pocket constraints and fitness costs that track with protective HLA backgrounds.
- **Keystone assessment:** Supports - KP4 (constrained), KP6 (co-evolution). Rationale: allele-linked mutation dynamics highlight constraint and selection.
- **Evidence type & confidence:** Clinical cohort, High confidence given sample size and consistent allele-level patterns.
- **Contradictions/nuance:** Heterogeneity across epitopes; correlative evidence; not every protective allele shows rapid evolution.

A.18 Innate Immune Control of HIV [4]

- **Core question/approach:** Review of innate recognition and control mechanisms in HIV, centered on KIR-HLA genetics, NK education, and viral evasion.

- **Key findings:** KIR/HLA receptor-ligand coexpression relates to slower progression; NK cells expand during acute infection; HIV Nef downregulates HLA-A/B while sparing HLA-C, preserving inhibitory KIR ligands and balancing CTL evasion. Fig. 1, Fig. 3; pp. 3-4, 8-10.
- **Mechanistic link:** Inferred - peptide-sensitive KIR engagement by pHLA plus Nef selective modulation of class I integrates NK licensing and activation with CTL pressure, maintaining inhibitory KIR tone at scale via preserved HLA-C.
- **Keystone assessment:** Supports - KP1 (triad), KP2 (quantitative education), KP3 (viral subversion), KP12 (display control preserves inhibition). Rationale: synthesis ties NK education, KIR-HLA axes, and Nef display control to system-level balance.
- **Evidence type & confidence:** Review/perspective, Moderate confidence summarizing multiple modalities.
- **Contradictions/nuance:** Some KIR-Bw4 physical interactions and peptide dependencies remain incompletely resolved across all allotypes.

A.19 Immunogenetics of Spontaneous Control of HIV [58]

- **Core question/approach:** Review that integrates GWAS and functional data to explain genetic determinants of control, emphasizing HLA-B pocket residues and HLA-C expression regulation.
- **Key findings:** GWAS of 974 controllers vs 2,648 progressors identified 313 SNPs at $p < 5 \times 10^{-8}$, all within MHC-I; structural focus on HLA-B residues 62/63/67/70/97 lining the peptide-binding groove; HLA-C -35 variant correlates with expression and control; 3′UTR miR-148 binding site modulates HLA-C surface expression. Fig. 2-4.
- **Mechanistic link:** Inferred - pocket chemistry shapes CTL epitope topology, while HLA-C expression eQTLs and 3′UTR regulation tune quantitative presentation and NK education thresholds.
- **Keystone assessment:** Supports - KP2 (quantitative tuning; HLA-C expression), KP1 (triad integration), KP4 (constrained epitopes). Rationale: genetics connects geometry and expression to control.
- **Evidence type & confidence:** Review/perspective, Moderate confidence grounded in large-scale data.
- **Contradictions/nuance:** The -35 signal can be confounded by LD in some cohorts; causal variant and mechanism vary by ancestry.

A.20 Herpes simplex virus lymphadenitis is associated with tumor reduction in a patient with chronic lymphocytic leukemia [5]

- **Core question/approach:** Case report linking HSV lymphadenitis with spontaneous tumor reduction in CLL, with histopathology and immunophenotyping.
- **Key findings:** HSV-1 lymphadenitis temporally coincided with tumor reduction prior to CLL-directed therapy; lymph node biopsy confirmed HSV and robust immune infiltration; precise percentage reduction not reported; course documented in Fig. 1-2.

- **Mechanistic link:** Circumstantial - acute viral inflammation likely shifted innate and adaptive balance (potential NK/T activation), though specific KIR-HLA peptide effects were not measured.
- **Keystone assessment:** Indirect - KP7 (immunoregulatory wiring). Rationale: illustrates set-point rebalancing with clinical impact.
- **Evidence type & confidence:** Case report, Low confidence due to single-subject design.
- **Contradictions/nuance:** Alternative causes for tumor fluctuation cannot be excluded; mechanistic assays were limited.

A.21 HLA Class I-Mediated HIV-1 Control in Vietnamese Infected with HIV-1 Subtype AE [59]

- **Core question/approach:** Clinical cohort (N=536) assessing HLA class I associations with viral load and CD4 in subtype AE infection.
- **Key findings:** HLA-C*12:02 associated with lower viral load (median 4.22 vs 4.57 $\log_{10}$ copies/mL, p=0.016) and higher CD4 (370 vs 297 cells/µL, p=0.040); HLA-C*15:05 associated with higher viral load (4.80 vs 4.54, p=0.022) and lower CD4 (238 vs 304, p=0.014); HLA-B*52 and HLA-C*12:02 showed consistent protective signals (Tables 1 and 4; pp. 3-4).
- **Mechanistic link:** Inferred - allele-specific peptide presentation (B*52, C*12:02) and potential KIR engagement calibrate activation thresholds; direct binding and education assays not performed.
- **Keystone assessment:** Supports - KP2 (quantitative tuning via HLA-C effects), KP6 (population and strain differences). Rationale: ancestry and AE-specific allele effects align with differential control.
- **Evidence type & confidence:** Clinical cohort, High confidence given N and consistent directionality.
- **Contradictions/nuance:** LD with nearby variants and AE lineage specificity limit generalizability; mechanistic axis inferred rather than demonstrated.

A.22 Broadly Reactive Human CD8 T Cells that Recognize an Epitope Conserved between VZV, HSV and EBV [60]

- **Core question/approach:** Can a single conserved herpesvirus peptide elicit human CD8 T cells that cross-recognize EBV, VZV and HSV, and what is the HLA restriction? Mapped responses with HLA-B*18 tetramers and CD8 T cell clones.
- **Key findings:** A conserved 9-mer derived from EBV BCRF1, VZV ORF16 and HSV-1 UL27 was identified and shown to be recognized by HLA-B*18:01/03-restricted CD8 T cells. Cross-reactivity was demonstrated by tetramer binding and IFN-γ assays; clonal lines recognized all three peptides (Fig. 4-5; n and effect sizes not reported).
- **Mechanistic link:** *Direct* - TCR cross-reactivity to a conserved peptide presented by HLA-B*18:01; peptide conservation preserves CTL visibility across viruses. Axis: TCR recognition of conserved pHLA; no KIR data (Fig. 4-5).

- **Keystone assessment:** Supports - KP4 (constrained epitopes); KP5 (imprinting on geometry). The same conserved pHLA is targeted across pathogens, consistent with geometric constraint.
- **Evidence type & confidence:** Functional virology; **Moderate** confidence due to direct assays but limited reported n and quantitation.
- **Contradictions/nuance:** HLA restriction is narrow (B*18); breadth and population frequency of such cross-reactivity are unclear; NK/KIR arm not assessed.

A.23 Genotypic and Functional Impact of HIV-1 Adaptation to Its Host Population during the North American Epidemic [29]

- **Core question/approach:** How much have HLA-driven escape mutations spread in North American HIV, and did they alter viral function? Linked HLA and HIV Gag/Nef from historic (1979-1989) vs modern (2000-2011) samples, with phylogenetics and functional assays.
- **Key findings:** Background Gag HLA-associated polymorphisms were higher in modern vs historic sequences (median 3.7% vs 2.0%); HLA-targeted codons diversified more over time (45.2% vs 21.0%; $p = 0.0002$). Gag replication capacity showed no era differences (Kruskal-Wallis $p = 0.6$), whereas modern Nef exhibited greater CD4 and HLA-I downregulation (both $p < 0.0001$). Fig. 1-4,7-8.
- **Mechanistic link:** *Inferred* - HLA-peptide-TCR pressures drive gradual escape accumulation; *plus* Nef-mediated class I display control reduces CTL visibility at the infection level (Fig. 3-4,7-8). Preservation of inhibitory NK tone was not directly tested.
- **Keystone assessment:** Supports - KP6 (host-pathogen coevolution); KP4 (escape constraints); KP2 (quantitative tuning); **KP12 (class I display control)**. Viral evolution mirrors host HLA landscape, and increased Nef-driven HLA-I downregulation aligns with inhibition-preserving display control.
- **Evidence type & confidence:** Clinical cohort; **High** confidence given sample sizes and multimodal analyses.
- **Contradictions/nuance:** Serum-based HLA typing in historic specimens may bias homozygosity; most escape accumulation is modest and allele-specific; HLA-A/B vs HLA-C specificity and NK inhibition effects were not dissected.

A.24 Coordinate linkage of HIV evolution reveals regions of immunological vulnerability [18]

- **Core question/approach:** Do coordinated sequence changes reveal structurally constrained regions that define vulnerable CTL targets? Used covariation analysis to infer coevolving sectors and mapped them onto structure.
- **Key findings:** Contact-dense sectors in Gag (and other proteins) overlap epitopes linked to control and imply multi-site constraints that restrict escape routes; sector topology and linkage are illustrated (Fig. 3-4; n and effect sizes not reported).

- **Mechanistic link:** *Inferred* - Epitope topology/contact density constrain mutation pathways, increasing fitness costs for escape. Axis: structural packing and peptide stability. (Fig. 3-4).
- **Keystone assessment:** Supports - KP4 (constrained epitopes); KP5 (imprinting on geometry). Constrained topology rationalizes durable CTL targets.
- **Evidence type & confidence:** Molecular/structural; **Moderate** confidence due to strong theory with limited direct functional validation.
- **Contradictions/nuance:** Sector predictions depend on datasets and alignments; not all proposed sectors have been experimentally stress-tested.

A.25 Adaptive Admixture of HLA Class I Allotypes Enhanced Genetically Determined Strength of Natural Killer Cells in East Asians [47]

- **Core question/approach:** Did admixture and selection reshape HLA-KIR architectures to strengthen NK education in Chinese Southern Han? Combined population genetics, KIR/HLA typing, and selection scans.
- **Key findings:** CHS haplotypes are enriched for multiple inhibitory KIR ligands; admixture introduced HLA-B*46:01 and B*58:01 with strong selection; 306 Chinese individuals were KIR/HLA typed (Fig. 1) and enrichment of inhibitory KIR and ligands documented (Fig. 4-6; Suppl).
- **Mechanistic link:** *Inferred* - Increased HLA-Bw4 and HLA-C1/C2 ligand supply tunes inhibitory KIR licensing and NK activation thresholds; quantitative ligand-receptor calibration (Fig. 4-6).
- **Keystone assessment:** Supports - KP10 (eco-geographic licensing); KP9 (licensing set-point); KP6 (coevolution). Admixture plus selection optimized inhibitory KIR-HLA pairing.
- **Evidence type & confidence:** Population genetics; **High** confidence from convergent genetic signals and cohort typing.
- **Contradictions/nuance:** Specific environmental drivers remain uncertain; functional NK assays are limited in the main text.

A.26 Association of Inhibitory Killer Cell Immunoglobulin-like Receptor Ligands With Higher *Plasmodium falciparum* Parasite Prevalence [61]

- **Core question/approach:** Do inhibitory KIR ligands associate with malaria burden in children? Ugandan cohort with HLA typing and longitudinal parasitology.
- **Key findings:** HLA-C2 increased parasite prevalence by 3.4 percentage points (95% CI 1.0-5.8; $P = 0.006$); HLA-Bw4 by 1.7 (95% CI 0.1-3.4; $P = 0.04$); HLA-C1 decreased by 2.2 (95% CI -3.9 to -0.4; $P = 0.02$). Each additional inhibitory ligand increased odds of symptomatic episodes (OR 1.31, 95% CI 1.05-1.63; $P = 0.017$) and parasite density slope (+0.16 $\log_{10}$). Fig. 2-4; Tables S4-S5.

- **Mechanistic link:** *Inferred* - HLA-C1/C2 and HLA-Bw4 tune inhibitory KIR licensing toward higher inhibitory tone, raising parasite burden; quantitative HLA-KIR axis (Fig. 2-4).
- **Keystone assessment:** Supports - KP9 (licensing set-point); KP2 (quantitative tuning). More inhibitory ligands map to more infection.
- **Evidence type & confidence:** Clinical cohort; **High** confidence given sample size and robust models.
- **Contradictions/nuance:** Exposure variation and lack of KIR genotypes limit causal inference.

A.27 Functional HPV-specific PD-1+ stem-like CD8 T cells in head and neck cancer [45]

- **Core question/approach:** Define stem-like HPV-specific CD8 T cells in human tumors and their modulation by PD-1 blockade and vaccination.
- **Key findings:** An HPV-specific PD-1+ TCF1+ stem-like CD8 subset was delineated and expanded after PD-1 therapy and vaccination; durable tumor infiltration and function documented (Extended Data Figs. 2-16; numeric n not reported in extract).
- **Mechanistic link:** *Direct* - TCR-defined stem-like reservoir supports responses under checkpoint modulation; axis: TCR recognition and PD-1 signaling.
- **Keystone assessment:** Indirect - KP5 (imprinting on geometry); KP7 (immunoregulatory wiring). Checkpoint wiring and memory state shape CTL effectiveness.
- **Evidence type & confidence:** Clinical cohort; **Moderate** confidence (direct phenotyping and intervention signals, but limited KIR/HLA linkage and details in extract).
- **Contradictions/nuance:** Cancer setting; class I restrictions and epitope topology not deeply dissected; NK arm not addressed.

A.28 HIV post-treatment controllers have distinct immunological and virological features [62]

- **Core question/approach:** What immune and virological features distinguish post-treatment controllers (PTC) from non-controllers (NC) after ART interruption?
- **Key findings:** In a CG-trial subset, PTC ($n = 22$) vs NC ($n = 37$) were separable by PLS-DA with AUC 0.91 (95% CI 0.83-0.97; 10-fold cross-validation; Fig. 2A). PTC displayed lower and steadier CA-RNA/IPDA signals over time; NK activation markers (CD69, CD38) tracked reservoir dynamics (Fig. 3-4). HLA-B*57 frequency was similar between groups.
- **Mechanistic link:** *Circumstantial* - Distinct immunoregulatory set-points and reservoir behavior associate with sustained control; axes: PD-1/T cell differentiation and NK activation.
- **Keystone assessment:** Indirect - KP7 (immunoregulatory wiring); KP5 (postnatal imprinting). Regulatory wiring aligns with clinical control independent of overt KIR/HLA effects.
- **Evidence type & confidence:** Clinical cohort; **Moderate** confidence due to robust classification but heterogeneous cohorts and limited direct mechanism.

- **Contradictions/nuance:** Causality cannot be inferred; cohort definitions and endpoints vary; KIR/HLA not directly implicated.

A.29 Structural topology defines protective CD8+ T cell epitopes in the HIV proteome [36]

- **Core question/approach:** The study applied structure-based network analysis across the HIV proteome and paired it with ex vivo $CD8^+$ T cell assays in controllers, intermediates, and progressors to identify epitopes with low mutational tolerance that align with protective HLA alleles.
- **Key findings:** Protective HLA alleles presented epitopes with higher network scores than risk alleles (Fig. 2E-F); controllers preferentially targeted high-score epitopes and had lower viral load (Spearman $\rho = -0.63$, $p<0.0001$; Fig. 3F-H,S8); mutating highly networked residues impaired infectivity and spread (Fig. 1F-H). Sample sizes included controllers $n = 46$, intermediates $n = 25$, progressors $n = 43$ in key comparisons (Fig. 3F-K).
- **Mechanistic link:** Direct - epitope topology at HLA anchor and TCR contact residues constrains escape and preserves CTL recognition; mapping of B*57-KF11 versus B*35-DL9 illustrates peptide-geometry effects underlying durable control (Fig. 2B-D).
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP2 (quantitative tuning). Rationale: high network-score epitopes are harder to mutate without fitness loss and are preferentially targeted in natural control.
- **Evidence type & confidence:** Molecular/structural, High; multiple modalities with clear functional perturbations and consistent cohort associations.
- **Contradictions/nuance:** KIR was not tested; dependence on available structures for network scoring limits breadth of immediate application.

A.30 Acute infectious mononucleosis generates persistent, functional EBNA-1 antibodies with high cross-reactivity to alpha-crystalline beta [6]

- **Core question/approach:** Prospective cohorts of acute infectious mononucleosis and EBV carriers with longitudinal serology, monoclonal antibody isolation, and competition assays to map EBNA-1 cross-reactivity and durability.
- **Key findings:** Acute IM participants (approximately $n = 98$) developed high-titer EBNA-1 IgG that persisted to at least 12 months; several mAbs cross-reacted with CRYAB, and competition studies supported shared epitope targeting; DRB1*15:01 was associated with stronger EBNA-1 responses. Figure-level effect sizes and exact p values were not visible in the text snippets reviewed.
- **Mechanistic link:** Circumstantial - the findings implicate a class II HLA humoral axis and cross-reactivity that could secondarily bias CTL or NK balance, rather than a direct class I HLA-peptide-KIR-TCR triad.
- **Keystone assessment:** Indirect - KP7 (immunoregulatory wiring), KP6 (host-pathogen coevolution). Rationale: persistent cross-reactive humoral responses point to wiring that can predispose to dysregulation.

- **Evidence type & confidence:** Clinical cohort, Moderate; prospective data but limited direct cellular-mechanistic mapping.
- **Contradictions/nuance:** Primary focus is humoral; CTL and NK mechanisms were not directly tested within this study.

A.31 Learning from HIV-1 to predict the immunogenicity of T cell epitopes in SARS-CoV-2 [50]

- **Core question/approach:** A physics-based classifier was trained on HIV CTL immunodominance and then applied to SARS-CoV-2, with ELISpot testing in patients for validation.
- **Key findings:** The classifier achieved AUC 0.71 in acute HIV and 0.66 in chronic HIV, outperforming netMHCpan4.0 and Calis et al. (Fig. 1A-B,G-H). ELISpot validation across 108 peptides showed weighted Pearson $r = 0.43$ at peptide level and $r = 0.82$ grouped by HLA (Fig. 3A-B).
- **Mechanistic link:** Inferred - features capture HLA binding and peptide similarity to self and pathogen, reflecting presentation quality and constraint that shape pHLA-TCR engagement and immunodominance.
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP2 (quantitative tuning). Rationale: performance depends on epitope constraint and presentation metrics that tune CTL responses.
- **Evidence type & confidence:** Molecular/structural, Moderate; robust cross-validation with limited SARS-CoV-2 patient testing.
- **Contradictions/nuance:** NK and KIR axes were not examined; generalization beyond tested alleles requires broader cohorts.

A.32 The first T cell response to transmitted-founder virus contributes to the control of acute viremia in HIV-1 infection [63]

- **Core question/approach:** Prospective mapping of earliest CTL responses to transmitted-founder viruses in acute HIV with concurrent sequencing and viral dynamics modeling.
- **Key findings:** Early CTL responses drove rapid viral escape with median rate approximately 0.14 day^{-1}, reaching approximately 0.36 in some cases (Fig. 6), and the breadth and timing of these responses associated with declines in acute viremia (Fig. 7). Constrained Gag targeting showed slower or costly escape trajectories.
- **Mechanistic link:** Circumstantial - CTL pressure on specific pHLA-TCR epitopes induces escape, exposing differential constraint rather than direct effects on KIR signaling.
- **Keystone assessment:** Supports - KP3 (viral subversion), KP4 (constrained epitopes), KP6 (host-pathogen coevolution). Rationale: escape kinetics and control depend on epitope constraint.
- **Evidence type & confidence:** Clinical cohort, Moderate; clear temporal mapping with moderate sample size.

- **Contradictions/nuance:** NK components not characterized; results reflect early infection dynamics that may shift later.

A.33 Immune correlates of HIV-1 reservoir cell decline in early-treated infants [64]

- **Core question/approach:** Longitudinal analysis of intact proviral reservoir trajectories in early-treated infants paired with host expression and NK checkpoint phenotyping.
- **Key findings:** Greater decline in intact provirus associated with lower HLA-A expression and reduced NKG2A on NK cells; HLA-B -21M/T status influenced HLA-E-NKG2A licensing set-points that aligned with stronger decline (Fig. 2F-G, Fig. 3D). Exact sample sizes and effect estimates were not visible in the snippets.
- **Mechanistic link:** Inferred - HLA-B leader peptides modulate HLA-E display and NKG2A education, tuning NK activation thresholds that relate to reservoir decay.
- **Keystone assessment:** Supports - KP9 (licensing set-point), KP2 (quantitative tuning). Rationale: leader-peptide driven education shifts quantitative NK surveillance.
- **Evidence type & confidence:** Clinical cohort, Moderate; coherent genotype-phenotype trends without peptide-level mapping.
- **Contradictions/nuance:** Infant immunobiology may limit generalization; no direct KIR-peptide assays.

A.34 Evasion of NKG2D-mediated cytotoxic immunity by sarbecoviruses [16]

- **Core question/approach:** Functional virology to identify sarbecovirus determinants that modulate NK recognition through NKG2D-ligand pathways.
- **Key findings:** Sarbecoviruses downmodulated MICA/B and other NKG2D ligands, reducing NK degranulation and killing; ORF6 and Nsp1 were principal effectors, with restoration of NK responses upon ligand rescue or blockade (e.g., Fig. 3).
- **Mechanistic link:** Direct - viral proteins attenuate NKG2D-ligand engagement, suppressing NK activation on infected cells at scale; this aligns with inhibition-preserving display control at the level of activating-ligand display.
- **Keystone assessment:** Supports - KP3 (viral subversion), KP7 (immunoregulatory wiring), KP12 (display control, NKG2D-ligand loss). Rationale: mechanistic disruption of a keystone NK axis with functional reversibility and large-scale display control.
- **Evidence type & confidence:** Functional virology, High; clear perturbation studies across strains and ORFs.
- **Contradictions/nuance:** Focuses on NKG2D rather than KIR; class I modulation context may vary by cell type.

A.35 HLA-B35-Px mediated acceleration of HIV-1 infection by increased inhibitory immunoregulatory impulses [43]

- **Core question/approach:** Clinical and cellular comparisons of HLA-B*35-Px versus -Py effects on dendritic cell inhibitory signaling and downstream T cell priming.

- **Key findings:** B*35-Px showed stronger engagement of inhibitory ILT4, elevated IL-10, reduced T cell priming, and faster disease progression than -Py; peptide and allotype context contributed to inhibitory strength (Figs. 1-3).
- **Mechanistic link:** Direct - specific HLA-B allotypes enhance ILT4-mediated inhibition, increasing immunoregulatory tone and attenuating effective CTL priming, an axis that can intersect with NK education indirectly.
- **Keystone assessment:** Supports - KP7 (immunoregulatory wiring), KP2 (quantitative tuning). Rationale: allotype-driven inhibitory signaling predisposes to excess inhibition and poorer control.
- **Evidence type & confidence:** Clinical cohort, High; mechanistic cellular data aligned with clinical phenotypes.
- **Contradictions/nuance:** Mechanism centers on ILT4 rather than KIR; peptide dependences vary by allele and context.

A.36 Host genetic determinants of HIV pathogenesis: an immunologic perspective [65]

- **Core question/approach:** Narrative synthesis of how host genetics, especially HLA class I and KIR, shape HIV outcomes, integrating cohort associations and mechanistic immunology.
- **Key findings:** The review highlights synergy between KIR3DS1 (or high-expressing KIR3DL1) and HLA-Bw4-80I, associated with delayed progression (relative hazard 0.53, P< 0.001; Fig. 1B). It summarizes strong HLA-B*57/B*27 associations with lower viremia and delayed disease, and discusses HLA-C expression genetics as a quantitative modifier of control (Fig. 1-2).
- **Mechanistic link:** *Circumstantial* - Triad framing: Bw4-80I tunes both inhibitory or activating KIR and CTL visibility via peptide presentation; HLA-C expression further calibrates inhibitory KIR thresholds and antigen load to TCR.
- **Keystone assessment:** Supports - KP1 (triad), KP2 (quantitative), KP7 (immunoregulatory wiring). Rationale: converging genetic and immunologic signals indicate KIR-HLA co-tune NK education and CTL surveillance.
- **Evidence type & confidence:** Review/perspective; **Moderate** confidence due to synthesis nature, though based on replicated cohort findings.
- **Contradictions/nuance:** Magnitude of KIR3DS1-Bw4 effects varies by cohort; mechanistic details for some axes inferred from multiple studies rather than shown in one system.

A.37 Distinct viral reservoirs in individuals with spontaneous control of HIV-1 [66]

- **Core question/approach:** Compared elite controllers and ART-suppressed individuals using near-full-length proviral sequencing and integration-site mapping to define reservoir quality and distribution.
- **Key findings:** EC (n=64) versus ART (n=41) had markedly depleted intact proviruses and integration patterns disfavoring reactivation (Fig. 1-3). Protective

HLA-B*27/B*57 alleles were enriched in EC (27.3% vs 8.8%, P=0.0012; Extended Data Table 1).

- **Mechanistic link:** *Inferred* - Enrichment of protective HLA suggests CTL targeting of conserved, structurally constrained epitopes that exact high fitness costs on escape, sculpting a crippled reservoir; KIR axis not measured.
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP5 (imprinting and geometry). Rationale: reservoir and HLA patterns align with costly escape at conserved sites.
- **Evidence type & confidence:** Clinical cohort; **High** confidence given clear EC vs ART differences and statistics.
- **Contradictions/nuance:** Cross-sectional design; groups not HLA-matched; absence of NK readouts limits direct triad inference.

A.38 HLA class-I-peptide stability mediates CD8+ T cell immunodominance hierarchies and facilitates HLA-associated immune control of HIV [67]

- **Core question/approach:** Quantified peptide-HLA stability for 186 optimal HIV epitopes across 18 HLA class I alleles using a TAP-deficient system; correlated stability with ex vivo immunodominance.
- **Key findings:** pHLA stability explained substantial variance in immunodominance ($r \approx 0.32$-0.67, $p < 0.001$ across donors; Fig. 2C-E, Fig. 3B; Table S3), with high-stability epitopes enriched under protective HLA backgrounds.
- **Mechanistic link:** *Direct* - Pocket chemistry and peptide quality set quantitative thresholds for TCR engagement; longer-lasting pHLA complexes promote dominance and control.
- **Keystone assessment:** Supports - KP2 (quantitative tuning), KP4 (constrained epitopes). Rationale: stability is a mechanistic, quantitative dial linking epitope biophysics to CTL hierarchy and protection.
- **Evidence type & confidence:** Molecular/structural; **High** confidence from direct measurements and coherent correlations.
- **Contradictions/nuance:** Stability not sufficient (outliers exist); NK/KIR arm not probed, so triad coupling is inferred.

A.39 Structural and regulatory diversity shape HLA-C protein expression levels [68]

- **Core question/approach:** Dissected coding and noncoding determinants of HLA-C surface abundance via hybrid constructs, reporter assays, structural analysis, and peptide-MHC biophysics.
- **Key findings:** HLA-C*05 showed ∼2-fold higher surface expression than C*07 in cells ($P < 0.0001$; Fig. 1C-F), despite C*07 having a stronger promoter in luciferase assays (Fig. 2B-F). Exons 2-3 dictated differential abundance via peptide-binding cleft architecture and thermal stability (5-10°C differences; Fig. 4-7), with broader peptide repertoires stabilizing high-expressers.

- **Mechanistic link:** *Direct* - Cis-variation in exons 2-3 and the 3′UTR quantitatively tunes HLA-C levels and peptide selectivity, calibrating inhibitory KIR engagement and TCR antigen load.
- **Keystone assessment:** Supports - KP2 (quantitative tuning), KP9 (licensing set-point). Rationale: genetically encoded expression differences provide a lever for NK education and CTL visibility.
- **Evidence type & confidence:** Population genetics with functional and structural assays; **High** confidence.
- **Contradictions/nuance:** NK functional consequences inferred, not measured; allele- and population-specific effects.

A.40 Population-Level Immune-Mediated Adaptation in HIV-1 Polymerase during the North American Epidemic [30]

- **Core question/approach:** Mapped HLA-associated viral adaptations in pol across the North American epidemic using phylogenetically corrected models that account for LD and founder effects.
- **Key findings:** Numerous codon-level HLA associations in pol were identified, resolving population-level adaptation signatures across the epidemic and clarifying methodological controls for confounding; full results summarized across figures and tables in J Virol 90:1244-1258.
- **Mechanistic link:** *Inferred* - Patterns imply CTL-driven escape under structural and fitness constraints in pol, consistent with costly, topology-limited adaptation.
- **Keystone assessment:** Supports - KP6 (host-pathogen coevolution), KP4 (constrained epitopes). Rationale: reciprocal adaptation is evident at population scale and points to fitness costs.
- **Evidence type & confidence:** Population genetics; **High** confidence given scope and controls.
- **Contradictions/nuance:** Focused on pol rather than whole proteome; functional costs inferred not universally validated.

A.41 Genotypic and Mechanistic Characterization of Subtype-Specific HIV Adaptation to Host Cellular Immunity [31]

- **Core question/approach:** Combined statistical mapping of HLA-associated polymorphisms across four subtypes and nine cohorts with targeted mechanistic validation of fitness effects.
- **Key findings:** Among n=464 participants, 1,140 allele-site tests (median 5.8 per allele) yielded 425 adapted residues across subtypes; subtype-specific, nonreciprocal cross-protection emerged, and select escape variants carried replication and fitness costs (Fig. 1-5; Tables S2-S4).

- **Mechanistic link:** *Inferred -¿ Direct* - Genomic escape maps inform targeted assays that confirm fitness trade-offs at specific residues, supporting constrained epitope topology.
- **Keystone assessment:** Supports - KP6 (coevolution), KP4 (costly escape). Rationale: cross-subtype adaptation with validated costs reflects reciprocal evolution under structural constraints.
- **Evidence type & confidence:** Population genetics with mechanistic add-ons; **High** confidence.
- **Contradictions/nuance:** Validation limited to subsets; geographic and subtype sampling may bias spectra; NK arm not evaluated.

A.42 HIV-1-Mediated Downmodulation of HLA-C Impacts Target Cell Recognition and Antiviral Activity of NK Cells [69]

- **Core question/approach:** Tested whether HIV-1 modulates HLA-C and how this alters NK recognition using patient-derived isolates, molecular mapping, and functional cytotoxicity assays.
- **Key findings:** Vpu-mediated HLA-C downmodulation varied by isolate and predicted increased NK degranulation and killing (e.g., ∼2-3× CD107a, p< 0.01; Fig. 1-4). Blocking inhibitory KIR2DL interactions restored inhibition patterns, confirming peptide-dependent KIR contributions (Fig. 3-4).
- **Mechanistic link:** *Direct* - Viral Vpu reduces HLA-C on targets, tuning class I display and weakening inhibitory KIR engagement with isolate-specific magnitude; peptide-sensitive KIR effects tie directly into the pHLA triad.
- **Keystone assessment:** Supports - KP3 (viral subversion), KP8 (NK/CTL pincer), KP1 (triad), KP12 (class I tuning, strain-variable). Rationale: class I level control by Vpu demonstrates scalable display tuning that can override single-epitope pincers, although in these data reduced HLA-C favors NK activation rather than inhibition-preserving tone.
- **Evidence type & confidence:** Functional virology; **High** confidence with isolate diversity and convergent functional readouts.
- **Contradictions/nuance:** Effect sizes depend on viral strain and donor KIR background; some isolates show stronger HLA-C loss with net NK activation, not inhibition-preserving control.

A.43 Thymic Selection of T-Cell Receptors as an Extreme Value Problem [70]

- **Core question/approach:** Develop a statistical-physics model of thymic selection in which TCR-peptide-MHC binding energies follow extreme-value statistics, linking selection thresholds to emergent cross-reactivity of the mature repertoire.
- **Key findings:** Using realistic numbers of self peptides ($M \approx 10^3 - 10^4$), the model delineates parameter regions where negative versus positive selection dominate and predicts a tunable cross-reactivity set-point for TCRs (*Fig. 2; p. 068103-3*).

- **Mechanistic link:** *Direct* - focuses on TCR cross-reactivity shaped by thymic selection thresholds over pMHC energy landscapes; no NK measurements but mechanistically specifies how peptide presentation and selection tune CTL sensitivity.
- **Keystone assessment:** Supports - KP5 (thymic imprinting), KP2 (quantitative). Rationale: quantifies how selection thresholds set the geometry and avidity of the TCR repertoire.
- **Evidence type & confidence:** Molecular/structural, *Moderate*: strong formal mechanism but no human functional validation in this paper.
- **Contradictions/nuance:** Theory-only assumptions (for example energy additivity) and no explicit KIR/HLA-C axis leave NK-CTL co-tuning unaddressed.

A.44 Effects of thymic selection of the T-cell repertoire on HLA class I-associated control of HIV infection [40]

- **Core question/approach:** Integrate the thymic-selection model with human data to test whether HLAs that present narrower self-peptidomes (for example HLA-B*57) select more cross-reactive TCRs that improve HIV control.
- **Key findings:** Two cohorts (1110 controllers; 628 progressors) were analyzed alongside model predictions; empirical patterns were consistent with stronger control where selection favored cross-reactive CTLs, though specific effect sizes are not reported in the author manuscript (*Fig. 1-2*).
- **Mechanistic link:** *Inferred* - HLA pocket chemistry and self-peptidome breadth bias TCR cross-reactivity and avidity, influencing CTL efficacy against conserved viral geometry.
- **Keystone assessment:** Supports - KP5 (thymic imprinting), KP2 (quantitative), KP4 (constrained epitopes). Rationale: connects HLA-driven selection to CTL features that preferentially target conserved structures.
- **Evidence type & confidence:** Molecular/structural, *Moderate*: coherent theory plus cohort testing, but incomplete quantitative reporting.
- **Contradictions/nuance:** NK/KIR arm not evaluated; the paper does not quantify direct peptide-dependent shifts in KIR engagement.

A.45 Summary from an international cancer seminar focused on human papillomavirus (HPV)-positive oropharyngeal cancers [71]

- **Core question/approach:** Seminar proceedings summarizing HPV+ oropharyngeal cancer epidemiology, biomarkers, prevention, treatment de-escalation, and survivorship.
- **Key findings:** The summary highlights unmet needs in screening and biomarker validation, and outlines clinical questions for optimizing therapy de-escalation; quantitative cohort outcomes are not the focus (*pp. 1-7*).
- **Mechanistic link:** *Circumstantial* - the discussion centers on viral oncoproteins (E6/E7) and tumor microenvironmental immunosuppression rather than explicit pHLA-KIR/TCR mechanisms.

- **Keystone assessment:** Indirect - KP3 (viral subversion), KP7 (immunoregulatory wiring). Rationale: frames how viral programs reshape immune control without direct molecular dissection of keystone axes.
- **Evidence type & confidence:** Review/perspective, *Low*: narrative synthesis without primary mechanistic data.
- **Contradictions/nuance:** Cancer context differs from acute viral control; does not address peptide-dependent KIR or thymic imprinting.

A.46 Human Leukocyte Antigen Genotype and Risk of HIV Disease Progression before and after Initiation of Antiretroviral Therapy [72]

- **Core question/approach:** Clinical cohort of 860 women assessing HLA allele/motif associations with baseline viremia and with immunologic and virologic responses after HAART.
- **Key findings:** Baseline viral load: B*57 $\beta = -0.7$ $\log_{10}$ copies/mL (95% CI -0.9 to -0.5, $P = 5 \times 10^{-11}$); Bw4 $\beta = -0.2$ (95% CI -0.4 to -0.1, $P = 0.009$). Post-HAART: B*57:01 OR=0.2 (0.0-0.9, $P = 0.03$), Bw4-80I OR=0.3 (0.1-1.0, $P = 0.04$); B*35(Px) OR=2.6 (1.2-5.9, $P = 0.02$) (*Tables 2-3; pp. 10828-10832*).
- **Mechanistic link:** *Inferred* - Bw4 (KIR3DL1 ligand) implicates NK education/thresholds alongside CTL specificity, quantitatively tuning outcomes before and after therapy.
- **Keystone assessment:** Supports - KP1 (triad integration), KP2 (quantitative), KP9 (licensing set-point). Rationale: genetic links align with co-tuned NK licensing and CTL efficacy.
- **Evidence type & confidence:** Clinical cohort, *Moderate*: large N and precise estimates, mechanistic axis inferred rather than directly tested.
- **Contradictions/nuance:** Associations differ by treatment era; cohort is women only; KIR genotypes not jointly modeled.

A.47 HIV Controllers Exhibit Enhanced Frequencies of Major Histocompatibility Complex Class II Tetramers [73]

- **Core question/approach:** Compare class II tetramer responses between controllers and progressors in ART-naive clade C infection and relate to clinical markers.
- **Key findings:** Controllers exhibit higher tetramer frequencies than progressors ($P < 0.0001$). In DRB1*11:01, Gag41-specific tetramer frequencies inversely correlate with viral load ($r = -0.50$, $P = 0.02$) (*Fig. 5-6*).
- **Mechanistic link:** *Circumstantial* - results imply quantitative CD4 T-cell help to conserved epitopes; no direct peptide-dependent KIR or HLA class I effects are measured.
- **Keystone assessment:** Indirect - KP2 (quantitative tuning), KP7 (immunoregulatory wiring). Rationale: helper magnitude tracks control, suggesting network-level tuning.
- **Evidence type & confidence:** Clinical cohort, *Moderate*: clear associations but mechanistic axis indirect.

- **Contradictions/nuance:** Findings specific to clade C; absence of NK metrics limits mapping to licensing hypotheses.

A.48 Conservation, Extensive Heterozygosity, and Convergence of Signaling Potential All Indicate a Critical Role for KIR3DL3 in Higher Primates [74]

- **Core question/approach:** Use comparative and population genetics to define KIR3DL3 evolution, diversity, and inferred function across catarrhine primates and global human groups.
- **Key findings:** KIR3DL3 is ubiquitous with 157 CDS alleles encoding 93 allotypes; human D2 domain shows dN/dS=2.16 ($P < 0.03$). Residue 147 (I/V) exhibits trans-species polymorphism and is retained across 80+ populations; the second ITIM is independently disrupted in great apes while the first ITIM remains conserved (*Figs. 1, 3-6; pp. 3-11*).
- **Mechanistic link:** *Inferred* - conservation of binding loops and ITIM architecture implies a conserved ligand and inhibitory function, plausibly in reproduction-linked immunoregulation; suggests NK education context.
- **Keystone assessment:** Supports - KP6 (coevolution), KP10 (eco-geographic licensing), KP7 (immunoregulatory wiring). Rationale: balancing selection and ubiquity indicate long-run coadaptation of NK checkpoints.
- **Evidence type & confidence:** Population genetics, *Moderate*: strong evolutionary signals but ligand and direct function unresolved.
- **Contradictions/nuance:** No identified ligand; cross-species conservation with human-specific diversity in Ig domains complicates functional inference.

A.49 HLA-B*14:02-Restricted Env-Specific CD8+ T-Cell Activity Has Highly Potent Antiviral Efficacy Associated With Immune Control of HIV Infection [75]

- **Core question/approach:** Define the potency of HLA-B*14:02-restricted Env-EL9 CTLs relative to canonical Gag responses and quantify associations between B*14:02 and HIV control.
- **Key findings:** EL9-specific CTLs show 24-fold higher functional avidity than Gag-DA9 (EC_{50} 0.84 vs 20.3 μM, $P < 0.0001$; *Fig. 3A*) and 9-fold greater response magnitude ($P = 0.003$; *Fig. 3B*). Wild-type EL9 is associated with lower viral loads (median 9,068 vs 21,546 copies/mL, $P = 0.05$) and higher CD4 counts (606 vs 455 cells/mm^3, $P = 0.005$; *Fig. 6C-E*). B*14:02 is enriched among controllers (OR 0.44 in whites, $P = 2 \times 10^{-7}$; OR 0.54 in blacks, $P = 0.02$; *Table 2*).
- **Mechanistic link:** *Direct* - HLA pocket and epitope geometry calibrate TCR avidity and antiviral efficacy; quantitative tuning of CTL potency by HLA subtype and peptide.
- **Keystone assessment:** Mixed - KP2 (quantitative) supported; KP4 (constrained epitopes) mixed because Env-EL9 escape showed limited fitness cost. Rationale: strong CTL potency without clear costly escape.

- **Evidence type & confidence:** Functional virology, *High*: multimodal assays and cohort genetics converge on mechanism.
- **Contradictions/nuance:** Env variability and limited analysis of NK/KIR mean triad-wide effects are not resolved.

A.50 Identification of an elaborate NK-specific system regulating HLA-C expression [76]

- **Core question/approach:** The study mapped NK-specific regulatory elements controlling HLA-C transcription and tested functional consequences on NK activity using donor-stratified expression and CD107a degranulation assays.
- **Key findings:** An NK-specific promoter/enhancer with an ETS motif drives HLA-C expression in NK cells; donors with an intact ETS site showed higher HLA-C and lower NK degranulation across four experiments with 4-9 donors each, $p<0.001$ (Fig. 7B-C); NK subset expression characterized in 16 volunteers (Fig. 1C).
- **Mechanistic link:** Inferred, expression-level tuning of HLA-C adjusts inhibitory KIR signaling, consistent with stronger KIR2DL1-mediated inhibition in high-expression donors (Fig. 7C).
- **Keystone assessment:** Supports - KP2 (quantitative), KP9 (licensing set-point). Rationale, NK-restricted control of HLA-C quantity calibrates inhibition thresholds.
- **Evidence type & confidence:** Molecular/structural, Moderate confidence due to clear mechanism but modest per-experiment N.
- **Contradictions/nuance:** Motif and allele specificity, T-cell arm not directly assayed.

A.51 Signatures of immune selection in intact and defective proviruses distinguish HIV-1 elite controllers [77]

- **Core question/approach:** The authors contrasted intact versus defective proviruses in elite controllers, using full-length sequencing and integration-site profiling to detect epitope footprints and selection.
- **Key findings:** Intact proviruses in elite controllers are depleted for predicted HLA-I epitopes relative to defective genomes and show distinct integration-site landscapes, indicating strong CTL-driven selection (Fig. 3-5, Extended Data; N not reported).
- **Mechanistic link:** Inferred, CTL pressure prunes contact-dense epitope space in genomes that persist, reshaping pHLA-TCR visibility (Fig. 3-5).
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP6 (host-pathogen coadaptation). Rationale, selection against conserved CTL targets implies high escape cost or compensatory constraints.
- **Evidence type & confidence:** Clinical cohort, Moderate confidence given consistent genomic patterns but indirect mechanism.
- **Contradictions/nuance:** Elite-controller findings may not generalize; epitope prediction and HLA context vary.

A.52 Progressive transformation of the HIV-1 reservoir cell profile over two decades of antiviral therapy [78]

- **Core question/approach:** Longitudinal profiling of reservoir cell phenotypes and integration sites during long-term ART, including two analytic treatment interruptions to track rebound sources.
- **Key findings:** In 55 long-term treated individuals, the reservoir progressively shifts toward central memory phenotypes with integration-site remodeling; in two cases, rebound traced to expanded clones and reversed with re-suppression (Fig. 4-6).
- **Mechanistic link:** Circumstantial, network-level immunoregulation favors persistence niches, indirectly implicating altered NK and CTL surveillance thresholds over time (Fig. 4-6).
- **Keystone assessment:** Supports - KP7 (immunoregulatory wiring). Rationale, reservoir reprogramming is consistent with surveillance thresholds that allow long-term persistence.
- **Evidence type & confidence:** Clinical cohort, Moderate confidence, robust longitudinal patterns but no direct KIR-HLA or epitope tests.
- **Contradictions/nuance:** ART-era biology, cohort heterogeneity, mechanism inferred.

A.53 HIV-1 Control by NK Cells via Reduced Interaction between KIR2DL2 and HLA-C*12:02/*14:03 [24]

- **Core question/approach:** Tested whether specific HLA-C allotypes reduce KIR2DL2 binding, lowering NK inhibition and improving HIV control, using binding and primary NK functional assays.
- **Key findings:** KIR2DL2 shows poor binding to HLA-C*12:02 and *14:03, with increased NK degranulation and cytotoxicity against these targets; allele-dependent differences replicated across assays (Fig. 2-3; effect sizes not reported).
- **Mechanistic link:** Direct, reduced inhibitory KIR2DL2-HLA-C engagement lowers activation thresholds, enhancing NK killing of HIV-1 targets (Fig. 2-3).
- **Keystone assessment:** Supports - KP2 (quantitative), KP9 (licensing set-point). Rationale, allele-specific dampening of inhibition strengthens NK effector function.
- **Evidence type & confidence:** Clinical cohort plus mechanistic assays, High confidence due to direct receptor-ligand effects replicated across modalities.
- **Contradictions/nuance:** Peptide context can modulate KIR binding; effects limited to specific HLA-C alleles.

A.54 HLA class I signal peptide polymorphism determines the level of CD94/NKG2-HLA-E-mediated regulation [25]

- **Core question/approach:** Systematically quantified how HLA-A/B/C/G signal-peptide variants control HLA-E loading and CD94/NKG2A/C recognition, with population frequency analyses.

- **Key findings:** Six of sixteen common SPs are functional; HLA-B -21M drives high HLA-E but lowest receptor recognition, competitively reducing CD94/NKG2A engagement; primary NK responses tracked reporter readouts (n=8, Fig. 3); BLCL panel n=360 linked genotype to HLA-E and recognition; NMDP and 1000G defined SP distributions and correlated with HCMV UL40 VL9 mimic frequencies (Fig. 4-6, Ext. Data).
- **Mechanistic link:** Direct, peptide-level competition tunes HLA-E surface and CD94/NKG2 signaling; UL40 VL9 mimic maintains NKG2A inhibition at infection scale (Fig. 3-6).
- **Keystone assessment:** Supports - KP9 (licensing set-point, NKG2A bias), KP2 (quantitative), KP3 (viral subversion), KP10 (eco-geographic licensing), KP12 (peptideome engineering). Rationale, leader-peptide chemistry and population frequencies predict calibrated inhibition, with UL40 mimicry preserving inhibitory tone.
- **Evidence type & confidence:** Molecular/structural with population data, High confidence given convergent functional and frequency analyses.
- **Contradictions/nuance:** Nonadditive SP competition complicates genotype-to-function inference; NKG2C responses differ.

A.55 HLA Zygosity Increases Risk of Hepatitis B Virus-Associated Hepatocellular Carcinoma [79]

- **Core question/approach:** Tested whether HLA class I and II zygosity predicts HBV-related HCC using multivariable survival models in a prospective cohort.
- **Key findings:** HLA-I homozygosity increased HCC risk (HR 1.36, P for trend=0.02); combined HLA-I plus HLA-II homozygosity HR 1.47 (P=0.02); adjusted results in Fig. 2 and Table 2 (N not reported in excerpt).
- **Mechanistic link:** Inferred, reduced peptide-presenting diversity likely dampens CTL and NK cooperation, favoring chronic inflammation and oncogenesis (Fig. 2).
- **Keystone assessment:** Supports - KP7 (dysregulation risk), KP6 (host-pathogen coadaptation). Rationale, less HLA diversity plausibly weakens keystone surveillance.
- **Evidence type & confidence:** Clinical cohort, Moderate confidence, robust association but indirect mechanism.
- **Contradictions/nuance:** Residual confounding possible; class II roles not parsed mechanistically.

A.56 A high-resolution HLA reference panel capturing global population diversity enables multi-ancestry fine-mapping [42]

- **Core question/approach:** Built a globally diverse HLA panel and performed multi-ancestry imputation to fine-map HIV set-point viral load.
- **Key findings:** The panel improved imputation across ancestries; fine-mapping identified independent HLA-B residue effects at 97, 67 and 156 in the peptide-binding groove, with stronger mapping in Africans using the new panel (Fig. 2-3; effect sizes not reported).

- **Mechanistic link:** Inferred, pocket-residue chemistry tunes peptide stability and TCR recognition, quantitatively linking HLA-B to viral control (Fig. 2-3).
- **Keystone assessment:** Supports - KP2 (quantitative tuning), KP6 (population diversity). Rationale, residue-level effects generalize across ancestries.
- **Evidence type & confidence:** Population genetics, High confidence due to large-scale, multi-ancestry mapping.
- **Contradictions/nuance:** Imputation accuracy varies by locus and ancestry; KIR-related effects not modeled.

A.57 Fitness cost of escape mutations in p24 Gag in association with control of human immunodeficiency virus type 1 [80]

- **Core question/approach:** Does CTL escape in conserved Gag epitopes impair viral fitness and how does compensation restore replication? Patient-derived Gag sequences were cloned into chimeric viruses and tested for replication, coupled with cohort stratification by HLA-B*57/B*58:01.
- **Key findings:** Among B*57/B*58:01-positive early infections, escape at T242N in Gag arose in 74% of individuals; chimeras carrying T242N showed an 8.5% lower replicative capacity than wild type (0.66 vs 0.72, P=0.016), with compensatory polymorphisms restoring fitness (Fig. 1-3, Table 1).
- **Mechanistic link:** *Direct* - B*57/B*58:01-restricted CTL pressure drives T242N in a structurally constrained capsid epitope, reducing fitness until compensatory changes occur (Fig. 1-3).
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP6 (host-pathogen coevolution). Rationale: escape in a conserved hotspot imposes measurable fitness costs, consistent with constrained epitope targeting.
- **Evidence type & confidence:** Functional virology, High; direct perturbation with consistent cohort context.
- **Contradictions/nuance:** Fitness penalties vary with compensatory background and timing; not all escapes carry equal costs.

A.58 The impact of host genetic variation on infection with HIV-1 [81]

- **Core question/approach:** Review synthesizing GWAS, fine-mapping, and eQTL data to explain how host genetics shapes HIV acquisition and control.
- **Key findings:** Higher HLA-C expression associates with better control across African and European Americans; proposed mechanism involves a miR-148a site modulating HLA-C abundance and CTL visibility (Fig. 2a-c; detailed Ns and effect sizes not reported on the figure page).
- **Mechanistic link:** *Inferred* - quantitative tuning via HLA-C expression likely calibrates CTL thresholds and may influence KIR-mediated inhibition (Fig. 2). ; *Circumstantial* - review discussion of Nef and Vpu programmatic control of class I display is consistent with maintaining inhibitory NK tone while reducing CTL visibility at scale (KP12, not reported).

- **Keystone assessment:** Supports - KP2 (quantitative), KP6 (coevolution), KP9 (licensing set-point), KP12 (display control). Rationale: expression-level differences calibrate thresholds, and class I display control aligns with inhibition-preserving NK tone.
- **Evidence type & confidence:** Review/perspective, Moderate; integrative synthesis rather than a single large-N analysis within the article.
- **Contradictions/nuance:** Effects vary by ancestry and study design; many numbers summarized rather than itemized.

A.59 Topological perspective on HIV escape [19]

- **Core question/approach:** Perspective outlining how epitope network topology constrains escape and associates with clinical control.
- **Key findings:** Protective HLA alleles tend to present contact-dense, structurally constrained epitopes that limit mutational options and impose fitness costs on escape; illustrative figures, no explicit effect sizes.
- **Mechanistic link:** *Circumstantial* - epitope topology and constraint shape CTL recognition and the cost of escape; *Circumstantial* - proposes immunodominant but non-protective responses at variable sites as decoy targets that do not relieve inhibitory KIR engagement (KP11, not reported).
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP5 (imprinting on geometry), KP11 (decoy misdirection). Rationale: aligns conserved epitope targeting with durable control and highlights decoy misdirection risk.
- **Evidence type & confidence:** Review/perspective, Moderate.
- **Contradictions/nuance:** Not all individuals with protective HLA achieve control; other modifiers are acknowledged.

A.60 Immunogenetics of HIV disease [82]

- **Core question/approach:** Review of HLA and KIR contributions to HIV outcomes, collating cohort and mechanistic studies.
- **Key findings:** A continuum of protection is observed across KIR3DL1 expression groups with HLA-Bw4 subtypes (Fig. 6), and canonical HLA-B associations are summarized in Table 1 (protective B*57/B*27, risk B*35); numeric values are not detailed in the figure label.
- **Mechanistic link:** *Inferred* - NK education via KIR3DL1 with Bw4 and CTL specificity together set protection thresholds; quantitative patterns imply tuning. ; *Circumstantial* - review discussion of Nef-driven HLA-A/B downregulation with relative sparing of HLA-C and infection-driven peptideome shifts is consistent with maintaining inhibitory KIR and NKG2A tone while reducing CTL visibility (KP12, not reported).
- **Keystone assessment:** Supports - KP1 (triad), KP2 (quantitative), KP9 (licensing set-point), KP12 (display control). Rationale: integrated NK-CTL-HLA axes explain graded protection and align with class I display control.
- **Evidence type & confidence:** Review/perspective, Moderate.

- **Contradictions/nuance:** Effects depend on allele and ligand subtype; context and cohort differences matter.

A.61 Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1 [83]

- **Core question/approach:** Test whether specific KIR3DL1 subtypes with HLA-Bw4, especially B*57, modify progression and viremia in a large cohort.
- **Key findings:** In 1,496 HIV-positive individuals, B*57 plus KIR3DL1*h/*y reduced risk of CD4¡200 (RH 0.26, P=0.003) and AIDS1987 (RH 0.30, P=0.0005), while KIR3DL1*l/*x showed weaker, nonsignificant effects (RH 0.60, P=0.19; RH 0.50, P=0.06); effects were strongest with Bw4-80I, with declining viral-load odds ratios across KIR3DL1 expression strata (Fig. 2).
- **Mechanistic link:** *Inferred* - B*57 with high-expression KIR3DL1 and Bw4-80I likely enhances NK education and complements CTL pressure, lowering viremia.
- **Keystone assessment:** Supports - KP1 (triad), KP2 (quantitative), KP9 (licensing). Rationale: clear genotype interaction aligning NK licensing with CTL-restricted epitope targeting.
- **Evidence type & confidence:** Clinical cohort, High; large N with consistent patterns.
- **Contradictions/nuance:** Protection varies by KIR3DL1 expression group and Bw4 subtype.

A.62 Killer cell immunoglobulin-like receptor 3DL1 variation modifies HLA-B*57 protection against HIV-1 [84]

- **Core question/approach:** Identify genome-wide modifiers of B*57-mediated control; replicate and characterize mechanism with modeling and binding.
- **Key findings:** KIR3DL1 I47V was the sole genome-wide modifier; validation showed 47V enrichment in controllers (56.9%) vs noncontrollers (47.7%) (P=0.004; Table 1). Among B*57+ subjects, each 47V copy associated with -0.14 $\log_{10}$ VL and +24.88 CD4 cells per microliter (P=4.9e-18 and 1.5e-6; Table 2); effect was specific to B*57:01 (-0.36 $\log_{10}$ VL per 47V; P=1.7e-67; Table 3). Tetramer binding differed between KIR3DL1*001 and *015 despite similar SPR affinity (Fig. 2-3).
- **Mechanistic link:** *Direct* - positions 2, 47, 54 in KIR3DL1 modulate recognition of peptide-HLA-B*57:01, consistent with multivalent clustering effects and codominant genetic tuning.
- **Keystone assessment:** Supports - KP1 (triad), KP2 (quantitative), KP9 (licensing). Rationale: convergent genetic and biophysical data show precise KIR-HLA peptide specificity that calibrates inhibition.
- **Evidence type & confidence:** Clinical cohort, High; replicated association with mechanistic assays.
- **Contradictions/nuance:** Effect confined to B*57:01 and not B*57:03; some 47V carriers do not control.

A.63 Early immune adaptation in HIV-1 revealed by population-level approaches [85]

- **Core question/approach:** Use population-level analyses to chart how HLA-driven viral adaptation arises early and influences control.
- **Key findings:** Rapid accumulation of escape at HLA-restricted sites is observed early; higher adaptation scores associate with worse control, including among B*57 carriers; adaptation concentrates in conserved Gag regions (summary figures; site-specific Ns not consistently itemized).
- **Mechanistic link:** *Inferred* - early CTL escape reshapes the presented peptidome, altering immune pressure and the NK/CTL balance at the population scale.
- **Keystone assessment:** Supports - KP6 (coevolution), KP4 (constrained epitopes). Rationale: host HLA landscapes drive reciprocal viral changes at constrained targets.
- **Evidence type & confidence:** Population genetics, Moderate; broad scope with synthesized cohorts.
- **Contradictions/nuance:** Adaptation patterns vary by population and subtype; magnitude depends on local HLA frequencies.

A.64 T cell reactivity to the SARS-CoV-2 Omicron variant is preserved in most but not all individuals [86]

- **Core question/approach:** Are T cell responses to Omicron largely maintained despite spike mutations. The study evaluated antigen-specific T cell activation using peptide pools across vaccinated or previously infected donors.
- **Key findings:** The main conclusion is that most individuals preserved T cell reactivity to Omicron, though a minority showed measurable reductions to mutated regions. The attached PDF is a correction-only file that notes symbol mislabeling in Fig. 4D and Fig. 4E; sample sizes and effect sizes are not reported in this file.
- **Mechanistic link:** Circumstantial - preserved TCR recognition implies that many targeted epitopes remain conserved or structurally tolerant to spike variation, maintaining pHLA presentation and T cell sensing.
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP2 (quantitative tuning), KP5 (imprinting). Rationale: broad preservation of T cell reactivity indicates focus on conserved, constrained targets with limited escape.
- **Evidence type & confidence:** Clinical cohort; Low confidence given that only a correction page was provided and numerical details were not accessible.
- **Contradictions/nuance:** Not all donors preserved responses; precise subgroup effects and Ns not available in the provided PDF.

A.65 Prediction of differential Gag versus Env responses to a mosaic HIV-1 vaccine regimen by HLA class I [32]

- **Core question/approach:** Do specific HLA class I alleles predict whether CD8 T cell responses favor Gag or Env after a mosaic HIV vaccine. The authors reanalyzed trial immunogenicity with ICS and regression models including ancestry.

- **Key findings:** In combined Black participants (n=155), A*02:02 and B*45:01 associated with lower Env ICS (coefficients -0.67 and -0.71, P=0.0012 and 0.0036, FDR 0.066 and 0.072), while A*33:03 and B*57:02 associated with higher Env (0.96 and 1.3, P=0.0039 and 0.0057, FDR 0.072 and 0.078). B*57:03 increased CD8 Gag-Env responses overall (corrected P=0.00025), significant within East African (P=0.006) and South African (P=0.003) subsets. In White participants (n=81), C*05:01 and B*44:02 predicted higher Gag ICS (P=0.03). Key panels: Fig. 3A-3C, Fig. 4A-4D, Fig. 5B.
- **Mechanistic link:** Inferred - allele-specific pocket chemistry and peptide-binding spectra skew quantitative epitope targeting toward Gag or Env, shaping the vaccine-elicited repertoire.
- **Keystone assessment:** Supports - KP2 (quantitative tuning), KP4 (constrained epitope focus in Gag), KP5 (selection imprinting). Rationale: HLA types predicted which antigen sector dominated responses.
- **Evidence type & confidence:** Clinical cohort; Moderate confidence due to consistent signals with ancestry-aware analyses but moderate sample sizes.
- **Contradictions/nuance:** Effects differ by ancestry and allele frequency; several associations are near FDR thresholds.

A.66 A subset of HLA-DP molecules serve as ligands for the natural cytotoxicity receptor NKp44 [87]

- **Core question/approach:** Identify cellular ligands for NKp44 and test whether class II HLA-DP allotypes engage NKp44 in a peptide-sensitive manner. Methods included soluble receptor binding, SPR, blocking antibodies, and primary NK assays.
- **Key findings:** NKp44 bound HLA-DP401 with Kd 42.6 ± 16.2 µM (Fig. 1c-1d). NK activation and degranulation were modulated by HLA-DP401 and blocked by anti-NKp44 (Fig. 3g). Peptide cargo mattered: CTAG1 and HIV-1 Env peptides enabled activation while unrelated peptides did not (Extended Data Fig. 4). Primary donor assays showed consistent effects across n≈7 donors (Wilcoxon P=0.008).
- **Mechanistic link:** Direct - peptide-dependent HLA-DP-NKp44 binding tunes NK activation thresholds, extending pHLA control beyond class I to a class II-NK checkpoint axis.
- **Keystone assessment:** Supports - KP7 (immunoregulatory wiring), KP1 (triad-like cross-talk). Rationale: direct receptor-ligand binding and peptide dependence connect antigen presentation to NK control.
- **Evidence type & confidence:** Molecular-structural and functional assays; High confidence given direct binding and blocking data.
- **Contradictions/nuance:** Ligand activity limited to a subset of DP allotypes; affinity is modest and peptide choice can change direction of effect.

A.67 Viral and host mediators of non-suppressible HIV-1 viremia [88]

- **Core question/approach:** What drives persistent low-level viremia on ART without nonadherence or resistance. The study combined longitudinal plasma and proviral

single-genome sequencing with integration-site mapping, transcriptomics, and T cell assays.

- **Key findings:** Eight NSV participants produced 1,987 proviral and 222 plasma sequences; plasma virus was dominated by one to two clones without evolution (Fig. 1-2). Producer proviruses were enriched near H3K36me3 marks and larger than intact reservoirs in ART-suppressed controls (intact 4.3 vs 0.1 per million cells, P=0.001; Fig. 2). Compared with viremic controllers, NSV had significantly lower HIV-specific CD8 responses and no increase over ART-suppressed comparators (ELISPOT P=0.001-0.02; Fig. 5b). Bulk CD4 transcriptomics showed downregulated interferon pathways (Fig. 4). Escape mutation burdens varied by gene, with limited coupling to strong CTL pressure (Fig. 5d-5i).
- **Mechanistic link:** Circumstantial - viral clones persist via integration near active chromatin and within an immune milieu of muted IFN signaling and weaker CTL pressure.
- **Keystone assessment:** Supports - KP3 (viral subversion), KP7 (dysregulation wiring). Rationale: persistence reflects network-level imbalance rather than dominant adaptive pressure.
- **Evidence type & confidence:** Clinical cohort; Moderate confidence due to multi-modal evidence but small N.
- **Contradictions/nuance:** Mechanistic links to specific KIR-HLA axes were not directly tested; heterogeneity across participants.

A.68 Impact of HLA Allele-KIR Pairs on HIV Clinical Outcome in South Africa [27]

- **Core question/approach:** How do specific HLA-KIR combinations and composite scores relate to viral load, CD4 counts, and progression in South African cohorts. Genotyping and longitudinal clinical outcomes were analyzed.
- **Key findings:** HLA-C*16:01 with KIR2DL3 associated with higher viral load (P=0.02) and lower CD4 count (P=0.008) at first visit (Fig. 2-3). A Bw4S1 composite capturing KIR3DL1-Bw4 signaling predicted better outcomes across two populations (Fig. 1). Time-to-event models showed a deleterious KIR2DL3-C*16:01 combination with aHR 1.9 (95% CI 1.1-3.5, P=0.02) for earlier ART initiation or CD4¡200 (Table 3).
- **Mechanistic link:** Inferred - inhibitory KIR engagement by particular HLA-C allotypes, and licensing via Bw4-KIR3DL1, set NK activation thresholds that shape control.
- **Keystone assessment:** Supports - KP1 (triad integration), KP2 (quantitative tuning), KP6 (population context), KP9 (licensing set-point). Rationale: defined KIR-HLA pairs and composite tuning predict clinical outcomes.
- **Evidence type & confidence:** Clinical cohort; Moderate confidence due to consistent associations and biologic plausibility.
- **Contradictions/nuance:** Effects can vary by ancestry and LD; some B*58:02-related signals reverse in different populations.

A.69 Host genetic variation and HIV disease - from mapping to mechanism [89]

- **Core question/approach:** Synthesize genetic mapping with mechanistic immunology to explain host influences on HIV control.
- **Key findings:** Common host variants account for about 25% of set-point viral load variance, driven largely by HLA and CCR5. HLA-B alleles such as B*57 and B*27 are protective, and HLA-C expression contributes to control. Figures highlight mapping-to-mechanism connections (Fig. 1-2; p. 489-497).
- **Mechanistic link:** Inferred - HLA-peptide specificity sculpts CTL recognition and interacts with KIR-mediated NK education; expression-level tuning of class I alters surveillance thresholds. Also summarizes Nef and Vpu effects that tune class I display to reduce CTL visibility while preserving inhibitory NK tone at scale (p. not reported).
- **Keystone assessment:** Indirect - KP1 (triad), KP2 (quantitative), KP6 (coevolution), KP9 (licensing set-point), KP12 (display control). Rationale: review outlines class I display control with Nef and Vpu consistent with inhibition-preserving strategies.
- **Evidence type & confidence:** Review or perspective; Moderate confidence reflecting strength of underlying cited evidence rather than new data.
- **Contradictions/nuance:** Cohort eras and ancestries differ; mechanisms summarized rather than directly demonstrated in this article.

A.70 HLA-A03 and response to immune checkpoint blockade in cancer - an epidemiological biomarker study [90]

- **Core question/approach:** Is HLA-A*03 associated with clinical outcomes on PD-1 or PD-L1 blockade across cancer cohorts. The work pooled observational cohorts and trial datasets with meta-analytic models.
- **Key findings:** HLA-A*03 carriers had worse overall survival on anti-PD-1 or PD-L1 therapy (meta-analytic HR about 1.48) and shorter progression-free survival (HR about 1.31), with little heterogeneity. Effects were absent with CTLA-4 monotherapy or chemotherapy. Key panels include Fig. 3 (OS) and Fig. 5 (subgroups).
- **Mechanistic link:** Inferred - HLA-A*03-restricted immunopeptidomes and TCR repertoires may bias exhaustion thresholds or epitope visibility under PD-1-axis therapy, altering effectiveness.
- **Keystone assessment:** Supports - KP7 (immunoregulatory wiring), KP2 (quantitative tuning), KP5 (selection imprinting). Rationale: allele-specific outcome on a defined checkpoint axis fits Keystone wiring principles.
- **Evidence type & confidence:** Clinical cohort or pooled analyses; High confidence given consistent multi-cohort findings.
- **Contradictions/nuance:** Association is not causal and appears therapy-specific; tumor context and microenvironment could confound.

A.71 Positive selection of HIV-1 cytotoxic T lymphocyte escape variants during primary infection [91]

- **Core question/approach:** Longitudinal within-host study of primary HIV-1 infection combining viral sequencing with epitope-specific CTL mapping and functional assays to track selection of escape variants.
- **Key findings:** In an intensively studied subject, plasma HIV-1 RNA fell from 7.6×10^6 to 7×10^5 copies/mL as an immunodominant epitope escape variant arose and replaced wild-type; CTL clones (n=19 across the first three time points, n=18 at a later time point) lost recognition of the emergent variant (*Fig. 2-5*).
- **Mechanistic link:** *Direct* - TCR recognition of peptide-HLA drove rapid fixation of the mutant epitope (*Fig. 2-5*).
- **Keystone assessment:** Supports - KP3 (viral subversion), KP4 (constrained epitopes). Rationale: in vivo CTL-driven selection documents viral evasion at a keystone target, consistent with fitness-escape trade-offs.
- **Evidence type & confidence:** Functional virology; *Moderate* confidence due to single intensively profiled case but strong mechanistic mapping.
- **Contradictions/nuance:** Allele- and epitope-specific effects; broader cohort numbers not reported here.

A.72 Epitope length variants balance protective immune responses and viral escape in HIV-1 infection [46]

- **Core question/approach:** Determine how HIV-1 epitope length variants modulate both CTL responses and KIR engagement using peptide processing assays, KIR3DL1-HLA-B*57 binding, and CD8 T-cell functional readouts.
- **Key findings:** B*57-restricted Gag 11-mer variants altered pHLA topology, reduced KIR3DL1-Fc binding, and diminished CD8 T-cell recognition; quantitative magnitudes not reported here (*Fig. 2C-2D, Fig. 3E, Fig. 4C*).
- **Mechanistic link:** *Direct* - peptide-length-dependent tuning of KIR3DL1-HLA-B*57 engagement with concomitant effects on TCR recognition (*Fig. 2-4*).
- **Keystone assessment:** Supports - KP4 (constrained epitopes), KP8 (NK/CTL pincer). Rationale: the same conserved pHLA geometry synchronizes NK inhibition and CTL visibility.
- **Evidence type & confidence:** Molecular/structural; *Moderate* confidence (robust mechanistic assays but HLA/epitope specificity).
- **Contradictions/nuance:** Generalizability across epitopes and HLAs not established in this study.

A.73 Recombinant structures expand and contract inter and intragenic diversification at the KIR locus [41]

- **Core question/approach:** Map KIR gene-content haplotypes with copy number and identify recombination pathways across an extended cohort.
- **Key findings:** Among 4,512 individuals (9,024 chromosomes), 37 gene-content haplotypes were observed; rare submotifs collectively ∼7% (Table 3). A KIR2DL4 deletion

accounted for ∼2.3% of haplotypes; a KIR3DL2 deletion was present in 38/42 cA01—tB01-del7 haplotypes (*Fig. 2, Fig. 5, Fig. 7; p. 12-14*).

- **Mechanistic link:** *Inferred* - recurrent inter/intragenic recombination sculpts KIR architectures that condition NK education via HLA ligands (*Fig. 2, Fig. 7*).
- **Keystone assessment:** Supports - KP6 (host-pathogen coevolution), KP10 (eco-geographic licensing). Rationale: population-structured KIR diversity provides substrate for locally optimized NK licensing.
- **Evidence type & confidence:** Population genetics; *High* confidence given large n and clear structural validation.
- **Contradictions/nuance:** Some ancestries under-represented; several singleton haplotypes unresolved.

A.74 Analysis of Binding of KIR3DS1*014 to HLA Suggests Distinct Evolutionary History of KIR3DS1 [33]

- **Core question/approach:** Test whether KIR3DS1*014 binds HLA class I and define residue/peptide dependencies using soluble-Fc binding and mutational analyses.
- **Key findings:** KIR3DS1*014 bound Bw4 (80I) but not Bw6, with peptide dependence; altering key HLA pocket residues abrogated binding (*Fig. 2-4*).
- **Mechanistic link:** *Direct* - peptide-sensitive KIR3DS1*014-HLA-Bw4 engagement, mapping a triad axis that can couple to CTL-selected peptides (*Fig. 2-4*).
- **Keystone assessment:** Supports - KP1 (triad integration), KP8 (peptide-synchronized pincer). Rationale: shows NK receptor recognition of conserved pHLA surfaces under peptide control.
- **Evidence type & confidence:** Molecular/structural; *High* confidence due to direct binding and mutational evidence.
- **Contradictions/nuance:** Allele-specific (3DS1*014); breadth across Bw4 allotypes and peptide repertoires varies.

A.75 The Molecular Origin and Consequences of Escape from miRNA Regulation by HLA-C Alleles [92]

- **Core question/approach:** Define the origin and impact of a 3′UTR variant that disrupts miR-148a regulation of HLA-C, integrating expression assays with population analysis.
- **Key findings:** The escape variant increased HLA-C surface expression by ∼1.7-2.2-fold; ∼32.8% of chromosomes carried escape haplotypes; event dated ∼3-5 MYA (*Fig. 2-3*).
- **Mechanistic link:** *Inferred* - higher HLA-C expression calibrates KIR engagement and NK licensing set-points, with potential effects on CTL presentation (*Fig. 2-3*).
- **Keystone assessment:** Supports - KP2 (quantitative tuning), KP9 (licensing set-point), KP6 (coevolution). Rationale: a regulatory polymorphism tunes a keystone ligand quantitatively with clear selection signatures.
- **Evidence type & confidence:** Population genetics; *High* confidence from coherent functional and population signals.

- **Contradictions/nuance:** Clinical phenotype links are indirect in this paper; allele context matters.

A.76 NKp44/HLA-DP-dependent regulation of CD8 effector T cells by NK cells [44]

- **Core question/approach:** Identify and quantify an NK checkpoint controlling proliferating CD8 T cells using ex vivo donor assays and HLA-DP transductants.
- **Key findings:** Across donors ($n = 32$), NKp44 blockade reduced NK degranulation/lysis of proliferating CD8 T cells by ∼30-60% (*Fig. 3D-3F*); NKp44-Fc bound HLA-DP transductants with EC_{50} ∼2.1-4.6 µg/mL (*Fig. 2B-2D, Fig. 4F*).
- **Mechanistic link:** *Direct* - NKp44-HLA-DP engagement restrains CD8 effector expansion.
- **Keystone assessment:** Supports - KP7 (immunoregulatory wiring). Rationale: a checkpoint axis links innate recognition to control of adaptive effector pools.
- **Evidence type & confidence:** Molecular/structural; *Moderate* confidence (direct mechanism, ex vivo scope).
- **Contradictions/nuance:** Context-specific magnitude likely varies with activation state and antigen history.

A.77 Copy Number Variation of KIR Genes Influences HIV-1 Control [34]

- **Core question/approach:** Test whether KIR copy number modulates HIV-1 set-point viral load and NK function, modeling with HLA-B alleles and validating in functional assays.
- **Key findings:** Effective KIR3DS1 count inversely associated with set-point viral load ($p=4.2\times10^{-6}$; combined $p=2.8\times10^{-4}$); KIR3DL1-surface copy predictive (p=0.020; combined p=0.0085); significance retained after HLA/KIR adjustment (p=0.0075) (Table 3-4). NK inhibition increased with KIR3DS1 (p=0.007) and 3DS1×3DL1 interaction (p=0.022) (*Fig. 2C*).
- **Mechanistic link:** *Inferred* - quantitative KIR dosage tunes NK thresholds in the presence of Bw4-80I, aligning genetics with function.
- **Keystone assessment:** Supports - KP2 (quantitative tuning), KP1 (triad integration). Rationale: dose-dependent KIR-HLA axis links NK calibration to virologic control with functional support.
- **Evidence type & confidence:** Clinical cohort; *High* confidence given large n, replication across models, and functional assays.
- **Contradictions/nuance:** CNVs not allele-resolved; peptide dependence not addressed in this study.

A.78 KIR/HLA Pleiotropism: Protection against Both HIV and Opportunistic Infections [93]

- **Core question/approach:** Does a compound KIR-HLA genotype modulate HIV outcomes and opportunistic infections? Clinical cohorts of HIV-1-infected individuals

were stratified by KIR3DS1 with HLA-B Bw4-80I; a subset was analyzed for viral load set point.

- **Key findings:** KIR3DS1+Bw4-80I was associated with fewer opportunistic infections (RH=0.58, p=0.004) but not malignancies (RH=1.42, p=0.254) (Fig.1). Set-point viremia was lower in KIR3DS1/Bw4-80I+ vs others (Ln mean 9.4 vs 10.1; p=0.01) (Table 2).
- **Mechanistic link:** *Inferred* - synergy of KIR3DS1 with HLA-Bw4-80I implies an NK-HLA axis that tunes antiviral pressure and, indirectly, CTL opportunity; direct binding or peptide dependence were not measured (Fig.1; Table 2).
- **Keystone assessment:** Supports - KP1 (triad); KP6 (coevolution). Rationale, a KIR-HLA genotype shapes disease risk and viral control in humans.
- **Evidence type & confidence:** Clinical cohort; *Moderate* confidence given large N but lack of direct mechanistic assays.
- **Contradictions/nuance:** Benefit limited to opportunistic infections; malignancy outcomes not improved; effect depends on Bw4-80I background.

A.79 Sequence and Phylogenetic Analysis of the Untranslated Promoter Regions for HLA Class I Genes [94]

- **Core question/approach:** Do HLA class I promoter/UTR polymorphisms form phylogenetic groups that track expression differences? Comparative promoter sequencing and expression profiling across donors.
- **Key findings:** Promoter diversity (LZ divergence): HLA-B 1.9%, HLA-A 1.8%, HLA-C 0.9% (Fig.1). mRNA expression was quantified in 178 European American donors for HLA-B and 215 for HLA-A; promoter groupings tracked expression (Fig.2).
- **Mechanistic link:** *Inferred* - promoter/UTR architecture tunes class I expression levels, adjusting quantitative thresholds for TCR engagement and KIR/NKG2A education.
- **Keystone assessment:** Supports - KP2 (quantitative). Rationale, genetic control of class I expression provides a mechanism for ligand dosage effects.
- **Evidence type & confidence:** Population genetics; *Moderate* confidence (clear expression groupings, indirect to NK/CTL function).
- **Contradictions/nuance:** Lacks direct functional assays linking promoter groups to NK/CTL outcomes.

A.80 Elevated HLA-A expression impairs HIV control through inhibition of NKG2A-expressing cells [26]

- **Core question/approach:** How do HLA-A expression levels influence HIV control and the NKG2A/HLA-E checkpoint? Multi-cohort regressions linked HLA-A eQTLs to viral load and CD4, with ex vivo NK/T-cell assays interrogating NKG2A-HLA-E.
- **Key findings:** Higher HLA-A expression increased viral load (slope 0.22 vs 0.06 log10/z; interaction $p=5.3\times10^{-9}$) and decreased CD4 counts (-37.8 cells/µL per z; $p=5.9\times10^{-94}$). NKG2A+ KIR- NK degranulation inversely correlated with HLA-A (r=-0.77, p=0.02); HLA-E correlated with HLA-A (r=0.43, $p=5\times10^{-4}$) (Figs.3-4; Table 1).

- **Mechanistic link:** *Direct* - increased class I expression augments HLA-E-mediated NKG2A inhibition, suppressing NK/CD8 responses; blockade restores function in vitro (Figs.3-4).
- **Keystone assessment:** Supports - KP2 (quantitative), KP7 (regulatory axis), KP9 (NKG2A licensing). Rationale, expression-quantitative effects couple to checkpoint-mediated inhibition.
- **Evidence type & confidence:** Clinical cohort with mechanistic assays; *High* confidence.
- **Contradictions/nuance:** Effects vary by HLA-B leader (-21M/T), indicating genotype-dependent magnitude.

A.81 Understanding the heterogeneity of alloreactive natural killer cell function in kidney transplantation [95]

- **Core question/approach:** Which NK subsets drive alloreactivity under missing-self, and how does their balance relate to graft injury? High-dimensional ex vivo mapping across donors with validation in CTOT01 and CTOT19.
- **Key findings:** NKG2A+ KIR- NK cells often dominate missing-self alloreactivity (Figs.3-5). In transplant cohorts, higher NKG2A+KIR- fraction correlated with lower dd-cfDNA and fewer ABMR events, for example r=-0.38 (p=0.00845), r=-0.33 (p=0.0122), r=-0.44 (p=0.0283), r=-0.41 (p=0.0408) (Fig.8). CTOT01 n=70; CTOT19 n=26.
- **Mechanistic link:** *Direct* - functional readouts tie licensing through NKG2A vs KIR to effective alloreactivity and clinical injury signals.
- **Keystone assessment:** Supports - KP1 (triad), KP9 (licensing set-point). Rationale, education route predicts effector dominance and outcomes.
- **Evidence type & confidence:** Clinical cohort; *Moderate* confidence (multi-modal, preprint).
- **Contradictions/nuance:** Immunosuppression and HLA contexts vary; external replication pending.

A.82 High-dimensional analysis of NK cells in kidney transplantation uncovers subsets associated with antibody-independent graft dysfunction [96]

- **Core question/approach:** Do specific NK subsets associate with antibody-independent graft dysfunction? CyTOF/flow profiling at baseline (n=50) and during ABMR (n=76) with clustering and correlation to graft metrics.
- **Key findings:** NKG2A/KIR-defined clusters associated with dysfunction; representative correlations with kidney function or injury markers: r≈-0.38 (p=0.0086), r≈-0.36 (p=0.0208) in CTOT01; r≈-0.45 (p=0.023), r≈-0.41 (p=0.041) in CTOT19 (Fig.4).
- **Mechanistic link:** *Direct* - repertoire architecture, weighted by NKG2A/KIR, indicates quantitative licensing thresholds relevant to tissue injury.
- **Keystone assessment:** Supports - KP9 (licensing), KP7 (regulatory wiring). Rationale, licensing balance tracks organ injury independent of donor-specific antibodies.

- **Evidence type & confidence:** Clinical cohort; *Moderate* confidence (robust stats, moderate N).
- **Contradictions/nuance:** Cross-sectional components and treatment confounding limit causal inference.

A.83 Associations Between Human Leukocyte Antigen Class I Variants and the *Mycobacterium tuberculosis* Subtypes Causing Disease [28]

- **Core question/approach:** Do class I HLA alleles associate with the Mtb subtype causing disease? Case-control analysis with high-resolution HLA typing.
- **Key findings:** Protective HLA-B*15:03 (OR 0.46, p=0.0004); susceptibility HLA-B*58:02 (OR 7.39, p=1.1×10^{-5}) and HLA-C*06:02 (OR 5.06, p=2.76×10^{-5}). N=636: 424 cases, 212 controls (Table 2).
- **Mechanistic link:** *Inferred* - class I polymorphisms alter epitope presentation geometry, shaping CTL/NK pressure and associating with strain-level disease.
- **Keystone assessment:** Supports - KP6 (coevolution). Rationale, allele-pathogen subtype mapping indicates reciprocal adaptation.
- **Evidence type & confidence:** Population genetics; *Moderate* confidence (strong ORs, single geography).
- **Contradictions/nuance:** Population structure and exposure differences may confound; no epitope-level mechanism shown.

A.84 NKG2A and HLA-E define an alternative immune checkpoint axis in bladder cancer [17]

- **Core question/approach:** How does the HLA-E/NKG2A axis shape tumor immunity and response to PD-L1 therapy in bladder cancer? scRNA-seq (n=8), flow/IHC (n=25), functional blockade (monalizumab), and survival analyses (TCGA BLCA, IMvigor210).
- **Key findings:** HLA-I LOH in TCGA BLCA was 21.8%; tumors downregulated HLA-ABC/E yet retained DNAM-1 ligands (Fig.2). NKG2A+ CD8 T cells showed TCR-independent, DNAM-1-mediated cytotoxicity that was restored by NKG2A blockade in an HLA-E-dependent manner (Fig.6). KLRC1^{high} tumors had better survival under PD-L1 blockade (IMvigor210; Fig.7).
- **Mechanistic link:** *Direct* - HLA-E engages NKG2A to inhibit CD8/NK effector programs; blockade reverses inhibition and correlates with tumor HLA-E levels (Figs.2,6-7).
- **Keystone assessment:** Supports - KP7 (immunoregulatory axis), KP9 (NKG2A-biased licensing). Rationale, a checkpoint axis wired by a non-classical class I ligand shapes surveillance and clinical benefit.
- **Evidence type & confidence:** Clinical cohort with functional validation; *High* confidence.
- **Contradictions/nuance:** Survival benefit concentrated in CD8A/PD-1-high strata; tumor HLA-E expression is heterogeneous.

A.85 Identification of the ancestral killer immunoglobulin-like receptor gene in primates [97]

- **Core question/approach:** Comparative genomics and phylogenetic analyses across primate species, with resequencing and NK-cell expression profiling, to identify an ancestral KIR gene.
- **Key findings:** A conserved inhibitory receptor gene (KIR3DL0) is present across primates for ˜50 million years and is expressed in NKp46^{+} cells, not in T or B cells; resequencing of 86 unrelated individuals supported an intact coding gene and lineage relationships (Figs. 1-4).
- **Mechanistic link:** *Inferred* - conservation of an inhibitory KIR lineage implies a stable HLA class I-KIR educational axis shaping NK thresholds rather than a transient, species-specific adaptation (Figs. 1-4).
- **Keystone assessment:** Supports - KP6 (host-pathogen coevolution), KP10 (eco-geographic licensing). Rationale: deep conservation of a KIR lineage indicates long-run coadaptation with class I ligands.
- **Evidence type & confidence:** Population genetics, *Moderate* confidence (broad phylogeny and expression, but no direct pHLA-KIR binding tested).
- **Contradictions/nuance:** Expansion patterns differ by species; findings are evolutionary and indirect with respect to peptide- and allele-specific interactions.

A.86 KIR2DL2 Enhances Protective and Detrimental HLA Class I-Mediated Immunity in Chronic Viral Infection [98]

- **Core question/approach:** Multi-cohort clinical genetics to test whether the inhibitory receptor KIR2DL2 modifies HLA class I associations with outcomes in chronic viral infection.
- **Key findings:** KIR2DL2 altered both protective and detrimental HLA class I associations with disease phenotype, enhancing or attenuating effects depending on HLA allele-context (summary, Figs. 2-4; statistics not uniformly reported in the PDF snippet).
- **Mechanistic link:** *Inferred* - KIR2DL2 engagement with HLA-C1-presented peptides likely recalibrates NK inhibition and interacts with CTL control, explaining direction flips in HLA effects (model discussion).
- **Keystone assessment:** Supports - KP1 (triad), KP2 (quantitative), KP7 (regulatory wiring). Rationale: a single KIR allele can flip HLA class I associations, consistent with NK-CTL cross-regulation.
- **Evidence type & confidence:** Clinical cohort, *Moderate* confidence (clear genetic interaction patterns, mechanistic binding not demonstrated).
- **Contradictions/nuance:** Effect direction varies by allele and infection; lacks peptide-level or structural confirmation.

A.87 Host Genetics of HIV Acquisition and Viral Control [99]

- **Core question/approach:** Narrative review of candidate-gene and GWAS evidence linking host genetics to HIV acquisition and control.
- **Key findings:** GWAS consistently highlight HLA-B*57 as the strongest determinant of viral control; an upstream HLA-C variant associates with higher HLA-C expression and better control; KIR/HLA combinations and KIR3DL1/3DS1 copy-number affect control when HLA-B ligands are present (Fig. 1-2 narrative; cited primary studies).
- **Mechanistic link:** *Circumstantial* - peptide presentation (HLA-B) and ligand quantity (HLA-C expression) appear to tune CTL and NK thresholds; epitope mutations can abrogate or enhance KIR-HLA interactions, shifting effector responses.
- **Keystone assessment:** Supports - KP2 (quantitative), KP4 (constrained epitopes/-fitness costs), KP6 (coevolution), KP12 (class I display control). Rationale: synthesis of host-genetic effects is consistent with canonical HIV class I display modulation that reduces CTL visibility while preserving inhibitory tone.
- **Evidence type & confidence:** Review/perspective, *Moderate* confidence (synthesizes replicated findings, but secondary and heterogeneous).
- **Contradictions/nuance:** The HLA-C expression-control link has debated magnitude; several acquisition GWAS underpowered.

A.88 Global diversity and evidence for coevolution of KIR and HLA [21]

- **Core question/approach:** Global population-genetic analysis of KIR gene content and HLA ligand frequencies with correlation tests across populations.
- **Key findings:** Significant population-level correlations between inhibitory/activating KIR and their HLA ligands, and geographic structure consistent with balancing selection (specific coefficients not reported in snippet).
- **Mechanistic link:** *Inferred* - matched clines of KIR and HLA frequencies indicate selection on the HLA-KIR axis rather than neutrality, consistent with long-term host-pathogen pressures.
- **Keystone assessment:** Supports - KP6 (coevolution), KP10 (eco-geographic licensing). Rationale: global coupling implies reciprocal adaptation and licensing optimization.
- **Evidence type & confidence:** Population genetics, *High* confidence (broad comparative dataset, convergent patterns).
- **Contradictions/nuance:** Correlational by design; does not specify peptide-level mechanisms or directionality of selection.

A.89 HLA-C levels impact natural killer cell subset distribution and function [100]

- **Core question/approach:** Flow cytometry and functional assays relating HLA-C surface expression to NK subset composition and function in healthy donors (n=154) and HIV-infected individuals (n=28).

- **Key findings:** Higher HLA-C expression associated with fewer $CD56^{neg}$ NK cells in healthy donors ($r \approx -0.43$, Fig. 2B) and reduced proportions of certain KIR^+ subsets ($r \approx -0.27$, Fig. 3D); similar trends observed in the HIV cohort (figures).
- **Mechanistic link:** *Inferred* - quantitative ligand abundance tunes inhibitory KIR signaling and NK education, shifting subset distributions and functional thresholds (Figs. 2-3).
- **Keystone assessment:** Supports - KP2 (quantitative tuning), KP9 (licensing set-point). Rationale: HLA-C level calibrates NK licensing and responsiveness.
- **Evidence type & confidence:** Clinical cohort, *Moderate* confidence (consistent associations; observational).
- **Contradictions/nuance:** Effect sizes vary by subset and infection status; some adjusted p-values not clearly reported.

A.90 Characterization of Mycobacterium tuberculosis-Specific Cells Using MHC Class II Tetramers [101]

- **Core question/approach:** HLA-DR tetramer-based enumeration and phenotyping of Mtb-specific $CD4^+$ T cells with longitudinal sampling.
- **Key findings:** $Tetramer^+$ $CD4^+$ T cells display stable frequencies across visits, Th1-biased cytokines, and defined memory/activation phenotypes; clonotypes track longitudinally (e.g., Fig. 1F-J, Fig. 2).
- **Mechanistic link:** *Circumstantial* - maps class II epitope geometry and TCR usage, informing thymic/postnatal imprinting rather than direct HLA-I/KIR mechanisms.
- **Keystone assessment:** Indirect - KP5 (thymic/postnatal imprinting), KP7 (immunoregulatory wiring). Rationale: defines helper T-cell epitope targeting that shapes downstream immunity.
- **Evidence type & confidence:** Clinical cohort, *Moderate* confidence (well-described phenotypes; scope limited to CD4/HLA-II).
- **Contradictions/nuance:** No direct NK or HLA-I/KIR data; relevance to NK-CTL pincer is indirect.

A.91 Polymorphic residues in HLA-B that mediate HIV control distinctly modulate peptide interactions with both TCR and KIR molecules [7]

- **Core question/approach:** Structural analyses and cellular assays to determine how HLA-B pocket residues tune peptide-dependent engagement by TCRs and KIRs.
- **Key findings:** Pocket residues 97, 67, and 156 dictate peptide conformation/stability and differentially modulate TCR versus KIR binding; specific 11-mer peptides induced cross-reactive KIR recognition while preserving CTL visibility (Figs. 1-3).
- **Mechanistic link:** *Direct* - peptide-dependent pHLA-B geometry jointly controls TCR and KIR engagement, demonstrating triad integration and quantitative tuning.
- **Keystone assessment:** Supports - KP1 (triad), KP2 (quantitative), KP8 (peptide-synchronized detection), KP11 (decoy diversion). Rationale: same pHLA can preserve

CTL visibility while enhancing inhibitory KIR engagement, consistent with decoy diversion potential.

- **Evidence type & confidence:** Molecular/structural, *High* confidence (structural mapping plus functional binding/activation).
- **Contradictions/nuance:** Effects are peptide- and allele-specific; generalization across all HLA-B allotypes may vary.

A.92 The Major Genetic Determinants of HIV-1 Control Affect HLA Class I Peptide Presentation [102]

- **Core question/approach:** Multi-cohort GWAS with fine-mapping of HLA class I amino acids to identify determinants of elite/viremic control and set-point viremia.
- **Key findings:** Discovery and replication across European and African cohorts identified four independent MHC SNPs explaining 23% of viremia variance, with strongest signals in HLA-B. HLA-B*57 associated with protection (OR=5.1, P=1.7×10^{-21}); additional loci rs9264942 near HLA-C (OR=2.9, P=2.8×10^{-35}), HCP5 (OR=3.6, P=3.4×10^{-21}), and ZNRD1/RNF39 (OR=2.0, P=1.0×10^{-16}) (Table 1). Amino-acid positions in HLA-B peptide-binding groove, notably 97 (P=4×10^{-45}), 70 (P=2×10^{-25}), and 67 (P=4×10^{-12}), associate with control and with $\log_{10}$ set-point viral load in an independent Swiss cohort (Fig. 3A-C).
- **Mechanistic link:** Inferred, peptide-binding pocket chemistry at HLA-B positions 97/70/67 tunes peptide stability and TCR engagement, quantitatively shifting CTL thresholds and viremia.
- **Keystone assessment:** Supports, KP2 (quantitative), KP6 (coevolution). One-line rationale, binding-groove residues with large effect sizes localize mechanism to antigen presentation.
- **Evidence type & confidence:** GWAS, High confidence due to large N, multi-cohort replication, and convergent fine-mapping to specific residues.
- **Contradictions/nuance:** Signals concentrated in HLA-B; independent HLA-A effects limited; LD leaves room for linked mechanisms.

A.93 Novel KIR3DL1 Alleles and Their Expression Levels on NK Cells: Convergent Evolution of KIR3DL1 Phenotype Variation? [103]

- **Core question/approach:** Allele discovery and flow-cytometric profiling of KIR3DL1 across donors; site-directed mutagenesis to dissect determinants of surface expression.
- **Key findings:** KIR3DL1 allotypes segregate into high/low/null cell-surface expression groups; certain novel allotypes (e.g., *053) display markedly reduced surface density compared with *005/*015 (Fig. 4-5). Some low-expression allotypes exhibit intracellular retention; promoter variation does not explain the phenotype (Fig. 5).
- **Mechanistic link:** Direct, KIR3DL1 allotype-dependent receptor abundance calibrates inhibitory signaling upon Bw4 engagement, tuning NK activation thresholds.
- **Keystone assessment:** Supports, KP2 (quantitative). Rationale, allele-specific surface density directly modulates inhibitory receptor availability.

- **Evidence type & confidence:** Molecular/structural, Moderate confidence given clear mechanistic assays but limited functional readouts against HLA-Bw4 targets.
- **Contradictions/nuance:** Allele-specific effects; functional cytotoxic consequences not fully quantified in this study.

A.94 HLA-C cell surface expression and control of HIV/AIDS correlate with a variant upstream of HLA-C [10]

- **Core question/approach:** Association of a promoter-proximal variant (-35C/T) with HLA-C expression levels and clinical markers of HIV control; allele-specific expression assays.
- **Key findings:** The -35C allele correlates with higher HLA-C surface expression by flow and with allele-specific clone count imbalance in heterozygotes (Fig. 2a, Fig. 3). Genetic association links -35C to improved control of HIV-1 infection in multiple cohorts (Table 1).
- **Mechanistic link:** Inferred, higher HLA-C expression increases ligand availability for inhibitory KIR2DL1/2/3 and enhances CTL antigen display, shifting NK education and CTL effectiveness.
- **Keystone assessment:** Supports, KP2 (quantitative), KP9 (licensing set-point). Rationale, upstream variant elevates HLA-C surface density tied to clinical control.
- **Evidence type & confidence:** Population genetics, High confidence based on replicated associations and direct expression measurements.
- **Contradictions/nuance:** Relative contributions of NK versus CTL arms not separated; effect sizes may vary among HLA-C allotypes and ancestries.

A.95 Impact of protective killer inhibitory receptor-human leukocyte antigen genotypes on natural killer cell and T-cell function in HIV-1-infected controllers [104]

- **Core question/approach:** Genotype-phenotype study of controllers stratified by KIR3DL1-Bw4 combinations; assays of NK cytotoxicity and cytokines plus HIV-specific CD8 responses.
- **Key findings:** Protective KIR3DL1*h with HLA-Bw4-80I associates with higher NK cytotoxicity and IFN-γ production compared with nonprotective genotypes (Fig. 1-2). NK functional potency inversely correlates with HIV-specific CD8 responses ($\rho = -0.8321$, $P = 0.001$; n=12) in a subset (Fig. 2).
- **Mechanistic link:** Direct, peptide-HLA-Bw4 sensitizes educated KIR3DL1*h NK cells, linking NK licensing to effector potency and shaping CTL set-points.
- **Keystone assessment:** Supports, KP1 (triad), KP2 (quantitative). Rationale, protective KIR-HLA genotype couples NK education to measurable effector gains.
- **Evidence type & confidence:** Clinical cohort, Moderate confidence given modest sample sizes but coherent functional readouts.
- **Contradictions/nuance:** Controllers studied post hoc; generalizability to typical progressors needs caution; causality between NK and CTL responses inferred.

A.96 Trans-ancestral fine-mapping of MHC reveals key amino acids associated with spontaneous clearance of hepatitis C in HLA-DQβ1 [105]

- **Core question/approach:** Trans-ancestral MHC fine-mapping to pinpoint class II amino acids linked to HCV clearance across cohorts.
- **Key findings:** Fine-mapping localizes the primary signal to HLA-DQβ1 residue 26 (Leu) with strong association to spontaneous clearance; multi-ancestry modeling refines credible sets and implicates pocket chemistry (Fig. 2; Table 1).
- **Mechanistic link:** Inferred, DQβ1 pocket residues alter peptide binding and CD4 TCR help, modulating antiviral effectiveness.
- **Keystone assessment:** Supports, KP2 (quantitative), KP6 (coevolution). Rationale, specific class II residues explain outcome across ancestries via altered presentation.
- **Evidence type & confidence:** Population genetics, High confidence due to large N and convergent residue-level mapping.
- **Contradictions/nuance:** Focus on class II; implications for NK/KIR are indirect and require integration with class I data.

A.97 Genetic variation that determines TAPBP expression levels associates with the course of malaria in an HLA allotype-dependent manner [13]

- **Core question/approach:** eQTL analysis of TAPBP (tapasin) with malaria incidence and symptom severity, testing HLA effect modification.
- **Key findings:** Higher TAPBP expression eQTL associates with reduced malaria incidence (IRR=0.89, q=0.017) and odds of symptom-free status (OR=0.84, q=0.016), contingent on HLA allotype context (Fig. 3-4); replication in independent cohorts supports robustness.
- **Mechanistic link:** Inferred, tapasin abundance reshapes peptide loading/editing, stabilizing class I display and calibrating NK/CTL activation thresholds.
- **Keystone assessment:** Supports, KP2 (quantitative tapasin), KP9 (licensing set-point). Rationale, antigen-loading cofactor levels track with clinical course.
- **Evidence type & confidence:** Population genetics, Moderate confidence given observational eQTL links with consistent replication.
- **Contradictions/nuance:** HLA-specific interactions complicate generalization; direct peptide-repertoire shifts not measured.

A.98 Protective HLA Class I Alleles That Restrict Acute-Phase CD8+ T-Cell Responses Are Associated with Viral Escape Mutations Located in Highly Conserved Regions of Human Immunodeficiency Virus Type 1 [106]

- **Core question/approach:** Genome-wide identification of HLA-associated escape/reversion signatures and linkage to acute-phase immunodominant responses.

- **Key findings:** From 98 subtype B infections, 76 HLA-associated mutations (mostly in Gag/Pol/Nef) were identified, with 71% exhibiting reversion signatures (Fig. 1-2). For epitopes targeted acutely, residue conservation inversely correlates with HLA relative hazard (R=-0.565, P=0.028; improved to R=-0.775, P=0.0019 after outlier removal), implying constrained escape; covariation maps reveal compensatory routes (e.g., B57 TW10 T242N with H219Q/M228I) (Fig. 4-5; Table 2).
- **Mechanistic link:** Direct, CTL pressure on structurally constrained epitopes forces costly escape with compensatory mutations, limiting viral options.
- **Keystone assessment:** Supports, KP4 (constrained epitopes), KP6 (coevolution). Rationale, escape in conserved regions entails reversion/compensation consistent with fitness costs.
- **Evidence type & confidence:** Clinical cohort, Moderate confidence given robust genomic mapping and functional interpretation with limited acute-phase sample sizes.
- **Contradictions/nuance:** Primarily chronic infection data; structural constraints inferred from conservation and covariation rather than biophysical assays.

A.99 Killer cell immunoglobulin-like receptors are associated with common variable immune deficiency pathogenesis [107]

- **Core question/approach:** Do KIR genes and KIR-HLA receptor-ligand combinations influence risk of CVID-spectrum disease? Case-control study genotyped KIR and HLA in 175 cases and compared with local and 1958 British cohort controls using logistic regression and permutation testing.
- **Key findings:** Activating KIR2DS1 and KIR3DS1 associated with increased risk (OR=1.45, p=0.03; OR=1.54, p=0.01), as was inhibitory KIR2DL5 (OR=1.43, p=0.04). KIR3DS1+Bw4 overall OR=1.57, and stronger with Bw4-80T (OR=1.79, p=0.002). Strong inhibitory pairing KIR2DL1+C2 was protective (OR=0.58, p=0.002), whereas homozygous KIR2DL3+C1 increased risk (OR=1.88, p=0.002). Fig. 1, p. 5; Table 1, p. 6; empirical p=0.007 for combined significance.
- **Mechanistic link:** *Inferred* - Axis: KIR binding to HLA-Bw4 and HLA-C1/C2 groups calibrates NK activation thresholds and education. Weak inhibition via 2DL3+C1 and presence of activating 2DS1/3DS1 tilt toward activation; strong 2DL1+C2 inhibition is protective. No peptide dependence was tested.
- **Keystone assessment:** Supports - KP2 (quantitative), KP7 (immunoregulatory wiring), KP9 (licensing set-point). Rationale: genotype-defined inhibitory vs activating pairings map to NK licensing strength and correlate with disease risk.
- **Evidence type & confidence:** Clinical cohort, Moderate - adequate N with multiple significant effects, but single cohort and indirect mechanism.
- **Contradictions/nuance:** European ancestry only, phenotypes grouped as CHI, several associations nominal; Bw4-80T specificity differs from prior AIDS literature cited by authors; functional assays not performed in patients.

A.100 HLA Class I and II Diversity Contributes to the Etiologic Heterogeneity of Non-Hodgkin Lymphoma Subtypes [49]

- **Core question/approach:** Does HLA zygosity affect risk across NHL subtypes? Pooled analysis of 25 GWAS studies with imputed 4-digit HLA, modeling homozygosity at class I and II loci by subtype with per-locus trends.
- **Key findings:** DLBCL: class I per-locus OR=1.11 (p-trend=0.0008, FDR=0.003); B/C joint homozygosity OR=1.31 (1.06-1.60); DRB1 homozygote OR=2.10 (1.24-3.55). FL: class II per-locus OR=1.24 (p-trend¡1e-4, FDR=5e-4); fully homozygous OR=1.89 (1.37-2.61). MZL: HLA-B OR=1.34 (1.01-1.78), HLA-C OR=1.33 (1.04-1.70), DRB1 OR=1.45 (1.12-1.89). CLL/SLL showed modest, borderline trends. Tables 2-3, pp. 5-8.
- **Mechanistic link:** *Inferred* - Axis: HLA pocket diversity and peptide repertoire breadth. Homozygosity reduces antigen presentation diversity to CTL, potentially limiting tumor antigen surveillance and shifting thresholds within CTL-NK checkpoint interplay; quantitative per-locus effects at HLA-B/C and DRB1 support tuning.
- **Keystone assessment:** Supports - KP2 (quantitative), KP7 (dysregulation risk). Rationale: fewer distinct pHLA complexes correlate with greater lymphoma risk, consistent with impaired immune control.
- **Evidence type & confidence:** GWAS, High - very large N with replication across subtypes and FDR control; mechanism inferred.
- **Contradictions/nuance:** European ancestry only; HLA imputation not direct typing; heterogeneity within subtypes not resolved; some effects borderline, especially for CLL/SLL.

A.101 The Interaction of LILRB2 with HLA-B Is Associated with Psoriasis Susceptibility [23]

- **Core question/approach:** Do quantitative HLA-B interactions with the inhibitory APC receptor LILRB2 influence psoriasis risk? Two GWAS cohorts tested allele-specific LILRB2-HLA binding score variables in stepwise and multivariate models, adjusted for HLA alleles and ancestry PCs.
- **Key findings:** LILRB2-B showed independent protection: discovery OR=0.44 (0.28-0.68), p=2.33e-4; replication OR=0.50 (0.32-0.80), p=3.43e-3; combined OR=0.41 (0.30-0.55), p≈2.3e-9. LILRB2 is robustly expressed in cutaneous dendritic cells and overexpressed in lesional skin (fold 2.2-2.39, adj. p≤1.0e-9). Tables 1-2, p. 1293; Suppl. Fig. S1 and Table S2, p. 1295.e1-1295.e3.
- **Mechanistic link:** *Inferred* - Axis: HLA-B-LILRB2 inhibitory binding on APCs modulates costimulation and T-cell priming; stronger binding lowers risk, indicating quantitative tuning of an immunoregulatory checkpoint. No peptide-length or stability dependence tested here.
- **Keystone assessment:** Supports - KP2 (quantitative), KP7 (immunoregulatory wiring). Rationale: disease risk tracks with strength of inhibitory HLA-B engagement of an APC checkpoint and with receptor expression in lesions.

- **Evidence type & confidence:** GWAS, Moderate - replicated large-N genetic signal with coherent expression context, but mechanism inferred from binding scores external to the cohorts.
- **Contradictions/nuance:** Effect specific to HLA-B variable, potential LD with HLA-C*06:02, no patient-level functional assays; inference of APC effect relies on prior binding datasets cited by authors.

Appendix B Supplemental Tables

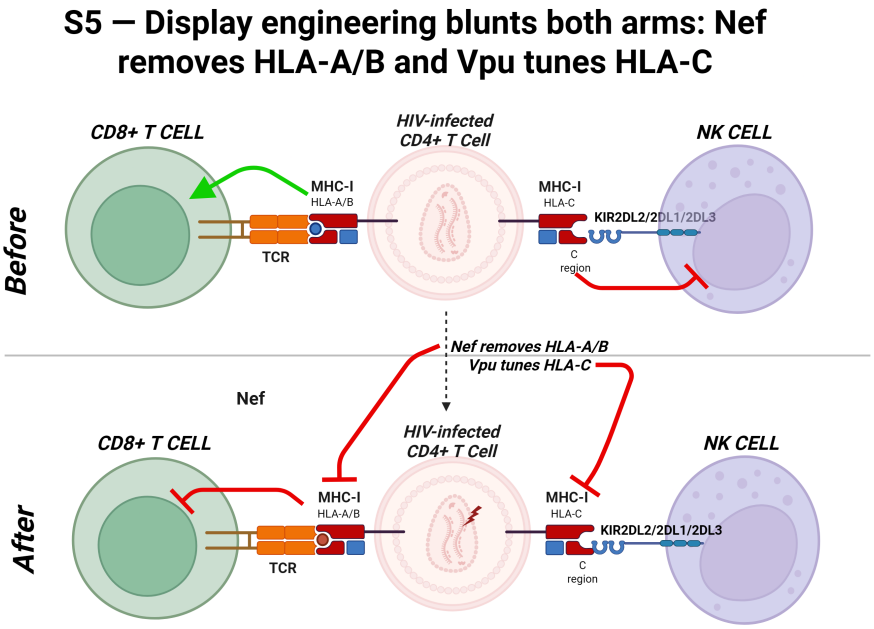

Fig. 5 S5 - Display engineering blunts both arms: Nef removes HLA-A/B and Vpu tunes HLA-C. *Definition and lead.* HIV edits antigen display to evade both CTL and NK control. Nef reduces HLA-A/B, eroding TCR surveillance, while Vpu selectively downregulates HLA-C, weakening HLA-C-restricted CTL and reshaping inhibitory KIR input (KP1, KP3). *Axes and class.* Left axis, peptide-HLA-A/B-TCR; right axis, HLA-C-KIR2DL1/2DL2/2DL3. Mechanism acts at display level rather than on a single constrained epitope (KP3 over KP4). *BEFORE.* Intact HLA-A/B/C on the infected $CD4^+$ T cell sustain CTL recognition and inhibit licensed NK via KIR-HLA-C (legend: HLA binding =; CTL ✓; NK ×; VL ↔). *AFTER.* Nef lowers HLA-A/B and Vpu lowers HLA-C to isolate-specific depths, diminishing HLA-C-restricted CTL and variably reducing inhibitory KIR engagement; licensed NK often remain suboptimal, so the net is reduced effector control and higher viraemia (legend: HLA binding ↓; CTL ×; NK × or weak ✓; VL ↑) (KP1, KP9). *Evidence.* Most primary HIV-1 clones downregulate HLA-C through Vpu, not Nef, and primary strains vary in magnitude; Vpu loss abrogates HLA-C reduction, and Vpu alone is sufficient to reduce HLA-C [14]. HLA-C reduction impairs suppression by HLA-C-restricted CTL [14]. HIV-1-mediated HLA-C downmodulation decreases KIR2DL1 and KIR2DL3 binding; despite this, HLA-C-licensed $KIR2DL^+$ NK cells show impaired antiviral activity relative to unlicensed cells, yet NK cells can sense strain-to-strain differences in HLA-C loss and respond more when loss is stronger (rheostat behavior) [15]. Peptide-HLA-C biophysics fine-tunes the same lever: for C*12:02 and C*14:03, CTL-selected or allele-specific contexts reduce pHLA-C surface stability without changing KIR2DL2 affinity, lowering inhibitory ligand density and enabling stronger $KIR2DL2^+$ NK activity [24]. *KP links.* KP1, coordinated tuning of a shared surface readout for CTL and NK; KP3, display engineering is the proximal checkpoint; KP8, KIR inhibition depends on peptide-HLA density and context; KP9, licensing set-points explain muted NK rescue when HLA-C falls; KP10, host HLA-C and KIR diversity shift outcomes for a given Vpu phenotype.

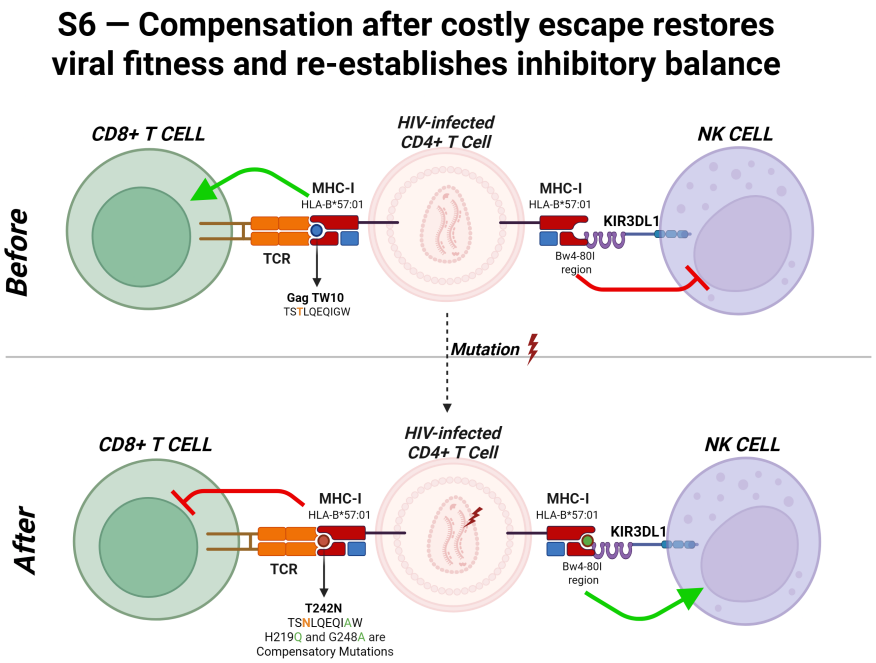

Fig. 6 S6 - Compensation after costly escape restores fitness and re-establishes inhibitory balance. A constrained, highly networked B*57:01-restricted epitope first undergoes a costly CTL escape, then gains compensatory substitutions that recover fitness and can reinstate strong inhibitory input at the B*57:01-KIR3DL1 axis, leaving CTL escape in place while NK returns to off (KP1, KP3, KP4, KP8, KP9). Network and sector analyses explain why such epitopes impose high fitness costs on multi-mutation trajectories and why compensation is selected rather than indefinite drift [18, 19]. *BEFORE*: CTL effectively recognizes a constrained B*57:01 target; licensed KIR3DL1^{+} NK cells are inhibited by robust Bw4 input. *AFTER - tick A, escape*: a peptide change at pΩ-1/-2 abrogates TCR recognition but incurs a fitness penalty within the linked sector; transiently, inhibitory tone may drop as display context shifts. *AFTER - tick B, compensation*: one or more compensatory substitutions mapped by positive sector correlations restore structural integrity and productive presentation, allowing strong B*57:01-KIR3DL1 engagement to return while CTL escape persists [18, 19]. **Rationale**: Sector mapping shows multidimensional constraints that make multiple mutations rare in vulnerable Gag regions and tie protection to epitopes with high topological connectivity; compensation follows costly escape along tolerated paths [18, 19].

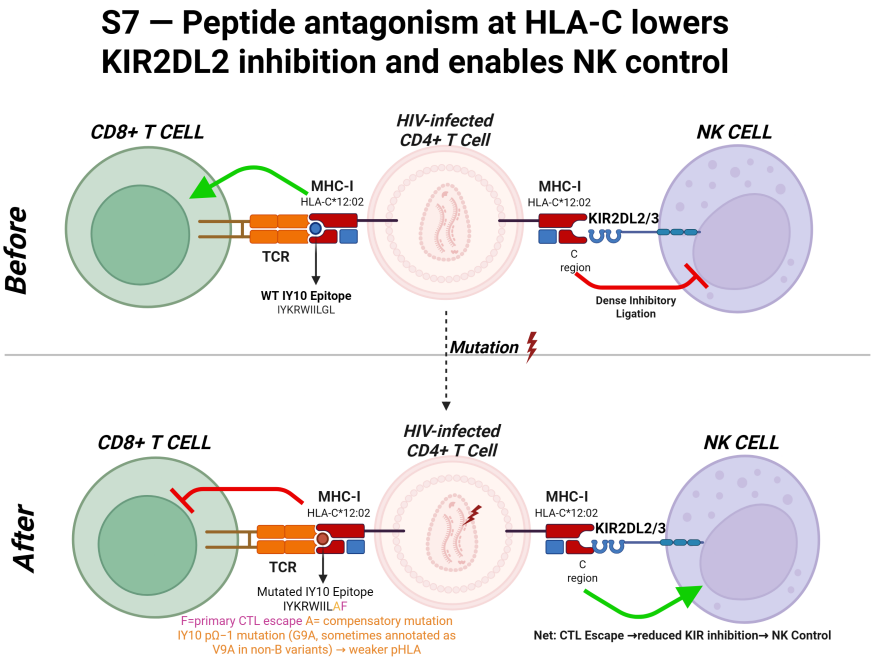

Fig. 7 S7 - Peptide antagonism at HLA-C lowers KIR2DL2 inhibition and enables NK control. *Concept.* Mixtures of self and viral peptides that differentially stabilize HLA-C modulate inhibitory KIR2DL2/3 occupancy, recalibrating NK inhibition without bulk loss of class I (triad integration, KP1; peptide-dependent KIR, KP8). [24] *Axes and epitope class.* Right interface, HLA-C1-KIR2DL2/3 checkpoint; left interface, peptide-HLA-TCR. The focal CTL epitope in the C*12:02 Pol-IY10 example is non-constrained (escape at pΩ with low fitness cost, KP4). [24] *BEFORE (left).* On an HLA-C1 background, well-stabilized peptide-HLA-C complexes densely ligate KIR2DL2/3, keeping licensed NK cells inhibited; CTL recognition of the displayed epitope may be intact. Net readout: HLA binding = or ↑; CTL ✓; NK ×; VL ↔ or ↑. [24] *AFTER (right).* Two routes reduce inhibitory ligation without increasing KIR affinity: (A) allele effect, HLA-C*14:03 versus HLA-C*14:02, where the same HIV peptide shows lower stabilization on C*14:03, yielding fewer pHLA ligands and stronger KIR2DL2^{+} NK reactivity and viral suppression (KP3, KP8, KP9); (B) escape effect, C*12:02 Pol-IY10 V9A at pΩ weakens peptide-HLA binding, lowering the pHLA expression index yet not increasing KIR2DL2 binding, thereby unmasking licensed NK effector function even as CTL pressure at that epitope is lost (KP1, KP3, KP4, KP8, KP9). [24] *Generalization to HLA-B-KIR3DL1.* Protective HLA-B residues partition effects across TCR and KIR interfaces: M67 and L156 stabilize pHLA, S70 shapes TCR docking, and V97 specifically tunes HLA-B*57:01-KIR3DL1 binding. Mutation at V97 reduces KIR3DL1 engagement and reporter activation across HIV epitopes, extending peptide-dependent KIR tuning beyond the HLA-C-KIR2DL2 axis (KP8, KP3). [7]

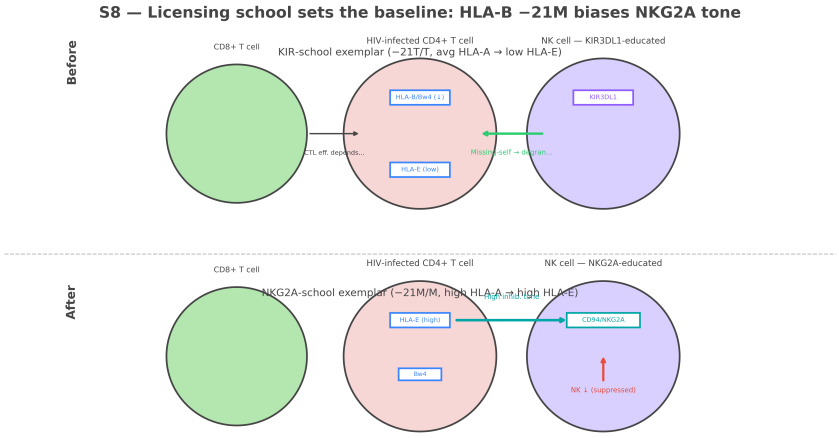

Fig. 8 S8 - Licensing school sets the baseline for NK responses. *Concept.* Host class I genetics preconfigures NK education along two schools that compete at infection: a KIR3DL1-Bw4 school versus an HLA-E-CD94/NKG2A school. HLA-B signal-peptide and HLA-A expression shape HLA-E supply and checkpoint strength (KP1, KP3, KP8, KP9, KP10). *BEFORE (KIR-school exemplar).* With lower HLA-E input (for example HLA-B -21T/T and average HLA-A expression), NK education is dominated by KIR3DL1-Bw4. Upon HIV infection, selective HLA-B/Bw4 downregulation creates missing-self and KIR3DL1-educated NK cells degranulate against autologous infected $CD4^+$ targets (NK ✓), while CTL effectiveness depends on the epitope context [8]. *AFTER (NKG2A-school exemplar).* HLA-B -21M haplotypes and higher HLA-A expression increase HLA-E on targets and bias education to CD94/NKG2A. This raises inhibitory tone and associates with higher viral load and lower CD4 counts over time, particularly in -21M/M donors (NK ×) [26]. Lin *et al.* refine the model by showing that only a subset of signal peptides are functional, that VL9 variants compete non-additively for HLA-E loading, and that the common HLA-B -21M block (SP-6B) stabilizes HLA-E yet confers low CD94/NKG2A recognition and can antagonize overall recognition, so net NKG2A tone depends on the mix of SP sources and HLA-E allotype [25]. *Integrated readout.* The licensing rheostat combines receptor density, ligand density and binding strength: KIR3DL1-Bw4 calibrates missing-self sensitivity and predicts killing of infected autologous cells, whereas HLA-E-CD94/NKG2A sets a tunable checkpoint that can dominate when ligand supply is high (KP9) [8, 25, 26].

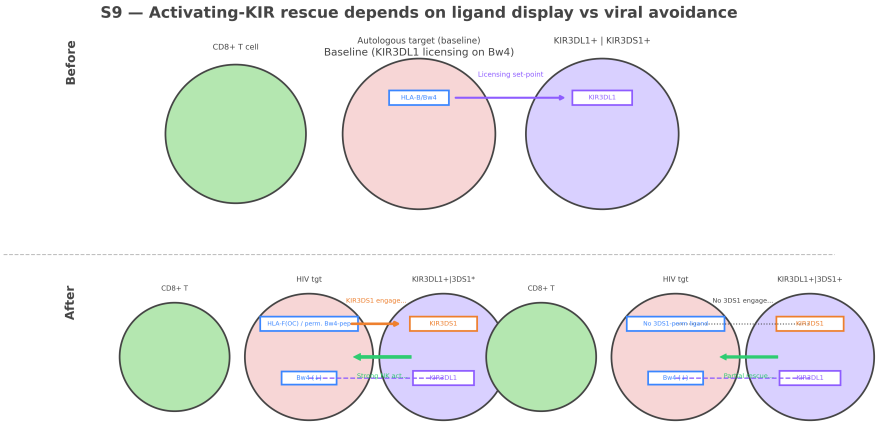

Fig. 9 S9 - Activating-KIR rescue depends on ligand display vs viral avoidance. *Definition.* We contrast two AFTER outcomes on an inhibitory set-point established by B*57:01-KIR3DL1 education (KP1, KP9): an *Engage* branch where KIR3DS1 finds a suitable ligand and boosts NK activation, and an *Avoid* branch where the virus minimizes or reshapes that ligand so NK help is muted (KP3). *Axes.* Inhibitory axis: B*57:01-KIR3DL1 (Bw4) calibrates responsiveness and predicts killing of autologous HIV-infected $CD4^+$ T cells; HIV reduces HLA-Bw4 on targets while preserving HLA-C, creating missing-self for $KIR3DL1^+$ NK cells [8]. Activating axis: KIR3DS1 can engage class I in a peptide- and allotype-sensitive manner, with direct Bw4 binding shown for the rare KIR3DS1*014 and for the W138G gain-of-binding mutant (KP8) [33]. *BEFORE.* Basal class I display educates $KIR3DL1^+$ NK cells via Bw4; KIR3DS1 engagement is contingent on ligand context or allotype (legend: HLA binding =; CTL ✓; NK baseline set by licensing; VL ↔) [8, 33]. *AFTER - Engage.* HIV reduces HLA-Bw4 (missing-self) and the infected cell presents a KIR3DS1-permissive ligand context (e.g., HLA-F open conformer or Bw4 with permissive peptide and KIR3DS1*014-like interface), yielding strong NK activation and cytolysis; legend: HLA binding ↓; CTL = or ×; NK ✓; VL ↓ [8, 33]. *AFTER - Avoid.* HIV still reduces Bw4 but does not provide an effective KIR3DS1 ligand, so activation relies on missing-self alone and rescue is incomplete; legend: HLA binding ↓; CTL = or ×; NK × or weak ✓; VL ↑ [8]. *KP links.* KP1 triad integration of CTL, inhibitory KIR3DL1-Bw4, and activating KIR3DS1; KP3 display-level tuning via viral modulation of HLA-B; KP8 peptide-receptor-allotype specificity for KIR3DS1 binding (W138G and *014 evidence); KP9 licensing explains graded NK rescue; KP10 ancestry-linked variation in KIR3DS1 allotypes influences engage-versus-avoid probabilities [8, 33].

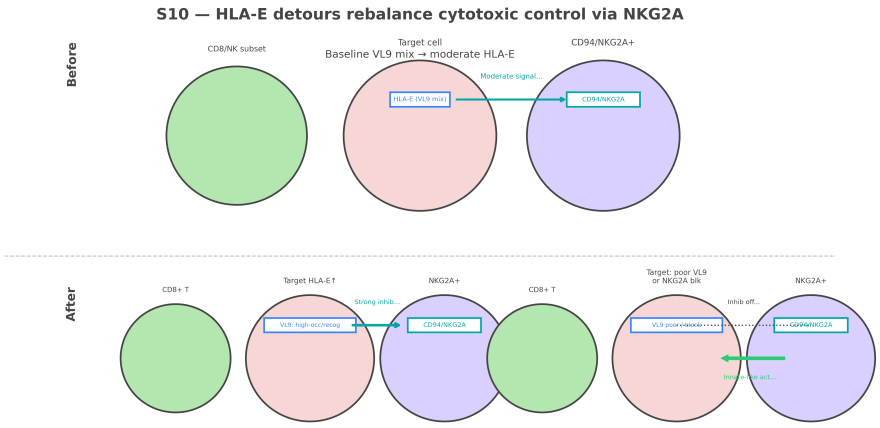

Fig. 10 S10 - HLA-E detours rebalance cytotoxic control via NKG2A. Variation in VL9 peptide loading to HLA-E, determined by host signal peptides and HLA-E allotype, tunes CD94/NKG2A checkpoint strength and can reroute cytotoxicity (KP1, KP2, KP3, KP8, KP9, KP10). Lin *et al.* show that only a subset of HLA-A/B/C signal peptides yield functional VL9 for HLA-E, that VL9s compete non-additively for loading, and that single-residue differences alter CD94/NKG2A engagement and NK inhibition [25]. In human tissue, NKG2A marks an alternative, switchable program on CD8 T cells; in bladder cancer, HLA-E inhibits NKG2A$^+$ CD8 and NK functions, and monalizumab restores degranulation toward HLA-E$^+$ targets with clinical links to benefit after PD-L1 blockade [17]. *BEFORE*: Baseline VL9 mix produces moderate HLA-E and tonic NKG2A signaling on NK and a subset of CD8 T cells; classical CTL recognize HLA-A/B/C. *AFTER A - stronger brake*: High-occupancy, high-recognition VL9 raises HLA-E and strengthens HLA-E-NKG2A inhibition, reducing cytotoxicity [25]. *AFTER B - checkpoint-off route*: Poor-recognition VL9 or NKG2A blockade lowers the inhibitory threshold and enables innate-like CD8 or NK activity, even when HLA-ABC is reduced [17, 25]. **Figure notes**: Label HLA-E allotype (E*01:01 vs E*01:03), VL9 source (e.g., SP-1C vs SP-6B), and the CD94/NKG2A interface; show two AFTER branches that diverge by VL9 recognition or therapeutic blockade.

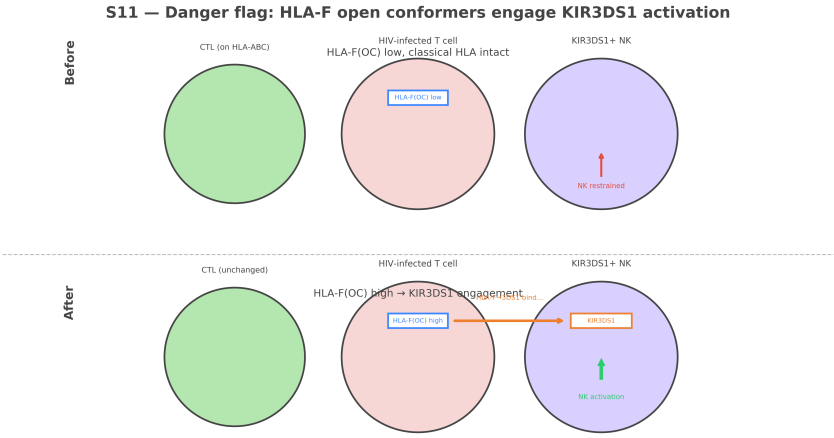

Fig. 11 S11 - Danger flag: HLA-F open conformers engage KIR3DS1 activation. *Concept.* On the same HIV-infected CD4$^+$ T cell that displays classical HLA class I for CTL, stress-induced HLA-F open conformers provide an activating cue to KIR3DS1 on NK cells, shifting the triad toward innate control (KP1, KP3). Residue-level rules show KIR3DS1 can be configured to recognize class I ligands: D1 positions 138, 163, 166 and D2 position 199 gate binding and signaling [33]. *BEFORE (left).* HLA-F(OC) low, classical HLA intact, net inhibitory input keeps licensed NK cells restrained (KP1, KP9). KIR3DS1 lacks an effective ligand, so NK cytotoxicity is minimal while CTL responses proceed. *AFTER (right).* HLA-F(OC) high enables HLA-F(OC)-KIR3DS1 engagement and NK activation even if CTL pressure is unchanged (KP1, KP3). Mechanistic anchors: glycine at KIR3DS1 D1:138 (as in KIR3DS1*014) confers Bw4 80I tetramer binding and reporter activation, whereas tryptophan at 138 abrogates recognition; epistasis with D2:199 further gates binding, requiring permissive 138/163/166/199 combinations (KP8) [33]. **Outcome legend:** classical HLA binding =; HLA-F(OC) ↑; CTL =; NK ✓; VL ↓.

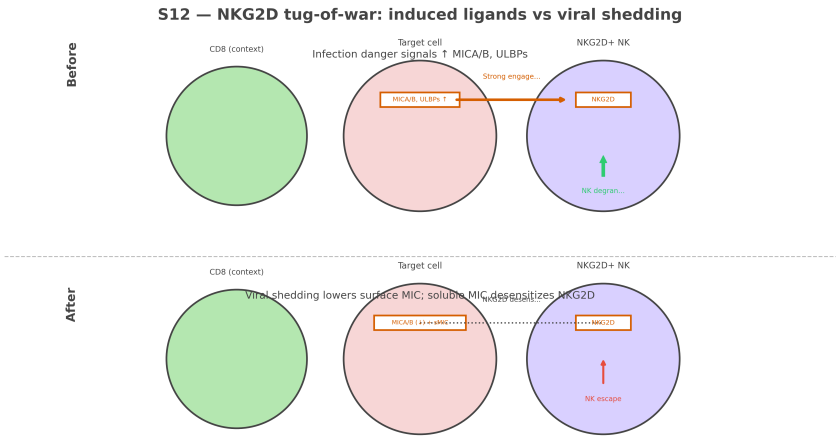

Fig. 12 S12 - NKG2D tug-of-war: induced ligands versus viral shedding. *Concept.* Early after infection, stress ligands (MICA/B, ULBPs) rise on the infected target and engage NKG2D, enabling NK killing alongside any ongoing CTL pressure (KP1, KP2). Viruses can then rewire display: proteolytic shedding removes MICA/B from the surface and releases soluble ligands that desensitize NKG2D, flipping the balance toward NK escape; in tissues where HLA-E remains, the HLA-E-CD94/NKG2A checkpoint further suppresses cytotoxicity (KP3, KP7). *BEFORE*: infection or danger signals increase surface NKG2D ligands on the target cell, producing strong NKG2D engagement and NK degranulation; CTL effectiveness depends on the peptide-HLA context but is not the primary driver here [16]. *AFTER*: viral display engineering induces MICA/B shedding, lowering surface ligands and raising soluble MIC-A/B that blunt NKG2D responsiveness; blocking shedding with antibody 7C6 restores NK recognition and killing, establishing causality for the NKG2D axis (therapeutic node) [16]. In parallel, HLA-E on targets inhibits NKG2A^{+} cytotoxic cells, and NKG2A blockade re-enables TCR-independent degranulation (second therapeutic node) [17]. **Outcome legend:** BEFORE - HLA binding =; CTL ✓; NK ✓; VL ↓. AFTER - HLA binding =; CTL ✓; NK ×; VL ↑.

Fig. 13 S13 - Vpu-driven HLA-C downregulation reshapes NK checkpoints and weakens HLA-C-restricted CTL. *Lead.* HIV-1 Vpu reduces HLA-C surface density on infected $CD4^+$ T cells, blunting HLA-C-restricted CTL while retuning inhibitory KIR inputs to NK cells (KP1, KP3). Primary viruses commonly downregulate HLA-C, unlike NL4-3, and the magnitude varies by strain and Vpu sequence [14]. *BEFORE.* With intact HLA-C, CTL recognition via pHLA-C is available, and KIR2DL1/2DL3 on NK cells bind C2/C1 ligands to enforce inhibition at the licensing set-point (KP9). Legend: HLA binding =; CTL ✓; NK ×; VL ↔ [15]. *AFTER.* Vpu lowers HLA-C (display-level checkpoint, KP3) while Nef may separately reduce HLA-A/B. Direct CTL cost: reduced suppression by HLA-C-restricted CTL. Innate balance depends on residual HLA-C and KIR affinity: licensed $KIR2DL^+$ NK cells remain partially inhibited by residual HLA-C and underperform versus unlicensed NK, yet NK cells sense strain differences-stronger HLA-C downregulation (e.g., JR-CSF WT) yields less KIR2DL1/2DL3 binding and higher NK inhibition of replication than a Vpu mutant with weaker HLA-C loss (KP8, KP9). Legend: HLA binding ↓; CTL ×; NK × or weak ✓ (strain dependent); VL ↑ [14, 15]. *KP links.* KP1, the same surface interface gates CTL via HLA-C and NK via KIR2DL receptors; KP3, Vpu edits display at HLA-C; KP8, KIR inhibition depends on peptide-HLA-C ligand density and receptor context; KP9, licensing set-points explain muted NK rescue when HLA-C falls modestly; KP10, host C1/C2 background and baseline HLA-C levels modulate outcomes [14, 15].

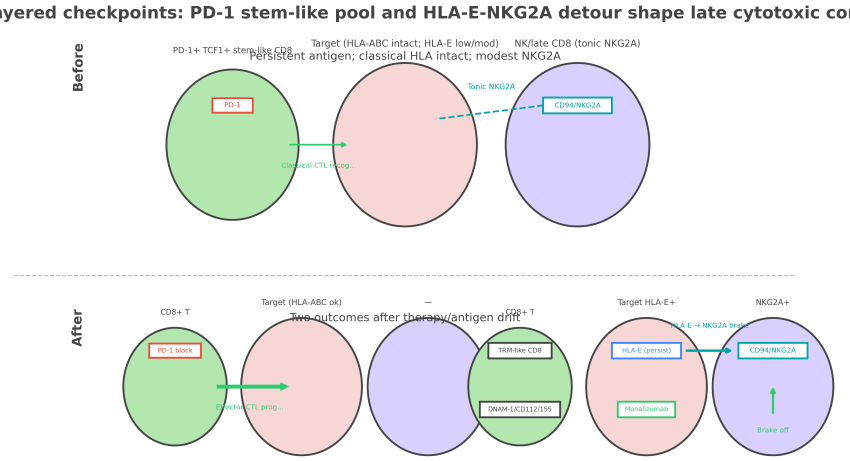

Fig. 14 S14 - Layered checkpoints: PD-1 stem-like pool and HLA-E-NKG2A detour shape late cytotoxic control. Chronically antigen-exposed tissues exhibit a two-layer architecture: an upstream PD-1 gate restraining a PD-1^+ TCF-1^+ stem-like CD8 pool, and a downstream HLA-E-CD94/NKG2A gate that can suppress cytotoxicity when HLA-A/B/C is diminished and HLA-E is present (KP1, KP2, KP3, KP8, KP9, KP10). In HPV^+ head-and-neck cancer, PD-1^+ TCF-1^+ stem-like CD8 T cells reside in stromal niches, share clonotypes with transitory and terminal states, and proliferate upon antigen to seed effector progeny [45]. In bladder cancer, NKG2A is acquired after PD-1 on intratumoral CD8 T cells, coinciding with TRM features; HLA-ABC is commonly reduced while HLA-E persists, and NKG2A blockade restores TCR-independent degranulation toward HLA-E^+ targets with clinical associations to benefit on PD-L1 therapy [17]. *BEFORE*: persistent antigen with intact classical display - PD-1^+ TCF-1^+ stem-like CD8 pool present; classical CTL on HLA-A/B/C; HLA-E low to moderate and tonic NKG2A signaling modest [45]. *AFTER branch A - PD-1 release*: PD-1 blockade enables stem-like proliferation and differentiation into effector-like TIM-3^+ GZB^+ $CD39^+$ progeny, improving CTL control when classical HLA remains available [45]. *AFTER branch B with late NKG2A*: when classical display is reduced, a PD-1^+ $NKG2A^+$ TRM-like branch uses DNAM-1-dependent missing-self recognition but is inhibited by HLA-E; monalizumab removes this brake, restoring degranulation and cytotoxic mediator release, with KLRC1 (NKG2A) linking to better outcomes after PD-L1 blockade [17]. **Figure notes**: show PD-1 on the stem-like CD8 pool feeding an effector stream upon blockade; depict HLA-E-NKG2A as a downstream lock that is released by monalizumab; annotate DNAM-1-CD112/CD155 for the TCR-independent route.

Table B1 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[51]	Method to isolate viable antigen-specific CD8+ T cells by surface-trapped TNF-α then single-cell RNA/TCR-seq and TCR re-expression.	Defined TNF+/CD69+ responders after 8 h; discovered HIV Gag EL9 and mapped HLA-A*68:02 restriction with nearly 2-fold higher IFN-γ than SA15 (Fig.4A-H; LOQ 50 SFC per 10^5; 1e6 PBMC per pool).	Direct - peptide-HLA-TCR mapping with functional restriction (Fig.4H).	Supports - KP4 (constrained epitopes); KP5 (imprinting)	Moderate	Molecular/structural	TNF-capture lower than ICS yet sortable; donor-specific; limited human n.
[37]	Cohort comparison of immunodominance in HLA-B*27:05 vs B*27:02 with epitope mapping.	Dominant B*27 responses more frequent in B*27:05 than B*27:02 (24/41 vs 8/33; p=0.006); B*27:05 targets Gag KK10/KY9, B*27:02 skews to Nef VW9 (Fig.1-3; Table 1).	Direct - peptide-HLA-TCR differences set hierarchies aligned with protection (Fig.1-3); Circumstantial - immunodominant but less protective Nef focus suggests decoy misdirection, NK not tested.	Supports - KP4 (constrained epitopes); KP5 (imprinting); KP11 (decoy immunodominance)	Moderate	Clinical cohort	Allele-specific hierarchy; fitness cost not directly measured; subtype context matters.
[48]	Viral footprinting by KIR genotype plus NK assays.	KIR2DL2 linked to Vpu polymorphisms after HLA control; NK CD107a degranulation rose from ∼4.1%±2.0 to ∼39.3%±6.7 against variant vs index in KIR2DL2/3+ donors, p¡0.0001 (Fig.1-2).	Inferred - KIR-HLA axis drives viral adaptation with functional NK shifts (Fig.2).	Supports - KP3 (viral subversion); KP6 (coevolution); KP1 (triad integration)	High	Population genetics	Functional tests with few donors; residual HLA confounding possible.
[9]	Large cohorts relating HLA-C expression to HIV set-point and progression.	Higher HLA-C expression linked to lower viral load (EA n=2527 p¡1e-7; AA n=1209 p=8e-6) and delayed CD4¡200 (HR 0.67, 95% CI 0.58-0.78; n=1069); more CTL responses and escape at HLA-C sites (Fig.1-3; Table 1).	Inferred - quantitative HLA-C tunes CTL visibility and NK education thresholds (Fig.1-3).	Supports - KP2 (quantitative tuning); KP9 (licensing set-point)	High	Clinical cohort	Proxy-based expression; allotype heterogeneity; NK phenotypes not directly measured.
[14]	Functional mapping of Vpu-driven HLA-C downregulation across primary clones plus CTL assays.	Most primary clones downregulated HLA-C (Fig.1B, ****p¡0.0001; **p¡0.005); effect mapped to a 149 bp vpu segment and key residues (Fig.2-3); weaker downregulation tied to less CTL suppression (Fig.6).	Direct - Vpu reduces HLA-C, decreasing CTL presentation and exerting class I display control across isolates; alters NK engagement (Figs.1-3,6).	Supports - KP3 (viral subversion); KP1 (triad integration); KP8 (NK-CTL pincer); KP12 (class I display control)	High	Functional virology	Clone and allotype variability; not all vpu variants equivalent.
[52]	PepWAS linking disease-associated predicted epitopes to set-point viral load in n=6311.	HLA-B disease-associated predicted epitopes explained ∼12.2% of spVL variance; env alone ∼6.4%; 132 HLA-B epitopes identified (Fig.2).	Inferred - quantitative peptide repertoire correlates with control, prioritizing conserved targets (Fig.2).	Supports - KP4 (constrained epitopes); KP2 (quantitative tuning)	High	Population genetics	Relies on binding predictions; limited in-study functional validation.
[22]	Population-genetic and computational tests of heterozygote advantage via peptide breadth and complementarity.	Heterozygosity at HLA-B and HLA-C associated with lower spVL (p=1.3e-6 and 2.8e-6); peptide breadth and divergence correlate with control (Kendall tau around -0.12 and -0.08; Figs.3-4).	Inferred - broader, complementary peptide presentation in heterozygotes enhances CTL coverage (Figs.3-4).	Supports - KP2 (quantitative tuning); KP6 (coevolution)	High	Population genetics	Depends on in silico pipelines; NK-specific mechanisms not modeled.

Table B2 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[53]	Functional virology: quantified Vpu-mediated HLA-C downmodulation using primary variants, flow cytometry, and genotype associations.	n=195 env clones; 6-fold threshold; 69 strong vs 117 weak; r=0.27, p=0.0005; allele-level r=0.68, p=0.03; population r=-0.57, p=0.01; Vpu required; Fig.3A-B, Fig.5A-D, Fig.6-8.	Direct - Vpu-HLA-C interaction shifts NK inhibition and CTL visibility; strain-variable class I tuning by Vpu aligns with display control.	Supports - KP3 (viral subversion); KP2 (quantitative tuning); KP6 (coevolution); KP9 (licensing); KP12 (class I tuning by Vpu)	High	Functional virology	Cell-type dependence; allele- and subtype-specific strength; not all isolates are strong.
[54]	Preview/perspective on Vpu-mediated HLA-C downmodulation.	Conceptual summary; numeric effects not reported.	Circumstantial - frames class I tuning by Vpu balancing CTL visibility and NK inhibition.	Indirect - KP3 (viral subversion); KP12 (class I tuning by Vpu)	Low	Review/perspective	Commentary only; no new N or effect sizes.
[55]	Review of HLA-KIR genetics and function shaping HIV outcomes.	Synthesizes associations of KIR3DL1/HLA-Bw4 with disease course; selection signals discussed; numbers not reported.	Circumstantial - triad framing of HLA-peptide-KIR with inferred CTL and NK balance.	Indirect - KP1 (triad integration); KP6 (coevolution); KP9 (licensing frameworks); KP10 (eco-geographic)	Low	Review/perspective	Allele- and ancestry-specificity; integrative not primary.
[12]	Population genetics plus molecular phenotyping of tapasin dependence vs HIV outcomes.	Tapasin-independent allotypes show broader peptide display and better HIV control; key panels Fig.1-3 with p-values (e.g., p_i0.01-0.0001).	Inferred - quantitative presentation quality tunes CTL visibility and KIR ligands; viral pathways target peptide loading.	Supports - KP2 (quantitative tuning); KP6 (coevolution); KP3 (viral subversion of loading)	Moderate	Population genetics	HLA-B*57 protective yet tapasin-dependent; cohort covariates matter.
[56]	Clinical cohort, single-cell, and organoid work probing class II-NKp44 axis in UC.	Meta-analysis (13,927 UC vs 26,764 controls) shows epithelial HLA-DP upregulation; NKp44 blockade rescues organoid viability.	Direct - epithelial HLA-DP engages NKp44 to drive cytotoxicity.	Supports - KP7 (immunoregulatory wiring to dysregulation)	High	Clinical cohort	UC-specific model; HLA-DP polymorphism not fully stratified.
[57]	Multi-cohort genetics with mechanistic assays across HIV-1, HCV, HTLV-1.	HIV-1: coef=-0.42±0.14, p=0.004; HCV: HR=0.44 (0.22-0.87), p=0.02; HTLV-1: OR=0.22 (0.08-0.60), p=0.006; requires protective HLA + iKIR.	Inferred - iKIR genotypes raise thresholds so protective HLA effects are amplified.	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP9 (licensing set-point)	High	Clinical cohort	Depends on joint presence of specific HLA and cognate iKIR; heterogeneity across viruses.
[8]	Ex vivo mapping of KIR3DL1/HLA-Bw4 binding and density effects on NK education and HIV killing.	Binding-reactivity correlations r^2 ≈0.33-0.41 ($p \leq 0.005$; Fig.4A-C); receptor density rescues weak affinity (Fig.5-6); Bw4 density predicts education r^2 ≈0.45-0.52 (p_i0.0001; Fig.7D-F); HIV reduces Bw4 MFI ∼60% with ∼15.5±9.3% infection; licensed KIR3DL1$^+$ NK kill infected autologous cells (Fig.8).	Direct - quantitative KIR3DL1-HLA-Bw4 interactions calibrate education and killing; infection reduces Bw4 density, evidencing class I display control.	Supports - KP2 (quantitative tuning); KP9 (licensing); KP3 (viral subversion); KP12 (class I display control)	High	Functional virology	B*27 weak binding yet high density yields strong education; subtype context matters.

Table B3 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[39]	Functional virology: measure replication capacity (RRC) of subtype C Gag CTL-escape mutants and relate to HLA-B*57/B*58:01 carriage.	Single mutants: T242N RRC 0.86, A146P 0.91, A163G 0.89; triple A146P+T242N+A163G RRC 0.62 vs WT=1.0; protective B*57/B*58:01 enriched among low RRC viruses. Fig.2A-2B; p. 2460-2468.	Direct - TCR-driven escape in B*57/B*58:01-restricted Gag reduces fitness; stepwise RRC decline with combined mutations (Fig. 2B).	Supports - KP4 (constrained epitopes; costly escape); KP2 (quantitative tuning)	High	Functional virology	Subtype C focus; modest losses for some single mutants; cohort context may modulate associations.
[38]	Functional virology plus cohort analysis: define TW10 T242N escape, compensatory capsid mutations, replication and cyclophilin A dependence, and in vivo viremia.	Compensation restores replication and associates with higher viremia (donors r=0.34, p=0.13; recipients r=0.59, p=0.02); reduced cyclophilin A dependence with compensation. p. 12608-12618; Fig. 2.	Direct - CTL escape disrupts capsid fitness/cyclophilin usage; H219Q/I223V/M228I compensate and increase viremia.	Supports - KP4 (constrained epitopes); KP2 (quantitative tuning)	Moderate	Functional virology	Donor vs recipient differences; heterogeneous compensation paths; no direct KIR-binding data.
[20]	Clinical cohort sequencing (N=98 seroconverters) to quantify escape and reversion within HLA-restricted Gag epitopes early.	80% of published CTL epitopes evolved early; B*57 epitopes rapidly reverted; 5 of 10 fastest-evolving epitopes restricted by control-associated alleles; pressure concentrated in Gag. p. 9216-9227; Fig. 1-2.	Circumstantial - allele-specific escape/reversion within HLA-restricted epitopes implies peptide-binding constraints linked to control.	Supports - KP4 (constrained epitopes); KP6 (host-pathogen coevolution)	High	Clinical cohort	Rates vary by epitope/allele; correlative design; not all protective alleles evolve rapidly.
[4]	Review of innate control emphasizing KIR-HLA genetics, NK education, and HIV evasion.	KIR/HLA receptor-ligand combinations associate with slower progression; NK expand in acute infection; Nef downregulates HLA-A/B while sparing HLA-C. Fig. 1, Fig. 3; pp. 3-4, 8-10.	Inferred - peptide-sensitive KIR-pHLA engagement plus Nef HLA-A/B downregulation with preserved HLA-C maintains inhibitory KIR tone at scale.	Supports - KP1 (triad integration); KP2 (education/tuning); KP3 (viral subversion); KP12 (display control preserves inhibition)	Moderate	Review/perspective	Some KIR-Bw4 interactions unresolved structurally; peptide specificity varies.
[58]	Review integrating GWAS and functional studies to explain genetic control signals (HLA-B pocket residues; HLA-C expression).	GWAS: 974 controllers vs 2,648 progressors; all genome-wide signals in MHC-I; key HLA-B residues 62/63/67/70/97; HLA-C -35 and 3′UTR miR-148 site tune expression. Fig. 2-4.	Inferred - pocket chemistry shapes CTL epitopes; HLA-C expression eQTL and 3′UTR regulation tune quantitative presentation and NK education.	Supports - KP2 (quantitative tuning; HLA-C expression); KP1 (triad integration); KP4 (constrained epitopes)	Moderate	Review/perspective	-35 effect partly confounded by LD; causal variant unresolved by ancestry.
[5]	Case report with immunopathology: HSV lymphadenitis coincident with CLL tumor reduction before therapy.	Temporal linkage of HSV-1 lymphadenitis with tumor reduction; histology confirms HSV and robust immune infiltrates; exact percent reduction not reported; Fig. 1-2.	Circumstantial - bystander viral inflammation rebalances innate/adaptive responses; specific KIR-HLA peptide effects not tested.	Indirect - KP7 (immunoregulatory wiring; dysregulation risk)	Low	Case report	Single patient; alternative explanations possible; mechanism unresolved.
[59]	Clinical cohort (N=536) evaluating HLA class I associations with set-point viral load and CD4.	C*12:02 lower VL (4.22 vs 4.57 $\log_{10}$ copies/mL, p=0.016) and higher CD4 (370 vs 297 cells/µL, p=0.040); C*15:05 higher VL and lower CD4; B*52 and C*12:02 protective. Tables 1,4; pp. 3-4.	Inferred - allele-specific peptide presentation and potential KIR engagement calibrate control; no direct binding measured.	Supports - KP2 (quantitative tuning via HLA-C); KP6 (population/strain differences)	High	Clinical cohort	LD may contribute; AE specificity limits generalization; context dependent.

Table B4 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[60]	Define whether CD8 T cells recognize one conserved herpesvirus epitope across EBV, VZV, HSV; HLA-B*18 tetramers and T cell clones.	Conserved 9-mer across EBV BCRF1, VZV ORF16, HSV-1 UL27 is recognized by HLA-B*18:01/03-restricted CD8 T cells; cross-reactivity by tetramer and IFN-γ (Fig. 4-5; n not reported). *Source:*	Direct - TCR cross-reactivity to conserved HLA-B*18:01 pHLA; peptide conservation maintains CTL recognition (Fig. 4-5). *Source:*	Supports - KP4 (constrained epitopes); KP5 (imprinting on geometry)	Moderate	Functional virology	HLA-B*18 restriction; NK/KIR not tested; several quantitative details not reported.
[29]	Historic vs modern North American cohorts with linked HLA and HIV Gag/Nef; phylogenetics plus functional assays.	HLA-selected sites diversify more (45.2% vs 21.0%; $p = 0.0002$); background Gag polymorphism frequencies 2x (3.7% vs 2.0%); Gag replication unchanged (Kruskal-Wallis $p = 0.6$); modern Nef shows higher CD4/HLA-I downregulation (both $p < 0.0001$). Fig. 1-4,7-8. *Sources:*	Inferred - HLA-peptide-TCR pressures fix escape with modest spread; plus Nef-mediated class I display control reduces CTL visibility (Fig. 3-4,7-8). *Sources:*	Supports - KP6 (coevolution); KP4 (escape constraints); KP2 (quantitative tuning); KP12 (class I display control)	High	Clinical cohort	Historic HLA typing; allele-specific effects; HLA-A/B vs HLA-C specificity and NK inhibition not directly dissected.
[18]	Sequence covariation to define coevolving sectors; structural mapping to identify constrained regions.	Contact-dense sectors overlap control-associated epitopes and restrict escape routes; multi-site constraints highlighted (Fig. 3-4; n not reported). *Source:*	Inferred - topology/contact density limit viable mutations, shaping HLA-peptide-TCR escape (Fig. 3-4). *Source:*	Supports - KP4 (constrained epitopes); KP5 (imprinting on geometry)	Moderate	Molecular/structural	Predictive framework; partial functional validation; alignment dependence.
[47]	Population genetics of HLA-KIR in Chinese Southern Han; admixture, selection, and KIR/HLA typing.	Enrichment of haplotypes encoding multiple KIR ligands; admixture introduced HLA-B*46:01 and B*58:01 under strong selection; 306 typed for KIR/HLA (Fig. 1,4-6; Suppl). *Sources:*	Inferred - increased HLA-Bw4 and HLA-C1/C2 ligand supply strengthens inhibitory KIR licensing, tuning NK thresholds (Fig. 4-6). *Source:*	Supports - KP10 (eco-geographic licensing); KP9 (licensing set-point); KP6 (coevolution)	High	Population genetics	Environmental drivers not pinpointed; East Asian focus; limited direct NK assays in-text.
[61]	Ugandan child cohort; test whether inhibitory KIR ligand carriage associates with malaria prevalence and disease.	HLA-C2: +3.4 percentage points (95% CI 1.0-5.8; $P = 0.006$); HLA-Bw4: +1.7 (95% CI 0.1-3.4; $P = 0.04$); HLA-C1: -2.2 (95% CI -3.9 to -0.4; $P = 0.02$); each additional inhibitory ligand OR=1.31 (95% CI 1.05-1.63; $P = 0.017$); density slope +0.16 $\log_{10}$. Fig. 2-4; Tables S4-S5. *Source:*	Inferred - HLA-C1/C2 and Bw4 tune NK education toward inhibition, elevating parasite burden; quantitative HLA-KIR axis (Fig. 2-4). *Source:*	Supports - KP9 (licensing set-point); KP2 (quantitative tuning)	High	Clinical cohort	Exposure heterogeneity; no direct KIR genotyping; association not causation.
[45]	Define HPV-specific PD-1+ TCF1+ stem-like CD8 T cells and responses to PD-1 blockade and vaccination.	Stem-like HPV-specific CD8 pool expands with PD-1 therapy/vaccination; durable function in HNSCC; detailed in Extended Data Figs. 2-16; numeric n not reported in extract. *Source:*	Direct - TCR-defined stem-like reservoir sustains responses under checkpoint modulation; immunoregulatory axis.	Indirect - KP5 (imprinting); KP7 (regulatory wiring)	Moderate	Clinical cohort	Cancer context; limited KIR/HLA linkage; several quantitative details not reported.
[62]	Compare PTC vs NC after ART interruption; integrate reservoir and immune phenotypes.	CG-trial: $n = 22$ PTC vs 37 NC; PLS-DA AUC 0.91 (95% CI 0.83-0.97; 10-fold CV; Fig. 2A); PTC show lower, steadier CA-RNA/IPDA; NK activation markers track reservoir dynamics (Fig. 3-4); similar HLA-B*57 frequency. *Sources:*	Circumstantial - network-level regulatory set-points correlate with post-treatment control; PD-1/T cell and NK activation axes.	Indirect - KP7 (regulatory wiring); KP5 (postnatal imprinting)	Moderate	Clinical cohort	Heterogeneous cohorts; causality not established; limited direct KIR/HLA analysis.

Table B5 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[36]	Structure-based network analysis of HIV proteins plus ex vivo CTL assays in controllers, intermediates, and progressors to identify mutationally constrained epitopes.	Protective alleles present higher network-score epitopes; controllers target these and have lower viral load (Spearman $\rho = -0.63$, $p<0.0001$; Fig. 3F-H,S8); mutating high-score residues impairs infectivity and spread (Fig. 1F-H).	Direct - topology of pHLA at HLA anchors and TCR contacts constrains escape and preserves CTL recognition (B*57-KF11 vs B*35-DL9, Fig. 2B-D).	Supports - KP4 (constrained epitopes); KP2 (quantitative tuning)	High	Molecular/structural	No KIR mapping; structural coverage drives generalizability.
[6]	Prospective cohorts of acute IM and EBV carriers with longitudinal serology and mAb competition to map EBNA-1 cross-reactivity.	Acute IM (n≈98) yielded persistent EBNA-1 IgG to 12 months; multiple mAbs cross-reacted with CRYAB; DRB1*15:01 associated with stronger responses; figure-level effect sizes not fully visible.	Circumstantial - class II HLA associations and EBNA-1-CRYAB cross-reactivity imply immunoregulatory coupling rather than direct class I-KIR-TCR triad.	Indirect - KP7 (immunoregulatory wiring); KP6 (host-pathogen coevolution)	Moderate	Clinical cohort	Humoral emphasis; limited T cell or NK mechanism; some stats not visible in text snippets.
[50]	Physics-based learning classifier trained on HIV CTL data to predict immunogenic epitopes, then tested on SARS-CoV-2 peptides with ELISpot validation.	AUC 0.71 in acute HIV and 0.66 in chronic; peptide-level weighted Pearson r=0.43 and HLA-grouped r=0.82 against ELISpot (Fig. 1A-B,G-H; Fig. 3A-B).	Inferred - pHLA binding plus similarity-to-self and pathogen capture presentation quality and constraint, shaping TCR engagement.	Supports - KP4 (constrained epitopes); KP2 (quantitative tuning)	Moderate	Molecular/structural	Small SARS-CoV-2 validation; no NK or KIR axis.
[63]	Longitudinal mapping of earliest CTL responses to transmitted-founder virus in acute HIV-1 with viral sequencing and modeling.	Early CTL responses drove rapid escape (median ≈0.14 day^{-1}, up to ≈0.36; Fig. 6); breadth/timing of early CTL associated with viremia decline (Fig. 7).	Circumstantial - CTL pressure induces peptide-specific escape, revealing constraint-dependent durability of pHLA-TCR recognition rather than KIR involvement.	Supports - KP3 (viral subversion); KP4 (constrained epitopes); KP6 (host-pathogen coevolution)	Moderate	Clinical cohort	Modest N; NK pathways not interrogated.
[64]	Prospective infant cohort on early ART with intact provirus quantification and immune phenotyping over time.	Intact reservoir decline correlated with lower HLA-A expression and reduced NKG2A; HLA-B -21M/T influenced HLA-E-NKG2A licensing set-points linked to stronger decline (Fig. 2F-G, Fig. 3D). Exact N not visible.	Inferred - HLA-B leader peptides tune HLA-E display and NKG2A education, shifting NK activation thresholds relevant to reservoir decay.	Supports - KP9 (licensing set-point); KP2 (quantitative tuning)	Moderate	Clinical cohort	Infant-specific physiology; peptide specificity not mapped.
[16]	Functional virology with sarbecoviruses and ORF perturbations to test NK recognition via NKG2D-ligand modulation.	Sarbecoviruses downmodulate MICA/B and other ligands, reducing NK degranulation; ORF6 and Nsp1 are key; restoration or blockade rescues NK responses (e.g., Fig. 3).	Direct - viral proteins downmodulate NKG2D ligands on infected cells, suppressing NK activation at scale; consistent with inhibition-preserving display control.	Supports - KP3 (viral subversion); KP7 (immunoregulatory wiring); KP12 (display control, NKG2D-ligand loss)	High	Functional virology	Focused on NKG2D, not KIR; class I effects are context dependent.
[43]	Clinical and cellular assays comparing HLA-B*35-Px vs -Py impacts on dendritic cell function and downstream T cell priming.	B*35-Px bound inhibitory ILT4 more strongly, increased IL-10, and reduced T cell priming, aligning with faster progression relative to -Py (Figs. 1-3).	Direct - HLA-B allotype-specific engagement of ILT4 increases inhibitory tone and reduces effective CTL priming; may intersect indirectly with NK education.	Supports - KP7 (immunoregulatory wiring); KP2 (quantitative tuning)	High	Clinical cohort	Mechanism centers on ILT4 rather than KIR; peptide dependences vary by allele.

Table B6 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[65]	Narrative review of host genetic HLA-KIR-TCR effects on HIV outcomes.	KIR3DS1 with HLA-Bw4-80I associated with slower progression (relative hazard 0.53, P< 0.001; Fig. 1B); HLA-B*57/B*27 linked to control; highlights HLA-C expression genetics.	Circumstantial - Triad framing of KIR3DS1/3DL1 with Bw4-80I shaping NK education and CTL visibility (Fig. 1-2).	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP7 (immunoregulatory wiring).	Moderate	Review/perspective	Cohort-specific effects; KIR3DS1-Bw4-80I synergy not universal.
[66]	EC vs ART reservoir profiling by near-full-length proviral sequencing and integration-site mapping.	EC n=64 vs ART n=41; intact proviruses depleted and unfavorably positioned in EC (Fig. 1-3); HLA-B*27/B*57 enriched in EC 27.3% vs 8.8% (P=0.0012; Ext. Data Table 1).	Inferred - Protective HLA focuses CTL pressure on conserved epitopes, sculpting a crippled reservoir; no direct KIR readout.	Supports - KP4 (constrained epitopes); KP5 (imprinting on epitope geometry).	High	Clinical cohort	Cross-sectional; comparator HLA not matched; NK axis not assayed.
[67]	TAP-deficient system quantifying stability of 186 optimal epitopes across 18 HLAs; correlated with ex vivo immunodominance.	pHLA stability correlates with immunodominance across donors (r≈0.32-0.67, p< 0.001; Fig. 2C-E, Fig. 3B; Table S3).	Direct - Quantitative pHLA stability (pocket chemistry and peptide quality) tunes CTL activation thresholds.	Supports - KP2 (quantitative tuning); KP4 (constrained epitopes).	High	Molecular/structural	Stability not sole determinant; allele/donor outliers; NK/KIR not tested.
[68]	Functional genetics and structural work dissecting determinants of HLA-C surface expression.	C*05 shows ∼2-fold higher surface expression vs C*07 despite stronger C*07 promoter in luciferase (P< 0.0001; Fig. 1C-F, Fig. 2B-F); exons 2-3 alter peptide repertoire and thermal stability (5-10°C shifts; Fig. 4-7).	Direct - Cis-variation (exons 2-3 and 3′UTR) modulates HLA-C abundance and peptide selectivity, calibrating inhibitory KIR engagement and TCR antigen load.	Supports - KP2 (quantitative tuning); KP9 (licensing set-point).	High	Population genetics	NK functional readouts absent; allele-specific effects; population diversity noted.
[30]	Population-genetic mapping of HLA-associated adaptation in HIV-1 pol with phylogenetic correction.	Numerous HLA-linked polymorphisms mapped in pol across the North American epidemic; explicit modeling of LD and founder effects.	Inferred - CTL-driven escape in pol implies structural and fitness trade-offs consistent with constrained epitopes.	Supports - KP6 (host-pathogen coevolution); KP4 (constrained epitopes).	High	Population genetics	Focus on pol; functional costs partly inferred.
[31]	Nine cohorts (four subtypes) mapping HLA-associated polymorphisms with targeted mechanistic tests.	n=464 participants; 1,140 allele-site tests (median 5.8); 425 adapted residues; subtype-specific nonreciprocal cross-protection; fitness costs validated for select sites (Fig. 1-5; Tables S2-S4).	Inferred -¿ Direct - Genomic mapping of CTL escape with mechanistic validation of fitness and replication costs.	Supports - KP6 (coevolution across subtypes); KP4 (costly escape and topology).	High	Population genetics	Mechanistic assays limited subset; geographic sampling biases; NK axis not profiled.
[69]	Primary-isolate and molecular studies of HIV-1 HLA-C modulation and NK consequences.	Patient isolates downmodulate HLA-C via Vpu; HLA-C MFI reductions track increased NK degranulation and killing (e.g., ∼2-3× CD107a, p< 0.01; Fig. 1-4); KIR2DL blockade restores inhibition.	Direct - Vpu reduces HLA-C, tuning class I display and weakening inhibitory KIR engagement with isolate-specific magnitude; peptide-sensitive KIR effects link triad.	Supports - KP3 (viral subversion); KP8 (NK/CTL pincer); KP1 (triad integration); KP12 (class I tuning, strain-variable).	High	Functional virology	Strain and donor KIR background matter; NK activation in HLA-C-low isolates, not inhibition-preserving; magnitude varies by isolate.

Table B7 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[70]	Statistical-physics model of thymic selection using extreme-value theory to map TCR-pMHC binding energies to repertoire selection; theory paper.	Parameterization consistent with $M \approx 10^3 - 10^4$ self peptides; model delineates regimes where negative vs positive selection dominate and predicts a tunable cross-reactivity set-point (Fig. 2, p. 068103-3).	Direct - TCR cross-reactivity set by thymic selection thresholds over pMHC energy distributions (Fig. 2).	Supports - KP5 (thymic imprinting); KP2 (quantitative tuning)	Moderate	Molecular/structural	Theory only; no NK axis addressed.
[40]	Theory plus human cohorts: prediction that HLAs presenting narrower self-peptidomes (e.g., B*57) select more cross-reactive TCRs; tested in controller vs progressor cohorts.	Two cohorts totaling 1110 controllers and 628 progressors were analyzed to test model predictions (Fig. 1-2); directionally consistent with enhanced control for cross-reactive repertoires; specific effect sizes not reported.	Inferred - HLA-driven thymic selection narrows self-peptide set and biases TCR cross-reactivity/avidity affecting CTL control (Fig. 1-2).	Supports - KP5 (thymic imprinting); KP2 (quantitative tuning); KP4 (constrained-epitope framing)	Moderate	Molecular/structural	Effect sizes not reported; NK/KIR arm not tested.
[71]	Seminar synthesis on HPV+ oropharyngeal cancer epidemiology, biomarkers, prevention, de-escalation, and survivorship; narrative review.	Highlights unmet needs in screening, biomarker development, and treatment de-escalation; numeric cohort outcomes not primary to this summary (pp. 1-7).	Circumstantial - Viral oncoproteins (E6/E7) and tumor microenvironment remodeling imply immune evasion axes; no direct pHLA-KIR/TCR tests.	Indirect - KP3 (viral subversion); KP7 (immunoregulatory wiring)	Low	Review/perspective	No primary mechanistic data; cancer context rather than acute infection.
[72]	Clinical cohort (n=860 women); regression models for baseline viral load and immunologic/virologic response to HAART by HLA motifs/alleles.	Baseline viral load: B*57 $\beta = -0.7$ $\log_{10}$ copies/mL (95% CI -0.9 to -0.5), Bw4 $\beta = -0.2$ (95% CI -0.4 to -0.1). Post-HAART: B*57:01 OR=0.2 (0.0-0.9), Bw4-80I OR=0.3 (0.1-1.0); B*35(Px) OR=2.6 (1.2-5.9) (Tables 2-3).	Inferred - Bw4 (KIR3DL1 ligand) and B*57 associations imply KIR licensing plus CTL specificity co-tune outcomes; quantitative links to viremia and HAART response.	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP9 (licensing set-point)	Moderate	Clinical cohort	Women only; post-HAART directions differ from untreated disease.
[73]	Clinical immunology in ART-naive clade C infection; class II tetramer staining and correlations with clinical markers.	Controllers show higher class II tetramer frequencies than progressors ($P < 0.0001$); in DRB1*11:01, Gag41-specific tetramers correlate with lower viral load ($r = -0.50$, $P = 0.02$) (Fig. 5-6).	Circumstantial - Increased CD4 T-cell help to conserved class II epitopes; no direct pHLA-KIR measurements (Fig. 5-6).	Indirect - KP2 (quantitative tuning); KP7 (immunoregulatory wiring)	Moderate	Clinical cohort	No NK/KIR arm; clade C cohort.
[74]	Comparative genomics and population genetics of KIR3DL3 across catarrhine primates and global human populations.	Ubiquitous KIR3DL3 with 157 CDS alleles encoding 93 allotypes; human D2 shows dN/dS=2.16 ($P < 0.03$); residue 147 dimorphism (I/V) shows trans-species polymorphism and is retained across 80+ populations (Figs. 1, 3-6).	Inferred - Evolutionary conservation of KIR3DL3 binding loops and tail ITIM architecture imply conserved ligand and immunoregulatory role; likely placentation-relevant (Figs. 1, 5-6).	Supports - KP6 (host-pathogen coevolution); KP10 (eco-geographic licensing); KP7 (immunoregulatory wiring)	Moderate	Population genetics	Ligand unknown; functional assays limited.
[75]	Functional virology and immunology with cohort genetics: compare Env-EL9 vs canonical Gag CTL responses; relate HLA-B*14 to control.	EL9 functional avidity $EC_{50} = 0.84\,\mu$M vs Gag-DA9 $20.3\,\mu$M (24-fold, $P < 0.0001$; Fig. 3A); response magnitude 9-fold ($P = 0.003$; Fig. 3B); lower viral loads and higher CD4 counts with wt EL9 (Fig. 6C-E); B*14:02 enriched among controllers (Table 2).	Direct - pHLA-TCR geometry yields exceptional CTL potency; quantitative tuning of antiviral efficacy by HLA-B*14 subtype and epitope (Figs. 3, 6; Table 2).	Mixed - KP2 (quantitative tuning) supports; KP4 (constrained epitopes) mixed (escape costs limited).	High	Functional virology	Env epitope variability; NK/KIR effects not measured.

Table B8 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[76]	Mapped NK-specific regulation of HLA-C with donor-stratified expression and NK functional assays.	NK-specific promoter/enhancer with ETS motif, higher HLA-C on NK cells and reduced CD107a in high-expression donors, p<0.001 (Fig.7B-C); NK subset expression assessed in 16 volunteers.	Inferred - expression-level tuning of HLA-C adjusts inhibitory KIR signaling, consistent with stronger KIR2DL1-mediated inhibition (Fig.7C).	Supports - KP2 (quantitative tuning); KP9 (licensing set-point)	Moderate	Molecular/structural	Allele and motif specific, T-cell arm not directly assayed.
[77]	Proviral sequencing and integration-site profiling in elite controllers versus comparators, assessing epitope footprints.	Intact proviruses in elite controllers are depleted for predicted HLA-I epitopes and show distinct integration-site landscapes (Fig.3-5, Extended Data; N not reported).	Inferred - CTL pressure prunes conserved epitope space in intact proviruses, shifting reservoir composition (Fig.3-5).	Supports - KP4 (constrained epitopes); KP6 (host-pathogen coadaptation)	Moderate	Clinical cohort	Elite-controller biology may not generalize; epitope prediction methods vary.
[78]	Longitudinal reservoir phenotyping and integration-site mapping during long-term ART, including ART interruption.	In 55 long-term treated individuals, reservoir shifts toward central memory with integration-site remodeling; rebound traced to expanded clones (Fig.4-6).	Circumstantial - network-level regulation favors persistence in specific niches, indirectly implicating altered NK/CTL thresholds (Fig.4-6).	Supports - KP7 (immunoregulatory wiring)	Moderate	Clinical cohort	No direct KIR-HLA or epitope-geometry measurements; ART-era specific.
[24]	Allele-specific dissection of KIR2DL2-HLA-C binding with NK functional assays and clinical linkage to HIV-1 control.	KIR2DL2 binds poorly to HLA-C*12:02 and *14:03, with increased NK degranulation and cytotoxicity; allele-dependent differences replicated (Fig.2-3; effect sizes not reported).	Direct - reduced inhibitory KIR2DL2-HLA-C engagement lowers NK activation threshold, enhancing target killing (Fig.2-3).	Supports - KP2 (quantitative tuning); KP9 (licensing set-point)	High	Clinical cohort	Peptide context may modulate KIR binding; allele specificity.
[25]	Systematic test of HLA-A/B/C/G signal-peptide variants on HLA-E loading and CD94/NKG2A/C recognition, with population analyses.	Six of sixteen SP variants functional; HLA-B -21M yields high HLA-E but lowest receptor recognition, competitively reducing CD94/NKG2A engagement; primary NK responses tracked reporter signals (n=8, Fig.3); BLCL panel n=360 linked genotype to HLA-E and recognition; NMDP and 1000G quantified SP distributions and HCMV UL40 VL9 mimic correlations (Fig.4-6, Ext. Data).	Direct - peptide-level competition tunes HLA-E surface and CD94/NKG2 signaling; UL40 VL9 mimic maintains NKG2A inhibition at infection scale (Fig.3-6).	Supports - KP9 (NKG2A bias); KP2 (quantitative tuning); KP3 (viral subversion); KP10 (eco-geographic licensing); KP12 (peptideome engineering)	High	Molecular/structural	Nonadditive SP competition complicates genotype-to-function mapping; NKG2C differs from NKG2A.
[79]	Prospective cohort testing HLA zygosity versus HBV-related HCC by multivariable survival models.	HLA-I homozygosity increased HCC risk (HR 1.36, P trend=0.02); combined HLA-I plus HLA-II homozygosity HR 1.47 (P=0.02); Fig.2 and Table 2 (N not reported in excerpt).	Inferred - reduced peptide-presenting diversity likely dampens CTL and NK cooperation, favoring oncogenesis (Fig.2).	Supports - KP7 (dysregulation risk); KP6 (host-pathogen coadaptation)	Moderate	Clinical cohort	Residual confounding possible; class II role not mechanistically parsed.
[42]	Built a globally diverse HLA panel and applied multi-ancestry imputation to fine-map HIV spVL.	New panel improved imputation across ancestries; fine-mapping identified independent HLA-B residue effects at 97, 67 and 156 in the peptide-binding groove, with stronger mapping in Africans (Fig.2-3; effect sizes not reported).	Inferred - pocket-residue chemistry tunes peptide stability and TCR recognition, linking HLA-B to viral control (Fig.2-3).	Supports - KP2 (quantitative tuning); KP6 (population diversity)	High	Population genetics	Imputation accuracy varies by locus and ancestry; KIR effects not modeled.

Table B9 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[80]	Functional virology using patient-derived Gag chimeras; cohort stratified by HLA-B*57/B*58:01.	T242N emerged in 74% among B*57/B*58:01-positive; chimeras with T242N had 8.5% lower replicative capacity than wild type (0.66 vs 0.72, P=0.016), with compensatory mutations restoring fitness (Fig. 1-3, Table 1).	Direct - CTL-driven escape in B*57/B*58:01-restricted Gag epitope reduces fitness; compensation restores replication (Fig. 1-3).	Supports - KP4 (constrained epitopes); KP6 (host-pathogen coevolution)	High	Functional virology	Fitness cost depends on compensatory background and timing.
[81]	Review of host genetic effects, integrating GWAS, fine-mapping, and eQTLs.	Higher HLA-C expression associates with better control across African and European Americans (Fig. 2a-c; numbers not reported).	Inferred - quantitative HLA-C expression tunes CTL surveillance and possibly KIR thresholds (Fig. 2). ; Circumstantial - Nef and Vpu-modulated class I display consistent with inhibition-preserving NK tone and reduced CTL visibility (KP12, not reported).	Supports - KP2 (quantitative tuning); KP6 (coevolution); KP9 (licensing set-point); KP12 (display control)	Moderate	Review/perspective	Effect sizes and Ns summarized; population heterogeneity.
[19]	Perspective linking epitope network topology to escape routes and control.	Protective HLAs target constrained, contact-dense epitopes where escape is costly; numeric estimates not reported.	Circumstantial - epitope topology constrains viable mutations; Circumstantial - proposes immunodominant non-protective CTL responses as potential decoys without relieving inhibitory KIR engagement (KP11, not reported).	Supports - KP4 (constrained epitopes); KP5 (imprinting on geometry); KP11 (decoy misdirection)	Moderate	Review/perspective	Framework-level claims; variability among B*57 carriers noted.
[82]	Narrative review of HLA and KIR influences on HIV outcomes.	Fig. 6 shows continuum of relative hazards and odds ratios across KIR3DL1 expression with HLA-Bw4; Table 1 summarizes protective vs risk HLA-B associations (numbers not reported in figure text).	Inferred - KIR3DL1-HLA-Bw4 licensing and CTL targeting co-tune protection; quantitative continuum suggests threshold calibration (Fig. 6). ; Circumstantial - summarizes Nef-mediated HLA-A/B downregulation with relative HLA-C sparing and peptideome shifts maintaining inhibitory KIR and NKG2A tone (KP12, not reported).	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP9 (licensing set-point); KP12 (display control)	Moderate	Review/perspective	Allele- and subtype-specific effects; context dependence.
[83]	Large clinical cohort with KIR3DL1 subtype and HLA-B analysis for progression and viral load.	N=1,496; B*57 + KIR3DL1*h/*y reduced risk of CD4¡200 (RH 0.26, P=0.003) and AIDS1987 (RH 0.30, P=0.0005); weaker, nonsignificant effects in KIR3DL1*l/*x; Bw4-80I dependence; viral-load odds ratios declined across KIR3DL1 expression strata (Fig. 2).	Inferred - high-expression KIR3DL1 with HLA-Bw4-80I, especially B*57, strengthens NK education and CTL-NK synergy (Fig. 2).	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP9 (licensing set-point)	High	Clinical cohort	Effect varies by KIR3DL1 expression group; strongest with Bw4-80I and B*57.
[84]	Genome-wide search in B*57+ controllers and noncontrollers, replication, mixed-effects modeling, and binding assays.	KIR3DL1 I47V is the sole genome-wide modifier; validation: 47V 56.9% in controllers vs 47.7% in noncontrollers (P=0.004); in B*57+ subjects, each 47V copy associated with -0.14 $\log_{10}$ VL and +24.88 CD4 cells per microliter (P=4.9e-18 and 1.5e-6); specific to B*57:01 (-0.36 $\log_{10}$ VL per 47V; P=1.7e-67); tetramer binding differed for KIR3DL1*001 vs *015 (Fig. 1-3, Tables 1-3).	Direct - peptide-HLA-B*57:01-sensitive KIR3DL1 engagement varies by positions 2, 47, 54; codominant tuning of inhibition.	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP9 (licensing set-point)	High	Clinical cohort	Effect confined to B*57:01; some 47V carriers are noncontrollers.
[85]	Population-level analysis of HLA-driven viral adaptation in early infection.	Early, population-level escape accumulates at HLA-restricted sites; higher adaptation scores link to poorer control, including among B*57 carriers; hotspots in conserved Gag regions (summary figures; Ns per site not consistently reported).	Inferred - early CTL escape reshapes peptidome visibility and shifts immune balance, consistent with coevolution.	Supports - KP6 (host-pathogen coevolution); KP4 (constrained epitopes)	Moderate	Population genetics	Patterns vary by population and subtype; magnitude depends on local HLA frequencies.

Table B10 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[86]	Does T cell reactivity to Omicron persist after vaccination or infection; activation assays using peptide pools across donors.	Most but not all individuals preserved T cell reactivity to Omicron; a subset showed reduced responses to mutated regions. The attached PDF is a correction noting symbol mislabeling in Fig. 4D-4E; detailed Ns or effect sizes not reported in this file.	Circumstantial - TCR recognition of conserved epitopes with limited impact of spike mutations on pHLA presentation and T cell sensing (Fig. 4D-4E referenced).	Supports - KP4 (constrained epitopes); KP2 (quantitative tuning); KP5 (imprinting)	Low	Clinical cohort	Correction-only PDF, numbers not reported; not all donors preserved responses.
[32]	Trial immunogenicity re-analysis with ICS and statistical modeling to test whether class I HLA predicts Gag-versus-Env targeting.	In combined Black participants (n=155), A*02:02 lower Env ICS (-0.67, P=0.0012, FDR=0.066), B*45:01 lower Env (-0.71, P=0.0036, FDR=0.072), A*33:03 higher Env (0.96, P=0.0039, FDR=0.072), B*57:02 higher Env (1.3, P=0.0057, FDR=0.078). B*57:03 increased CD8 Gag-Env responses (corrected P=0.00025) with ancestry-stratified significance in East African (P=0.006) and South African (P=0.003). White participants (n=81), C*05:01 and B*44:02 associated with higher Gag ICS (P=0.03). Key panels: Fig. 3A-3C, Fig. 4A-4D, Fig. 5B.	Inferred - allele-specific HLA pocket chemistry and peptide binding biases determine quantitative targeting of Gag versus Env by CD8 T cells (Fig. 3-5).	Supports - KP2 (quantitative tuning); KP4 (constrained epitope focus in Gag); KP5 (selection imprinting)	Moderate	Clinical cohort	Effects vary by ancestry and allele frequency; some FDR-adjusted P values near thresholds.
[87]	Biophysical binding, mutagenesis, and functional co-culture assays to identify NKp44 ligands among HLA-DP allotypes.	Soluble NKp44 bound HLA-DP401 with Kd 42.6 ± 16.2 µM (Fig. 1c-1d). NKp44 engagement by HLA-DP401 modulated activation markers and degranulation in NK cells, blocked by anti-NKp44 (Fig. 3g). Peptide content influenced NKp44-HLA-DP interactions, with CTAG1 and HIV-1 Env peptides enhancing NK activation (Extended Data Fig. 4); n≈7 donors (Wilcoxon P=0.008).	Direct - peptide-dependent class II HLA-DP engagement of NKp44 alters NK activation thresholds and effector function (Fig. 1, Fig. 3, Extended Data).	Supports - KP7 (immunoregulatory wiring); KP1 (triad-like cross-talk)	High	Molecular/structural	Active only for subset of DP allotypes; modest affinity; peptide specificity can flip effect.
[88]	Observational cohort with longitudinal single-genome sequencing, integration-site mapping, transcriptomics, and T cell assays.	Eight NSV participants produced 1,987 proviral and 222 plasma sequences; dominant plasma clones with no evolution (Fig. 1-2). Producer proviruses enriched near H3K36me3 and larger than intact reservoirs in ART-suppressed controls (4.3 vs 0.1 per million, P=0.001; Fig. 2). Lower HIV-specific CD8 responses than viremic controllers and no increase versus ART-suppressed (ELISPOT P=0.001-0.02; Fig. 5b). IFN-response genes downregulated (Fig. 4).	Circumstantial - immune dampening and integration near transcriptionally active chromatin permit persistent pHLA with inadequate CTL pressure (Fig. 1-5).	Supports - KP3 (viral subversion); KP7 (dysregulation wiring)	Moderate	Clinical cohort	Small N and heterogeneity; no direct KIR-HLA assays.
[27]	Prospective cohort genotyped for KIR and HLA, testing allele-pair effects, composite scores, and clinical endpoints.	HLA-C*16:01 with KIR2DL3 linked to higher viral load (P=0.02) and lower CD4 (P=0.008) at first visit (Fig. 2-3). Bw4S1 score predicted better outcomes across two populations (Fig. 1). Time-to-event: aHR 1.9 (95% CI 1.1-3.5, P=0.02) for earlier ART or CD4¡200 (Table 3).	Inferred - inhibitory KIR-HLA-C and Bw4-KIR3DL1 signaling calibrate NK thresholds shaping control and progression (Fig. 1-3).	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP6 (population context); KP9 (licensing set-point)	Moderate	Clinical cohort	Ancestry-specific allele structure and LD; some effects reverse by background.
[89]	Topical review linking GWAS signals to mechanistic immunology for HIV control.	Common host variants explain about 25% of set-point viral load variance, with HLA and CCR5 major contributors; HLA-B*57 and B*27 protective, HLA-C expression contributes (Fig. 1-2; p. 489-497).	Inferred - HLA-peptide selection impacts TCR and KIR pathways; expression-level tuning impacts NK education and CTL visibility (Fig. 1-2). Also summarizes Nef and Vpu effects tuning class I display to reduce CTL visibility while preserving inhibitory tone at scale (p. not reported).	Indirect - KP1 (triad integration); KP2 (quantitative tuning); KP6 (coevolution); KP9 (licensing set-point); KP12 (display control)	Moderate	Review/perspective	Cross-cohort synthesis with ancestry and era differences; not new primary data.
[90]	Pooled observational and trial-based analyses testing association between HLA-A*03 and outcomes on PD-1 or PD-L1 blockade.	HLA-A*03 carriers had worse overall survival on anti-PD-1 or PD-L1 therapy (HR about 1.48) and shorter progression-free survival (HR about 1.31); little heterogeneity. No effect with CTLA-4 monotherapy or chemotherapy. Key panels: Fig. 3, Fig. 5.	Inferred - allele-specific immunopeptidome under HLA-A*03 may bias exhaustion thresholds or epitope visibility on PD-1 axis, altering efficacy.	Supports - KP7 (immunoregulatory wiring); KP2 (quantitative tuning); KP5 (selection imprinting)	High	Clinical cohort	Association not causal; therapy-specific signal.

Table B11 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[91]	Longitudinal sequencing and CTL mapping during primary HIV-1 infection; functional CTL assays.	Viral RNA fell from 7.6×10^6 to 7×10^5 copies/mL as an escape variant fixed; CTL clones (n=19 early, n=18 later) lost recognition (Fig. 2-5).	Direct - TCR-peptide-HLA selection of escape (Fig. 2-5).	Supports - KP3 (viral subversion); KP4 (constrained epitopes).	Moderate	Functional virology	Single intensively profiled case; allele/epitope specificity; broader N not reported.
[46]	Structural and functional analysis of HIV-1 epitope length variants; peptide processing, KIR3DL1 binding, CD8 assays.	11-mer variants in B*57 Gag altered pHLA topology, reduced KIR3DL1-Fc binding, and diminished CD8 recognition; magnitudes not reported here (Fig. 2C-2D, 3E, 4C).	Direct - peptide-length-dependent KIR3DL1-HLA-B*57 engagement and TCR recognition (Fig. 2-4).	Supports - KP4 (constrained epitopes); KP8 (NK/CTL pincer).	Moderate	Molecular/structural	HLA/epitope specific; breadth across epitopes not reported.
[41]	Population-scale KIR haplotyping with copy number; breakpoint/phylogeny; $n = 4{,}512$ individuals.	37 haplotypes across 9,024 chromosomes; rare submotifs ∼7% (Table 3); KIR2DL4 deletion ∼2.3%; KIR3DL2 deletion in 38/42 cA01—tB01-del7 (Fig. 2, 5, 7; p. 12-14).	Inferred - KIR gene-content recombination shapes NK education via HLA ligands (Fig. 2, 7).	Supports - KP6 (host-pathogen coevolution); KP10 (eco-geographic licensing).	High	Population genetics	Some ancestries under-represented; 10 singletons unresolved.
[33]	KIR3DS1*014-Fc binding to HLA class I; mutational dependence.	KIR3DS1*014 bound Bw4 (80I) not Bw6; binding was peptide/pocket-residue dependent; key mutations abrogated binding (Fig. 2-4).	Direct - peptide-sensitive KIR3DS1*014-HLA-Bw4 engagement (Fig. 2-4).	Supports - KP1 (triad integration); KP8 (peptide-synchronized pincer).	High	Molecular/structural	Specific to 3DS1*014; binding breadth across Bw4 allotypes/peptides varies.
[92]	HLA-C 3′UTR miR-148a escape variant: expression and population impact.	HLA-C surface MFI increased ∼1.7-2.2-fold; ∼32.8% of chromosomes carry escape haplotypes; event dated ∼3-5 MYA (Fig. 2-3).	Inferred - elevated HLA-C expression calibrates KIR engagement and NK education (Fig. 2-3).	Supports - KP2 (quantitative tuning); KP9 (licensing set-point); KP6 (coevolution).	High	Population genetics	Clinical outcome links are indirect; allele-context dependent.
[44]	Ex vivo donor assays and transductants to define NKp44-HLA-DP regulation of proliferating CD8 T cells.	NKp44 blockade reduced NK degranulation/lysis of proliferating CD8s by ∼30-60% across donors ($n = 32$) (Fig. 3D-3F); NKp44-Fc bound HLA-DP transductants with EC_{50} ∼2.1-4.6 µg/mL (Fig. 2B-2D, 4F).	Direct - NK checkpoint (NKp44) engages HLA-DP on activated CD8s (Fig. 2-4).	Supports - KP7 (immunoregulatory wiring).	Moderate	Molecular/structural	Ex vivo context; antigen specificity and in vivo magnitude may vary.
[34]	HIV cohort genetics with KIR CNV and functional NK assays; models including HLA-B.	KIR3DS1 count inversely associated with set point ($p=4.2\times10^{-6}$; combined $p=2.8\times10^{-4}$); KIR3DL1-surface copy predictive (p=0.020; combined p=0.0085); adjusted model p=0.0075 (Table 3-4). NK inhibition: KIR3DS1 (p=0.007) and 3DS1×3DL1 interaction (p=0.022) (Fig. 2C).	Inferred - KIR3DS1/3DL1 dosage tunes NK thresholds with Bw4-80I synergy (Fig. 2C, Table 3-4).	Supports - KP2 (quantitative tuning); KP1 (triad integration).	High	Clinical cohort	CNVs not allele-resolved; peptide dependence not addressed.

Table B12 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[93]	Clinical cohorts of HIV-1-infected individuals; compound genotype analysis of KIR3DS1 with HLA-B Bw4-80I; viral load set point subset.	KIR3DS1+Bw4-80I reduced OIs (RH=0.58, p=0.004) but not malignancies (RH=1.42, p=0.254) (Fig.1); lower set-point viremia in KIR3DS1/Bw4-80I+ vs others (Ln mean 9.4 vs 10.1; p=0.01) (Table 2).	Inferred - KIR3DS1 with HLA-Bw4-80I synergizes to reduce HIV burden and OIs, implying NK-HLA tuning that affects CTL/NK balance (Fig.1; Table 2).	Supports - KP1 (triad integration); KP6 (host-pathogen coevolution)	Moderate	Clinical cohort	Effect limited to OIs, not malignancies; lacks direct binding data; allele-specific (Bw4-80I).
[94]	Comparative sequencing and phylogeny of HLA-A/B/C promoter regions; expression profiling in donors.	Promoter diversity: HLA-B 1.9%, HLA-A 1.8%, HLA-C 0.9% (LZ divergence). Expression in 178 EA donors (HLA-B) and 215 (HLA-A); promoter groupings track mRNA (Figs.1-2).	Inferred - Promoter/UTR polymorphisms modulate class I expression, tuning thresholds for TCR and KIR via quantity of pHLA (Figs.1-2).	Supports - KP2 (quantitative tuning)	Moderate	Population genetics	Indirect link to NK/CTL function; expression-function mapping not directly shown.
[26]	Multi-cohort regressions linking HLA-A expression eQTLs to HIV viremia and CD4; ex vivo NK/T assays and NKG2A/HLA-E analyses.	Higher HLA-A expression associates with higher VL (slope 0.22 vs 0.06 log10/z, $p_{int}=5.3\times10^{-9}$) and lower CD4 (-37.8 cells/µL per z; $p=5.9\times10^{-94}$). NKG2A+ KIR- degran inversely correlates with HLA-A (r=-0.77, p=0.02); HLA-E correlates with HLA-A (r=0.43, $p=5\times10^{-4}$). (Figs.3-4; Table 1).	Direct - HLA-A-driven HLA-E engagement of NKG2A sets inhibitory tone for NK/CD8, tuning control of HIV (NKG2A blockade; degran assays; Figs.3-4).	Supports - KP2 (quantitative tuning); KP7 (immunoregulatory axis); KP9 (NKG2A-biased licensing)	High	Clinical cohort	Effect sizes vary by -21M/T; observational with mechanistic support.
[95]	High-dimensional ex vivo mapping of NK alloreactivity under missing-self; validation in kidney transplant cohorts (CTOT01, CTOT19).	NKG2A+ KIR- NK cells dominate alloreactivity; subset dominance varies (Figs.3-5). Post-transplant, higher NKG2A+KIR- fraction correlates with lower dd-cfDNA/ABMR (e.g., r=-0.38, p=0.00845; r=-0.33, p=0.0122; r=-0.44, p=0.0283; r=-0.41, p=0.0408; Fig.8). CTOT01 n=70; CTOT19 n=26.	Direct - licensing/education via NKG2A vs KIR quantified by functional assays (Figs.3-5, 8).	Supports - KP1 (triad integration); KP9 (licensing set-point)	Moderate	Clinical cohort	Preprint; immunosuppression and HLA contexts vary across cohorts.
[96]	CyTOF/flow of recipient NK repertoires at baseline and during ABMR; clustering and association to graft outcomes.	Baseline n=50; ABMR n=76. NKG2A/KIR-defined clusters associate with antibody-independent dysfunction; correlations with function/eGFR: r≈-0.38 (p=0.0086), r≈-0.36 (p=0.0208), r≈-0.45 (p=0.023), r≈-0.41 (p=0.041) (Fig.4).	Direct - NK subset architecture (NKG2A/KIR) indicates quantitative licensing set-points linked to injury (Fig.4).	Supports - KP9 (licensing set-point); KP7 (regulatory wiring in tissue injury)	Moderate	Clinical cohort	Cross-sectional elements; therapy confounding possible.
[28]	Case-control analysis testing HLA class I alleles vs Mtb strain causing disease.	Protective allele HLA-B*15:03 (OR 0.46, p=0.0004); susceptibility HLA-B*58:02 (OR 7.39, $p=1.1\times10^{-5}$) and HLA-C*06:02 (OR 5.06, $p=2.76\times10^{-5}$). N=636 (424 cases, 212 controls). (Table 2).	Inferred - class I polymorphisms shape epitope presentation to CTL/NK, associating with infecting Mtb lineages (Table 2).	Supports - KP6 (host-pathogen coevolution)	Moderate	Population genetics	Population structure/exposure may contribute; mechanistic epitopes not shown.
[17]	Multi-omic tumor profiling (scRNA-seq n=8, flow n=25, IHC) plus functional blockade and survival analyses.	HLA-I LOH in TCGA BLCA: 21.8%. NKG2A+ CD8 T cells show TCR-independent, DNAM-1-mediated cytotoxicity restored by NKG2A blockade; $KLRC1^{high}$ associates with better survival under anti-PD-L1 (Figs.2, 6-7).	Direct - HLA-E-NKG2A inhibitory axis gates CD8/NK effector programs; checkpoint reversal restores function (Figs.2, 6-7).	Supports - KP7 (immunoregulatory axis); KP9 (NKG2A-biased licensing)	High	Clinical cohort	Benefit restricted to CD8A/PD-1-high strata; tumor HLA-E heterogeneous.

Table B13 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[97]	Comparative genomics and primate phylogeny of KIR; resequencing and NK expression.	An inhibitory KIR (KIR3DL0) conserved across primates for ~50 My; NKp46^{+} expression; resequencing in 86 unrelated individuals (Figs.1-4).	Inferred - KIR lineage architecture underpins HLA class I-KIR education thresholds (Figs.1-4).	Supports - KP6 (host-pathogen coevolution); KP10 (eco-geographic licensing)	Moderate	Population genetics	Species differences and lineage-specific expansions; no direct pHLA-KIR binding.
[98]	Multi-cohort clinical genetics testing whether KIR2DL2 modifies HLA class I associations.	KIR2DL2 altered both protective and detrimental HLA class I effects on outcomes (Figs.2-4).	Inferred - inhibitory KIR2DL2 with HLA-C1 peptides modulates NK set-points and CTL interplay.	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP7 (regulatory wiring)	Moderate	Clinical cohort	Allele- and infection-context specific; mechanism not directly shown.
[99]	Review of HIV host genetics across candidate and GWAS eras.	Strongest GWAS signal at HLA-B*57; upstream HLA-C variant associates with higher expression and control; KIR/HLA combinations and KIR3DL1/3DS1 copy-number link to control in presence of HLA-B ligand.	Circumstantial - peptide presentation and ligand abundance tune CTL and NK axes; epitope mutations can alter KIR-HLA binding.	Supports - KP2 (quantitative tuning); KP4 (constrained epitopes/fitness); KP6 (coevolution); KP12 (class I display control)	Moderate	Review/perspective	HLA-C expression link debated; some acquisition GWAS underpowered.
[21]	Global survey of KIR gene content and HLA ligands; correlation analyses.	Population correlations between KIR and matching HLA ligands indicate coevolution; geographic structure consistent with balancing selection (stats not reported here).	Inferred - matched global clines imply selection on the HLA-KIR axis.	Supports - KP6 (host-pathogen coevolution); KP10 (eco-geographic licensing)	High	Population genetics	Correlations are indirect; molecular mechanisms not specified.
[100]	Flow cytometry and functional assays linking HLA-C surface levels to NK subsets in healthy (n=154) and HIV (n=28).	Higher HLA-C expression associated with fewer CD56^{neg} NKs ($r \approx -0.43$, Fig.2B) and reduced proportions of certain KIR^{+} subsets ($r \approx -0.27$, Fig.3D); patterns observed in HIV cohort.	Inferred - ligand abundance tunes inhibitory KIR signaling and NK education (Figs.2-3).	Supports - KP2 (quantitative tuning); KP9 (licensing set-point)	Moderate	Clinical cohort	Correlational; subset- and status-specific effects; adjusted p-values variably reported.
[101]	HLA-DR tetramers to enumerate and phenotype Mtb-specific CD4^{+} T cells longitudinally.	Stable tetramer^{+} frequencies, Th1-biased cytokines, and defined memory/activation states; clonal tracking over visits (e.g., Fig.1F-J, Fig.2).	Circumstantial - constrains class II epitope geometry and TCR imprinting rather than HLA-I/KIR.	Indirect - KP5 (thymic/postnatal imprinting); KP7 (regulatory wiring)	Moderate	Clinical cohort	Focus on HLA-II CD4 responses; no direct HLA-I/KIR data.
[7]	Structural and functional tests of how HLA-B pocket residues affect peptide-dependent TCR and KIR engagement.	Residues 97, 67, 156 tune peptide conformation/stability and differentially modulate TCR vs KIR binding; specific 11-mer peptides created cross-reactive KIR recognition while preserving CTL visibility (Figs.1-3).	Direct - peptide-dependent pHLA-B geometry jointly controls TCR and KIR engagement.	Supports - KP1 (triad integration); KP2 (quantitative tuning); KP8 (peptide-synchronized detection); KP11 (decoy diversion)	High	Molecular/structural	Peptide- and allele-specific effects; generalizability varies across HLA-B allotypes.

Table B14 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[102]	Multi-cohort GWAS of HIV-1 control with fine-mapping to HLA amino acids; discovery/replication cohorts (n≈974 controllers; n≈2,648 progressors).	Four independent MHC SNPs (plus CCR5) explain 23% of viremia variance; HLA-B*57 OR=5.1; rs9264942 (HLA-C) OR=2.9; HCP5 OR=3.6; ZNRD1/RNF39 OR=2.0 (Table 1). HLA-B aa 97/70/67 associate with control and with $\log_{10}$ set-point VL (Fig. 3A-C).	Inferred - pocket residues at HLA-B 97/70/67 tune peptide presentation and TCR recognition.	Supports - KP2 (quantitative tuning); KP6 (host-pathogen coevolution).	High	GWAS	HLA-B-dominant signals; residual LD may reflect linked effects.
[103]	Allele discovery + flow cytometry of KIR3DL1 expression; mutagenesis to test determinants.	Novel KIR3DL1 alleles define high/low/null expression; e.g., *053 low vs. *005/*015; intracellular retention for *028/*053; promoter variants not explanatory (Fig. 4-5).	Direct - KIR3DL1 allotype-determined surface density calibrates inhibitory signaling to Bw4.	Supports - KP2 (quantitative tuning).	Moderate	Molecular/structural	Allele-specific; functional killing against Bw4 not shown.
[10]	Variant mapping of -35C/T upstream of HLA-C; flow assays; clinical associations.	-35C associates with higher HLA-C surface expression (clone counts; Fig. 2a) and improved HIV control (Table 1); allele-specific expression in heterozygotes (Fig. 3).	Inferred - increased HLA-C expression enhances KIR2DL1/2/3 ligation and CTL display.	Supports - KP2 (quantitative tuning); KP9 (licensing set-point).	High	Population genetics	Contribution of NK vs. CTL not separated; effect sizes vary by cohort/allotype.
[104]	Controllers (n≈37) stratified by KIR3DL1-Bw4 genotype; NK/T-cell functional assays.	Protective KIR3DL1*h + Bw4-80I shows higher NK cytotoxicity and IFN-γ vs. nonprotective genotypes; NK inhibition inversely correlates with HIV-specific CD8 responses ($\rho = -0.8321$, $P = 0.001$; n=12) (Fig. 1-2).	Direct - peptide-HLA-Bw4 engagement of educated KIR3DL1*h NK cells enhances effector function.	Supports - KP1 (triad integration); KP2 (quantitative tuning).	Moderate	Clinical cohort	Modest n; controller-enriched; causality inferred.
[105]	Trans-ancestral MHC fine-mapping for HCV clearance.	HLA-DQβ1 residue 26 (Leu) and related pocket residues explain spontaneous clearance across ancestries (Fig. 2; Table 1).	Inferred - DQβ1 pocket chemistry tunes CD4 TCR help and antiviral effectiveness.	Supports - KP2 (quantitative tuning); KP6 (coevolution across ancestries).	High	Population genetics	Class II focus; NK/KIR implications indirect.
[13]	TAPBP eQTLs with malaria outcomes; HLA effect modification.	Higher TAPBP eQTL associates with lower incidence (IRR=0.89, q=0.017) and symptom reduction (OR=0.84, q=0.016) in specific HLA contexts; replication across cohorts (Fig. 3-4).	Inferred - tapasin levels reshape peptide loading/editing and class I display.	Supports - KP2 (tapasin tuning); KP9 (licensing set-point).	Moderate	Population genetics	HLA-dependent modification; peptide-repertoire shifts not directly measured.
[106]	Population mapping of HLA-associated escape/reversion and link to acute-phase targets.	76 HLA-associated mutations (Gag/Pol/Nef); 71% with reversion (Fig. 1-2). For acute-phase targets, residue conservation inversely correlates with HLA relative hazard (R=-0.565, P=0.028; improves to R=-0.775, P=0.0019 after outlier removal); compensatory routes (e.g., B57 TW10 T242N with H219Q/M228I) (Fig. 4-5; Table 2).	Direct - CTL pressure on constrained epitopes forces costly escape with compensation.	Supports - KP4 (constrained epitopes); KP6 (coevolution).	Moderate	Clinical cohort	Subtype B chronic infection emphasis; structural constraints inferred from conservation/covariation.

Table B15 Summary of literature review for Keystone Theory synthesis.

Ref.	Core question/approach	Key findings	Mechanistic link	Keystone assessment	Confidence	Evidence type	Contradictions/nuance
[107]	Case-control KIR and HLA genotyping in CVID-spectrum, logistic models.	n=175 cases, ¿2000 controls; 2DS1 OR=1.45 (p=0.03), 3DS1 OR=1.54 (p=0.01), 2DL5 OR=1.43 (p=0.04); 3DS1+Bw4-80T OR=1.79 (p=0.002); 2DL1+C2 protective OR=0.58 (p=0.002); 2DL3+C1 homozygous OR=1.88 (p=0.002). Fig. 1, p. 5; Table 1, p. 6.	Inferred - KIR-HLA receptor-ligand balance tunes NK thresholds, weaker inhibition and activating KIR tilt toward risk; strong 2DL1+C2 inhibition is protective.	Supports - KP2 (quantitative tuning); KP7 (immunoregulatory wiring); KP9 (licensing set-point).	Moderate	Clinical cohort	European ancestry only; grouped phenotypes; some nominal associations; needs replication; Bw4-80T effect differs from prior AIDS context.
[49]	Pooled GWAS-imputed HLA zygosity across 25 studies; subtype-specific trend tests.	DLBCL: class I per-locus OR=1.11 (p-trend=0.0008, FDR=0.003); B/C joint homozygosity OR=1.31 (1.06-1.60); DRB1 homozygote OR=2.10 (1.24-3.55). FL: class II per-locus OR=1.24 (p-trend¡1e-4, FDR=5e-4); fully homozygous OR=1.89 (1.37-2.61). MZL: B OR=1.34 (1.01-1.78), C OR=1.33 (1.04-1.70), DRB1 OR=1.45 (1.12-1.89). CLL/SLL modest, per-locus OR=1.05 (p-trend=0.029). Tables 2-3, pp. 5-8.	Inferred - Reduced HLA diversity narrows CTL-visible peptidome, shifting activation thresholds; locus-specific effects at B/C and DRB1 indicate quantitative tuning.	Supports - KP2 (quantitative tuning); KP7 (dysregulation risk).	High	GWAS	European-only; HLA imputed not typed; subtype heterogeneity; some trends borderline.
[23]	Two GWAS cohorts with allele-specific LILRB2-HLA-B binding scores in stepwise and multivariate models.	Discovery OR=0.44 (0.28-0.68), p=2.33e-4; replication OR=0.50 (0.32-0.80), p=3.43e-3; combined OR=0.41 (0.30-0.55), p≈2.3e-9; LILRB2 overexpressed in lesions (fold 2.2-2.39, adj. p≤1.0e-9). Tables 1-2, p. 1293; Suppl. Table S2, p. 1295.e3.	Inferred - Stronger inhibitory HLA-B-LILRB2 engagement on APCs lowers psoriasis risk by dampening T-cell priming; quantitative, HLA-B specific.	Supports - KP2 (quantitative tuning); KP7 (immunoregulatory wiring).	Moderate	GWAS	Binding scores external to cohort; effect HLA-B specific; LD with HLA-C*06:02; mechanism not directly tested in patients.

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