A geometric criterion links HIV-1 capsid topography to its biophysical properties and function

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Abstract

Mathematical models of virus capsid structure are pillars of modern virology, aiding the understanding of viral mechanisms and the design of antiviral interventions. Traditionally, the HIV-1 capsid core geometry is represented as a fullerene lattice, akin to the icosahedral models of spherical viruses in Caspar-Klug theory. However, recent studies revealed that many viral capsids deviate from such idealised lattices, with important functional implication. Here we demonstrate that this is the case also for the conical HIV-1 core geometries, in which the hexamer and pentamer boundaries form a pseudo-tiling rather than a perfectly aligned fullerene network. We introduce a triangular geometric criterion that quantifies local deviations of an HIV-1 atomic model from its idealised fullerene backbone. Using this criterion, we demonstrate that this difference in geometric organisation between idealised (fullerene) and actual (data-derived) capsid model has implications for the capsid's biophysical properties. We also discuss the use of the geometric criterion as a predictive tool regarding cofactor binding, exploiting its correlation with local curvature and topography. Our results establish a quantitative framework linking capsid geometry, curvature, and biophysical function, offering new perspectives for assembly inhibitor design and lentiviral vector engineering.

Introduction

The human immunodeficiency virus type 1 (HIV-1) is the predominant cause of the global HIV epidemic and acquired immunodeficiency syndrome (AIDS)[1–3]. During viral infection and replication, its protein shell, or capsid core, performs essential functions including encapsulating and shielding the viral genome from degradation, serving as a reaction vessel for reverse transcription, and facilitating its trafficking and nuclear import[4–7]. Due to these important roles, the capsid has become a central target for antiviral drug design[6–9]. On the other hand, HIV-based lentiviral vectors are also exploited as delivery systems for gene therapy applications, to treat genetic diseases, primary immunodeficiencies and cancers[10–13]. A better understanding of the biophysical properties and (dis)assembly mechanisms of the capsid core is therefore crucial for both antiviral and therapeutic applications.

As structure and function are intertwined, the mathematical modelling of viral capsid structure plays a significant role in virology. Unlike the abundant spherical viruses exhibiting icosahedral symmetry, the HIV-1 capsid has a distinct conical morphology (Fig. 1) composed of approximately 200 hexamers and 12 pentamers. The spherical capsid models from Caspar-Klug theory are a primary tool to classify and understand virus structure[14,15]. However, recent analyses show that many spherical viral shells deviate from these idealised lattices, with important functional consequences[16]. For example, different viruses with the same number of capsid proteins, that would traditionally be represented by the same hexagonal lattice architecture in Caspar-Klug theory, can have very different biophysical properties in terms of their resilience to fragmentation depending on their actual surface lattice type and relative orientation of their capsid proteins[17].

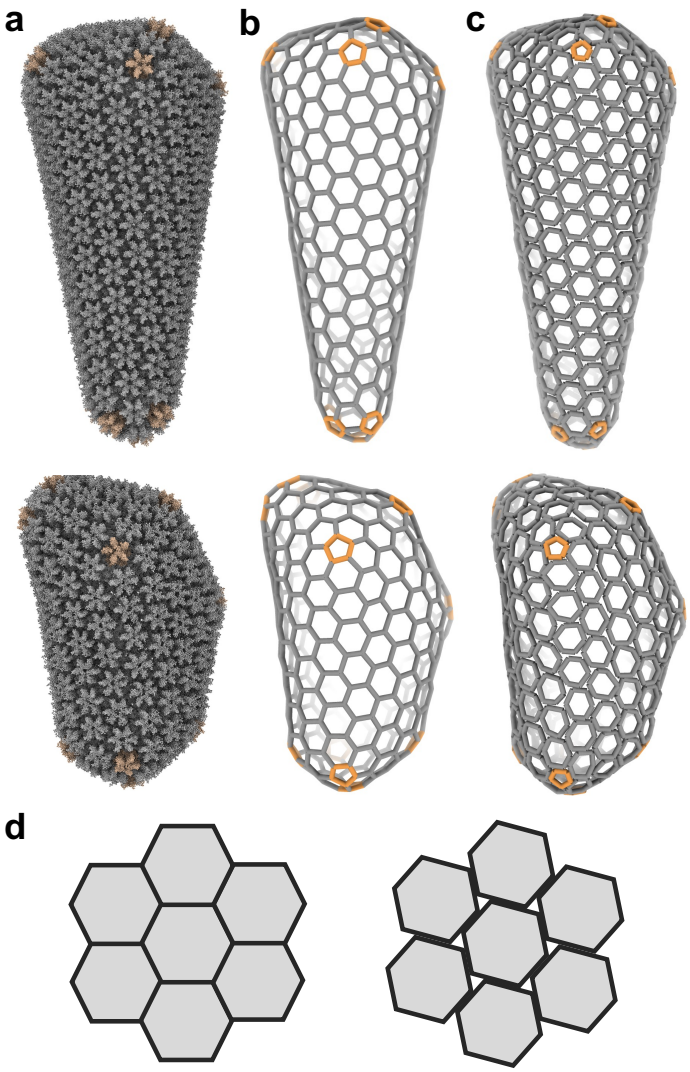

Fig. 1 | Comparison of an idealised, fullerene-style representation with the actual capsid geometry for two HIV-1 cores. a, Experimentally derived atomic models of the HIV-1 capsid (*vlp23* (top) and PDB: 3J3Y (bottom)). **b**, A fullerene-style representation of capsid geometry. **c**, Capsid geometry derived from the atomic positions of the CA hexamers and pentamers. **d**, Schematic representation of the discrepancy in geometric organisation between **b** and **c** (left: the fullerene/hexagonal lattice; right: the pseudo-tiling formulated by the profile of CA hexamers). CA hexamers and their respective geometric representations are coloured in grey while pentamers are coloured in orange.

By analogy, the HIV-1 capsid structure has standardly been represented over the past decades by an idealised fullerene or hexameric lattice containing pentameric insertions [18–21]. Yet, the imperfect alignment between adjacent hexamers/pentamers suggests that an alternative model[16,17] may be required to better capture its surface architecture (Fig. 1). To examine this, we compare three geometric frameworks: the fullerene lattice (a regular hexagonal network with 12 pentagonal insertions); the Kagome lattice (a rotated hexagonal

and pentagonal arrangement forming interlaced triangles); and a data-derived lattice constructed directly using the atomic positions of an identical residue (as explained below) to reproduce the actual orientations of the hexameric and pentameric lattice units. In contrast to the fullerene lattice, the data-derived lattice explicitly incorporates the triangular gaps between the capsomers. We demonstrate that this difference in geometric representation has consequences for how well the geometric model aligns with the biophysical properties of the HIV-1 capsid, such as those quantified via molecular frustration computations. This implies that choosing the correct geometric representation is paramount to best capture capsid functionality.

Advances in computational biology and cryo-electron microscopy (cryo-EM) have enabled atomistic reconstructions of entire HIV-1 capsids (Fig. 1a) following different modelling routines[20,22]. Such atomistic models are essential steps, in combination with experiment, in better understanding the mechanisms underpinning viral life cycles[23–25]. In addition, computer simulations identify capsid assembly and maturation pathways in agreement with *in vitro* maturation data[26–28], revealing the formation of a curled sheet in the bulk of the capsid as an intermediate step. Seam lines in the lattice architecture of the mature cone may originate from the junctions of these curled sheets. This suggests that local curvature and lattice geometry play a pivotal role in capsid function. However, the quantitative characterisation of CA lattice geometry – and its impact on the function of the conical HIV-1 capsid – remains underexplored. A previous study introduced three orientations of hexamers with high, intermediate, and low curvature in a tubular surface lattice[29]. Yet, describing curvature within the asymmetric conical lattice is considerably more complex. Although areas surrounding pentamers display higher curvature as expected, the overall lattice lacks simple geometric

regularity: adjacent capsomers exhibit tilting and twisting relative to one another[30], and individual capsomers possess intrinsic curvature themselves[31].

Here, we introduce a local geometric criterion that quantitatively characterises the arrangement and deformation of the conical HIV-1 surface lattice. We first demonstrate that the geometric properties of different carbon-fullerene cone structures, as captured by the geometric criterion, correlate strongly with their energy landscapes. We then extend this framework to the HIV-1 atomic model, linking geometric and biophysical properties of the capsid. Our analysis reveals that only the data-derived lattice model accurately reproduces the potential seam line location and associated molecular frustration patterns observed experimentally. By computing molecular frustration[32,33] at dimer interfaces, we demonstrate that regions of high frustration align with the seam line exclusively in the data-derived lattice, highlighting the importance of the choice of lattice representation in a coarse-grained model. We also show that the geometric criterion distinguishes between capsids reconstructed via different protocols, indicating that assembly history may imprint characteristic geometric signatures on the capsid lattice, that can be quantified by the geometric index introduced here.

To demonstrate the predictive power of our geometric index, we extend our analysis to host cofactor and small molecule binding. Cofactors such as cytoplasmic cyclophilin A (CypA)[34,35], and small molecular weight compounds like lenacapavir (LEN)[36–38] interact with specific surface sites of the CA lattice. It has been suggested that such binding sites may depend on local geometric features of the surface lattice[31], but this association has not yet been made precise. We demonstrate here that the geometric criterion correlates with local curvature and captures the site-specific geometric responses to cofactor or small molecule binding at the

two primary binding sites[39–41]. Binding at the CypA site induces a local increase in curvature, whereas binding at the phenylalanine-glycine (FG)-motif pocket produces an opposing flattening effect. These contrasting behaviours reveal a direct link between local geometry, curvature modulation, and cofactor function, suggesting that HIV-1 exploits surface topography to regulate its structural dynamics and life cycle.

Results

The geometric index of hexagonal surface lattice architectures. To quantify the geometric organisation of a hexagonal surface lattice architecture such as a fullerene cone, we introduce a triangular geometric index that captures local topographic features. As illustrated in Fig. 2a, a characteristic triangle (purple dashed lines) is initially defined at any threefold axis surrounded by three regular hexagons. Because hexagons in fullerene cones are typically distorted as they are part of a surface lattice, we also constructed analogous characteristic triangles at each local threefold axis of a fullerene cone (Fig. 2b & 2c). For each triangle, the shortest edge is highlighted in green. Its length and orientation in the surface lattice indicate the directions of maximum lattice compression. These shortest edges tend to align in the surface lattice, revealing local patches where hexagons are deformed collectively in a consistent direction to form smooth sheets. We therefore refer to the shortest edge at each local threefold axis as the geometric index, and its definition below will therefore capture both the length and the orientation of the shortest edge.

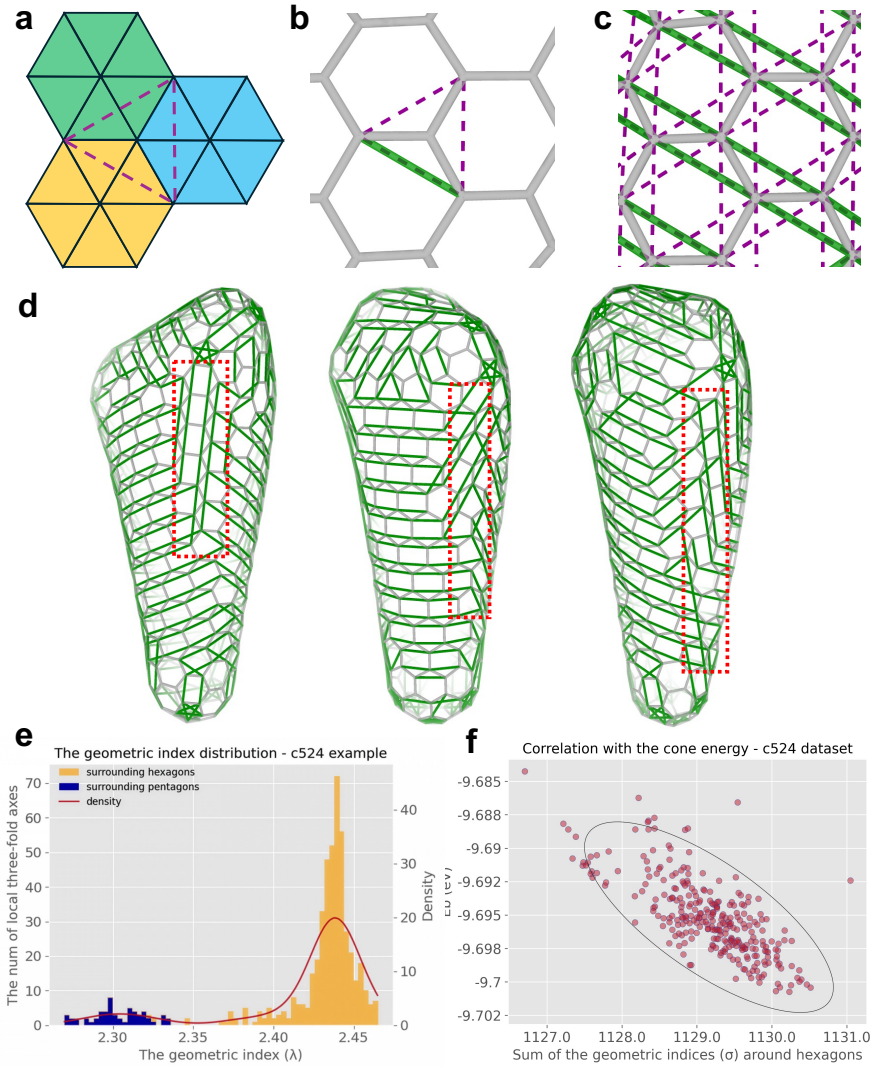

Fig. 2 | The characteristic triangle and the geometric index applied to the fullerene-lattice representation. **a**, A characteristic triangle (purple dashed lines) at a threefold axis surrounded by three regular hexagons. **b**, A characteristic triangle at a local threefold axis of a fullerene lattice (light grey solid lines), where the shortest edge (i.e., the geometric index) is highlighted in green. **c**, The characteristic triangle and its geometric index are extended to each local threefold axis of a fullerene lattice. **d**, The geometric indices (green lines) on the surface of a fullerene cone (C_{524} dataset). The geometric indices partially align, forming local sheets. These sheets are jointed together at seams (highlighted by red dashed frames). **e**, The distribution of the geometric indices across the cone in **d**. **f**, The sum of the geometric indices surrounding hexagons correlates with cone energy (shown here for cones in the C_{524} dataset).

For a fullerene cone model containing m vertices, representing the positions of the carbon atoms, each local threefold axis is labelled by $i \in I = \{1, 2, \ldots, m\}$. The magnitude of the geometric index at the ith local threefold axis is then defined as

$$\lambda_i := \min_{j \in \{1,\ 2,\ 3\}} l_{ij}, \qquad (1)$$

where l_{ij} denotes the length of the jth edge of the characteristic triangle. The orientation of the geometric index is defined as a bidirectional unit vector $\overleftrightarrow{v}_i$ pointing along the corresponding shortest edge. The complete set of geometric indices is therefore

$$\Lambda := \{(\lambda_i, \overleftrightarrow{v}_i) | i \in I\}, \qquad (2)$$

in which each element encodes both the local amount (λ_i) and the direction ($\overleftrightarrow{v}_i$) of lattice deformation.

Building on prior work[20] where fullerene models serve as structural backbones for HIV-1 capsid reconstruction, we generated carbon-based fullerene cones using the dedicated Fullerene program[42–45], followed by quantum tight-binding density functional theory (DFT) energy optimisation and capsid structure determination (see Methods). The Fullerene program was used to generate fullerene models of the HIV-1 capsid by adjusting ring spiral pentagon indices (RSPIs) in small increments. Modified input files were tested for validity based on carbon count and RSPI rules, with parallel searches identifying a small set of valid candidates. Three datasets of cone fullerene structures were constructed with 352 (C_{352}), 452 (C_{452}), and 524 (C_{524}) carbon vertices, respectively. Structural polymorphism within each dataset arises from variations in the positions of pentagons at both ends of the cone.

To examine how the geometric organisation of fullerene structures relates to their intrinsic energy, we mapped the geometric indices onto the surfaces of the computational models. Representative examples from C_{524} and C_{352} are shown in Fig. 2d and Supplementary Fig. 1a, respectively. Green lines denote geometric index directions, which partially align to form local sheets separated by seam lines. Typically, two to three seams appear in the bulk of each cone, joining adjacent sheets (red dashed frames). The distribution of the scalar component of the geometric index (its length) is bimodal in both examples (Fig. 2e and

Supplementary Fig. 1b). The indices computed at threefold axes surrounding pentagons (blue histograms in Fig. 2e and Supplementary Fig. 1b) are typically smaller than those around hexagons, indicating that the diagonals of the pentagons are generally shorter than those of the hexagons. Notably, the sum of the geometric indices $\sigma = \sum_{i \in I} \lambda_i$ for each cone is strongly correlated with the intrinsic energy of the structure E_b (Fig. 2f and Supplementary Fig. 1c), highlighting the role of the local geometric organisation in determining the overall energetic landscape of the fullerene cones.

Distinct topographies revealed by the geometric indices across HIV-1 capsid models. To compare the geometric organisations of different HIV-1 capsid models, we constructed three geometric representations based on the capsid atomic model *vlp23*[22]: a fullerene, a Kagome, and a data-derived surface lattice with vertices derived from the atomic positions of an identical residue in the dataset (see Methods). The basic lattice building blocks are shown in Fig. 3a-c (left), where black dots represent the vertices of the fullerene lattice, and grey dots those of the Kagome lattice. Coloured hexagons of equal size indicate the orientations of the hexagonal units in each lattice, with characteristic triangles outlined by purple dashed lines. The data-derived lattice can be considered an intermediate structure between the fullerene and Kagome model: the hexagons and pentagons in the Kagome lattice are rotated by ~30° relative to those in the fullerene lattice, while those in the data-derived lattice (Fig. 3c & 3d) exhibit an intermediate rotation – less than 30° – positioning them geometrically between the two idealised lattices.

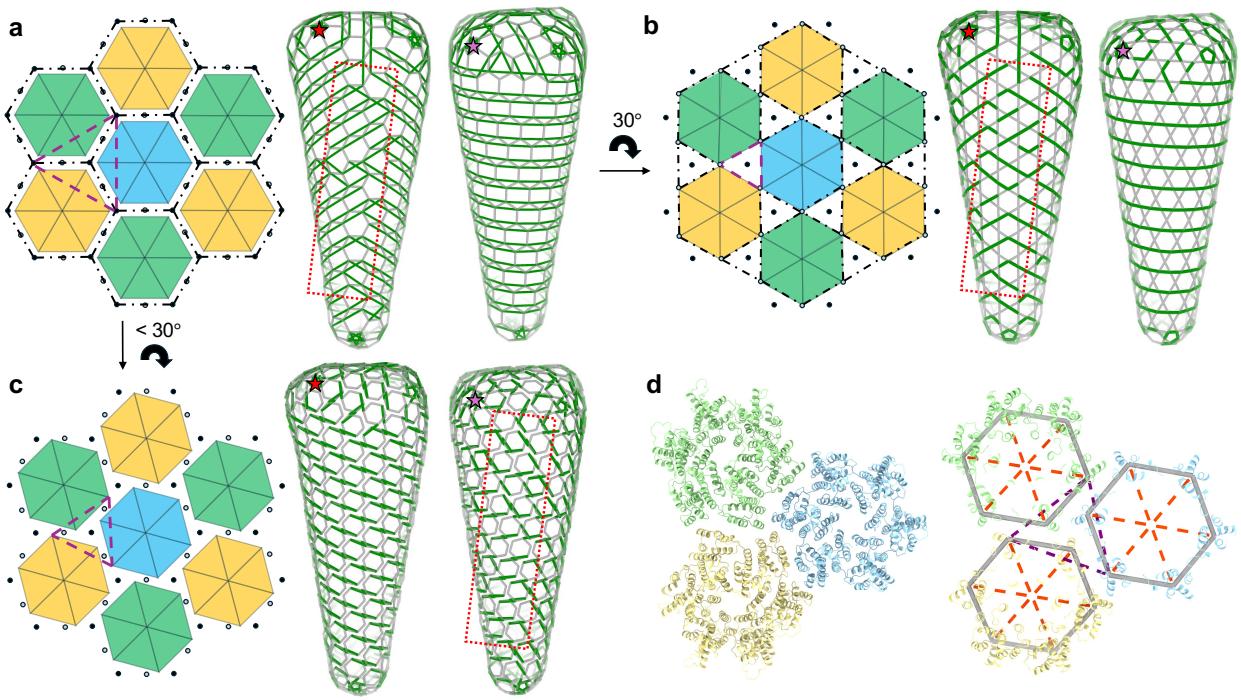

Fig. 3 | The distinct topographies of different HIV-1 capsid models, revealed by their geometric indices, in comparison. a, Left: The characteristic triangle of a fullerene-style lattice (purple dashed lines). Right: the reconstructed fullerene lattice for *vlp23* (see also Supplementary Fig. 3 & 5). A seam line in the bulk is indicated by a red dashed box. A pentamer is labelled by a red star for reference to the other cases. **b**, Left: The characteristic triangle for a Kagome lattice model, where each hexagon is rotated by 30° about the centre of the original hexagon in **a**. The characteristic triangles (purple dashed lines) correspond to the triangular gaps produced by such rotations between three mutually adjacent hexamers. Right: the reconstructed Kagome lattice for *vlp23* (see Supplementary Fig. 3 & 5). A seam line, located on the same side as in **a**, is indicated by a dashed box. **c**, Left: a pseudo-tiling mimicking the actual organisation of the CA hexamers; it is a geometry in between a fullerene and Kagome lattice, with hexagons rotated by less than 30°. The characteristic triangles (purple dashed lines) are of intermediate size compared with the other scenarios, with vertices situated between the fullerene (black dots) and Kagome lattice (grey dots). Right: the corresponding lattice geometry; the seam line in the bulk is on the opposite site compared with the other cases as can be seen with reference to the pentamer labelled by a light purple star. **d**, Left: three hexamers shown in different colours. Right: the profile of these three hexamers (light grey hexagons), constructed using N195 C_α. Orange dashed lines correspond to the diagonals, and the purple dashed lines indicate the characteristic triangle.

Side views of the three capsid models are shown in Fig. 3a-c (right), where the red and the purple stars mark the positions of pentamers on opposite sides of each structure. The geometric index orientations $\overleftrightarrow{v}$, represented by green lines, delineate the surface topography of each model. As indicated by the red dashed boxes, the seam lines identified by the geometric indices occur on the same side of the fullerene and Kagome surface lattices (red star) but are located on the opposite side in the data-derived model (purple star). This demonstrates that distinct geometric models produce markedly different surface

topographies, even when modelling the same capsid, and the geometric index provides a robust descriptor for capturing such differences. In subsequent sections, we correlate the topography encoded by the geometric index with the capsid's biophysical properties in support of the hypothesis that the data-derived model is a more accurate geometric representation.

Correlation between capsid topography and molecular frustration at dimer interfaces. To probe the local biophysical properties of the HIV-1 capsid, we extended the concept of molecular frustration from the Protein Frustratometer[32,33] to evaluate all interactions/bonds involving H9 helices at dimer interfaces. Briefly, the frustration level of a bond between two residues *i* and *j* is expressed as a minus Z-score, quantifying how favourable the native interaction is compared to a set of alternative (non-native) interactions. High local frustration often coincides with regions critical for binding or allosteric transitions. In the original approach, the frustration level of a residue is derived from the proportion of highly, neutrally, or minimally frustrated bonds surrounding it. Here, we generalised this concept to define the local frustration γ_i at the ith dimer interface (see Methods).

Fig. 4a (Movie 1) illustrates the reference frustration pattern as a baseline for a representative CA dimer interface (PDB: 2KOD). Dashed lines denote the interactions involving H9 helices, with red marking highly frustrated, green minimally frustrated, and grey neutral bonds. Representative interfaces of hexamers with the lowest and highest local frustration levels in *vlp23* are shown in Figs. 4b & c (Movie 2 and 3), respectively. Interfaces with high frustration exhibit a larger gap between the H9 helices and fewer interfacial bonds, whereas low-frustration interfaces show tighter helix packing and more bonds. This inverse correlation between bond number and local frustration is quantified in Fig. 4f. The distribution of

frustration levels across all dimer interfaces in *vlp23* is summarised in Fig. 4e, where the black arrows (a-c) point to the frustration levels of the interfaces in Fig. 4a-c. Interfaces with the top 50 highest frustration values are highlighted in red, and the next 51-100 in purple. The corresponding interfaces are mapped onto the capsid structure as coloured spheres (Fig. 4d).

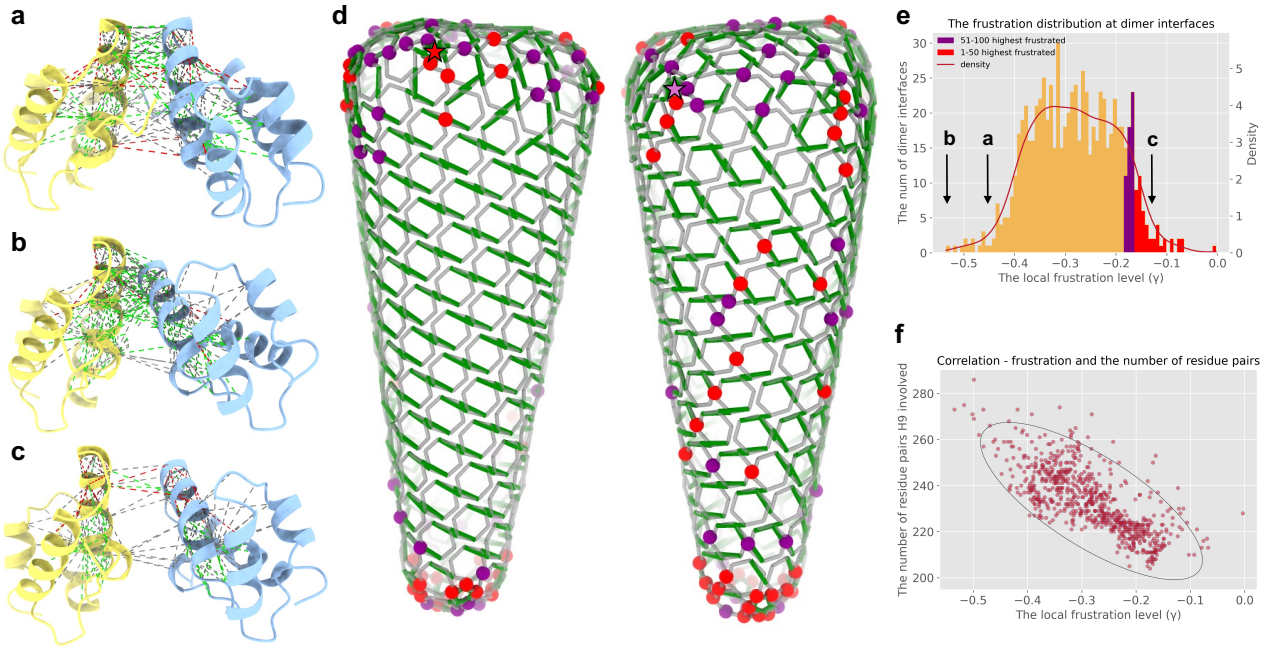

Fig. 4 | Molecular frustration at the dimer interface correlates with the capsid's topography given by the geometric index. a, The dimer interface (PDB: 2KOD), where the residue pairs corresponding to interactions made by amino acids in the H9 helices are shown as dashed lines (in red if highly frustrated, in green if minimally frustrated, and in grey if neutral). **b**, The dimer interface in *vlp23* across two hexamers with the lowest frustration level, and in **c**, with the highest frustration level. **d**, The data-derived geometric model with the geometric indices in green. The spheres in red represent top 50 highest frustrated ones; those in purple correspond to the top 51-100 highest frustrated interfaces. Left: side view of *vlp23* including the pentamer labelled by a red star, and Right: the pentamer labelled by a light purple star, the side on which the seam is located. The highly frustrated interfaces in the bulk are all on the seam side. **e**, The distribution of the local frustration levels across different dimer interfaces in *vlp23,* colour-coordinated with **d**. The black arrows point to the frustration levels of the interfaces in **a**, **b**, and **c**, respectively. **f**, The frustration level and the number of residue pairs involved in the helix interactions are correlated – the more interactions, the lower the frustration level.

Strikingly, the spatial distribution of frustration aligns with the topography represented by the geometric index (Fig. 4d). In addition to the concentration of frustration in the two end caps, which are dominated by seam lines, the highest frustrated interfaces in the capsid's midsection are co-located with the seam side of the data-derived model. We also mapped the 50 lowest-frustration dimer interfaces on the surface of *vlp23* (Supplementary Fig. 7);

however, no distinct spatial pattern was observed for their distribution. The colocation of frustration with the seam line of the CA lattice suggests that biophysical properties of the HIV-1 cone are intertwined with the underlying geometric organisation of its CA lattice. This highlights the importance of selecting a geometric model that not only captures the correct surface topology but also reproduces a capsid's intrinsic biophysical heterogeneity.

The geometric index distinguishes between HIV-1 capsid reconstruction protocols.

The seam line-associated frustration discussed above may also play a role in capsid assembly or disassembly. Here we use the geometric index to analyse if the reconstruction protocol applied to the cryo-EM data leaves imprints on the atomistic model. We perform a comparative analysis of three capsid models (*vlp23* Fig. 5a, PDB: 3J3Y Fig. 5b, and PDB: 3J3Q Fig. 5c): a fullerene, a Kagome, and a data-derived surface lattice model. The distributions of their geometric indices are shown as bar charts (Fig. 5), which act as fingerprints of the models. The density lines (purple for the fullerene, green for the Kagome, and red for the data-derived surface lattice) are plotted together with histograms that distinguish the geometric indices surrounding hexamers (orange) and pentamers (cyan). Corresponding pictorial representations of the characteristic triangles (grey surrounding hexamers, cyan surrounding pentamers) are displayed on the right in frames coloured to match the respective density lines.

For all capsids, the fullerene lattice exhibits a bimodal geometric index distribution, consistent with the behaviour observed in our computational carbon-fullerene cones. However, striking differences emerge in the data-derived and Kagome lattices. In *vlp23* (Fig. 5a), both lattices retain bimodal distributions, whereas in 3J3Y (Fig. 5b) and 3J3Q (Fig. 5c) the two peaks are merged into a single negatively skewed mode.

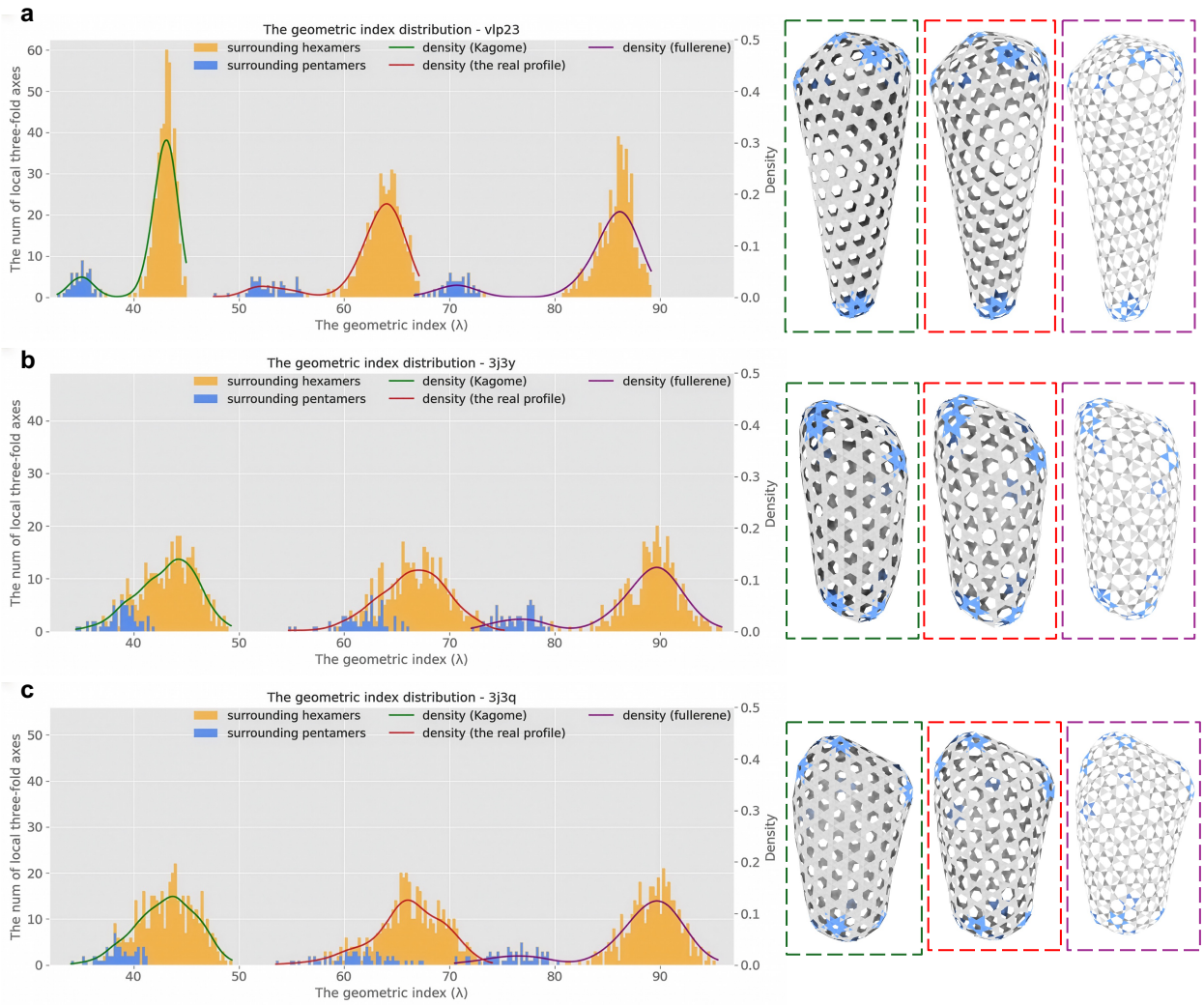

Fig. 5 | Data-derived models have distinct geometric index distribution profiles for different assembly scenarios. Left: the distribution of the geometric indices for the different geometric representations of (**a**) *vlp23* and (**b**) PDB: 3J3Y (**c**) PDB: 3J3Q. Here the real profile represents our data-derived model. The geometric index distribution of the data-derived model is bi-modal in *vlp23* but merged into a single peak in PDB: 3J3Y and 3J3Q. Right: capsid representation in terms of characteristic triangles (grey surrounding hexamers, cyan surrounding pentamers) for the fullerene lattice architecture (green dashed frame), Kagome lattice (purple dashed frame), and the data-derived model (red dashed frame).

These differences primarily reflect the distinct reconstruction and simulation protocols used to build each model. In *vlp23*, the complete capsid was first assembled by fitting capsomers (hexamers/pentamers) into a cryo-EM density map along a Hamiltonian path, followed by molecular dynamic (MD) relaxation of the entire structure[22]. In contrast, 3J3Y and 3J3Q were constructed through MD simulations applied initially to isolated patches composed of hexamers and pentamers, which were later concatenated onto a fullerene backbone and

further refined by MD[20]. The early relaxation of local patches likely allowed the geometry to adapt toward a local equilibrium before global assembly.

Consistent with this interpretation, Supplementary Fig. 8 shows that hexamers in *vlp23* remain close to regular hexagonal geometry, whereas those in 3J3Y and 3J3Q display marked distortions, as quantified by differences in their main diagonals. These contrasting reconstruction pipelines – global reconstruction followed by relaxation versus pre-equilibrated patch reconstruction – produce distinct geometric organisations, and potentially different biophysical properties of the resulting capsids. Although these structural variations originate from the modelling routines rather than direct physical processes, they provide insights into how alternative assembly scenarios might influence capsid architecture. Finally, mapping the geometric index orientations $\overleftrightarrow{v}$ onto the data-derived models (Supplementary Fig. 9) reveals some specific patterns, such as circular orientations consistent with the pre-assembled patches in 3J3Y and 3J3Q used in the reconstruction. This further supports the hypothesis that capsid assembly pathways and protocols leave measurable geometric imprints on the final topography that can be captured using the geometric index.

The geometric index captures local curvature and lattice distortions. To further explore the geometric information captured by the geometric index, we examined its relationship with local curvature in the data-derived model of the HIV-1 capsid *vlp23*. Fig. 6a illustrates seven neighbouring hexamers, each coloured distinctly, with four local threefold axes marked by characteristic triangles (grey). The geometric index of the central triangle is highlighted in magenta. We defined two curvature factors – the angles φ_1 and φ_2 – to quantify local surface bending (Fig. 6b). The two purple vectors (see top of Fig. 6b) represent the surface normal vectors of the triangles adjacent to the geometric index of the central triangle. The first

curvature factor, φ_1, is defined as the angle between these two normal vectors. The black vector (bottom of Fig. 6b) denotes the normal of the central triangle, while orange vectors correspond to the normal vectors of its three surrounding triangles. The second curvature factor, φ_2, is defined as the mean angle between the orange and black vectors.

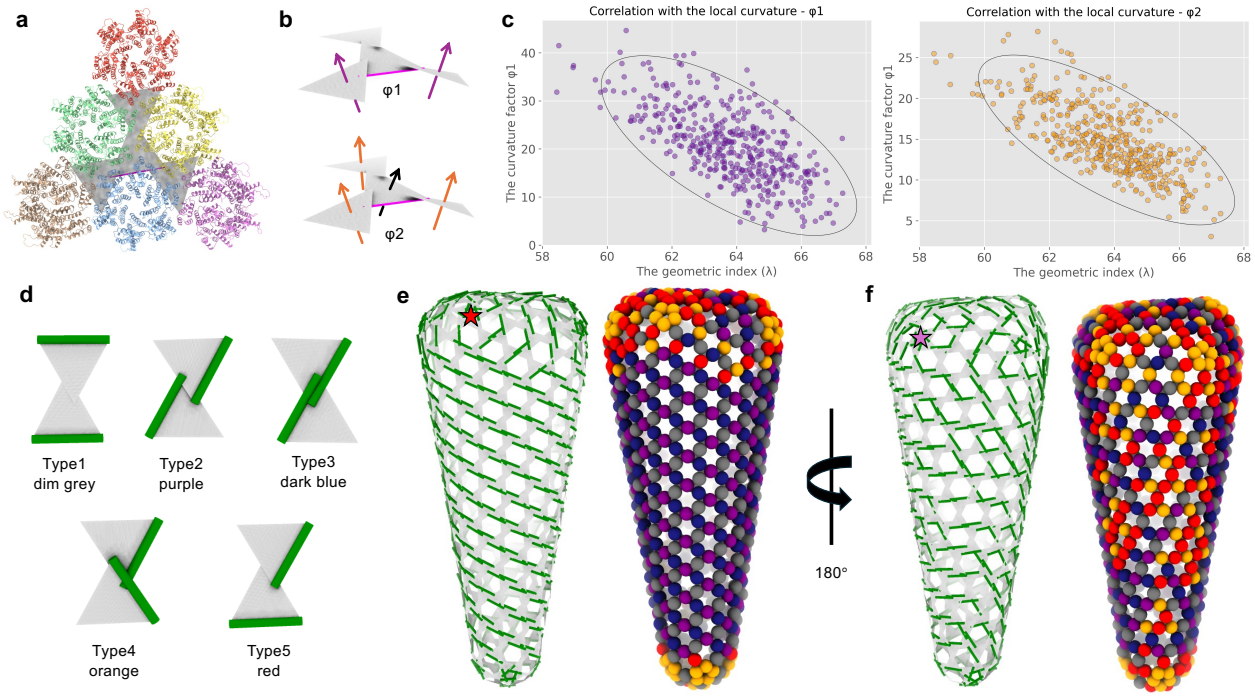

Fig. 6 | The geometric index of the data-derived model correlates with local geometric features. a, Four characteristic triangles (grey) corresponding to the six CA hexamers shown in different colours; the geometric index of the central triangle is indicated in magenta. **b**, The four characteristic triangles in **a**. Top: the two purple arrows represent the normal vectors of the two triangles connected by the line representing the geometric index of the central triangle. The angle between the two purple vectors is the curvature factor φ1 in **c**. Bottom: the three orange arrows represent the normal vectors of the three triangles surrounding the central triangle, and the black arrow is the normal vector of the central triangle. The average over the angles between the black vector and the three orange vectors, respectively, is the curvature factor φ2 in **c**. **c**, The geometric index correlates with the curvature factors φ1 (left) and φ2 (right) and is thus a suitable indicator of capsid geometry. **d**, Five types of local geometric organisations defined by the orientations of neighbouring geometric indices (green lines); types 1-3 are parallel, whereas types 4-5 are non-parallel. **e-f**, Characteristic triangles (grey) and geometric indices (green) on opposite sides of the capsid (red and light purple stars). Each pair of neighbouring threefold axes is colour-coded – dim grey (type 1), purple (type 2), dark blue (type 3), orange (type 4), and red (type 5). Parallel types from sheet-like regions on the red-star side, while non-parallel types cluster on the light-purple-star side and at both termini, coinciding with highly frustrated interfaces (Fig. 4).

As shown in Fig. 6c, the length of the geometric index (λ) is inversely correlated with local curvature: smaller geometric indices correspond to regions of higher curvature. This finding

confirms that the geometric index not only encodes lattice organisation but also serves as a quantitative indicator of local geometric deformation across the capsid surface.

In addition to its length, the orientational patterns of the geometric indices $\overleftrightarrow{v}$ are important to capture more detailed topographic features (Fig. 6d). Neighbouring geometric indices, represented by green lines, were grouped into five distinct types based on their relative orientations. In types 1-3, the indices are parallel, while in types 4 and 5 they are non-parallel. Fig. 6e and 6f (left) show pictorial representations of characteristic triangles (grey) and their geometric indices (green) on opposite sides of the capsid, denoted by the red and light purple stars, respectively. Each pair of neighbouring threefold axes was assigned one of the five types and colour-coded on the capsid surface – dim grey (type1), purple (type2), dark blue (type 3), orange (type 4), and red (type 5). The right panels of Fig. 6e and 6f (see also Movie 4) depict the corresponding twofold axes as coloured spheres.

The parallel configurations (type 1-3) predominate on the side marked by the red star, forming sheet-like surface regions, whereas non-parallel configurations (types 4-5) are concentrated on the opposite side (with the light purple star) and at both termini of the capsid. The accumulation of type 4 and 5 configurations at the highly frustrated dimer interfaces identified in Fig. 4 indicates a coupling between local topography and molecular frustration.

Together, these analyses establish that the geometric index – through both its length and orientation – provides a universal quantitative framework for describing capsid curvature and surface organisation. In the following section, we apply this metric to characterise the geometric features of cofactor and small-molecule binding regions and use this to predict putative CypA binding sites.

The geometric index reveals structural signatures at cofactor binding sites in tubular assemblies. Host cofactors interact with the HIV-1 capsid throughout the viral life cycle, coordinating processes such as trafficking, nuclear import, and uncoating[4]. Two primary binding interfaces have been identified on the capsid surface[39–41]. The first, a flexible loop between helices 4 and 5 in the CA N-terminal domain (CA_{NTD}), binds cytoplasmic cyclophilin A (CypA)[34,35] and the cyclophilin domain of nuclear pore component Nup358[46–48]. The second, a pocket at the interface between CA monomers, engages FG motifs from host proteins such as Nup153, Sec24C, and CPSF6[49–52], and accommodates small therapeutic molecules like lenacapavir (LEN)[36–38]. Not all such interfaces are occupied *in situ*, and the geometric determinants of these binding events remain poorly quantified. To address this, we applied the geometric index as a local descriptor to characterise capsid surface organisation at the cofactor and drug molecule binding regions.

We analysed experimentally available data sets (PDB: 6Y9W, 6Y9V, 6Y9X, 6Y9Y, 6Y9Z, and 6ZDJ) for six CypA-CA complexes of tubular assemblies exhibiting different helical symmetries. Monomers directly bound to CypA via the canonical CypA-binding loop were identified and coloured in cyan (Figs. 7a&b and Supplementary Fig. 10). Two monomers located around the same three-fold axis are coloured in lime and yellow, respectively. Characteristic triangles were constructed based on the N195 Cα in the C-terminal domains (CA_{CTDs}). The geometric index of each triangle (dashed cyan line) describes the local relationship between adjacent capsomers. Across all six complexes, the CypA-binding monomer consistently lies opposite the geometric index (the shortest edge) of the characteristic triangle, and the geometric index of the CypA-associated triangle is parallel to, but smaller than, that of its neighbouring triangle (purple dashed lines) – a configuration

corresponding to the type 2 dimer interfaces defined in Fig. 6d. This consistent pattern suggests that preferred CypA-binding sites coincide with type 2 configurations in the tubular lattice.

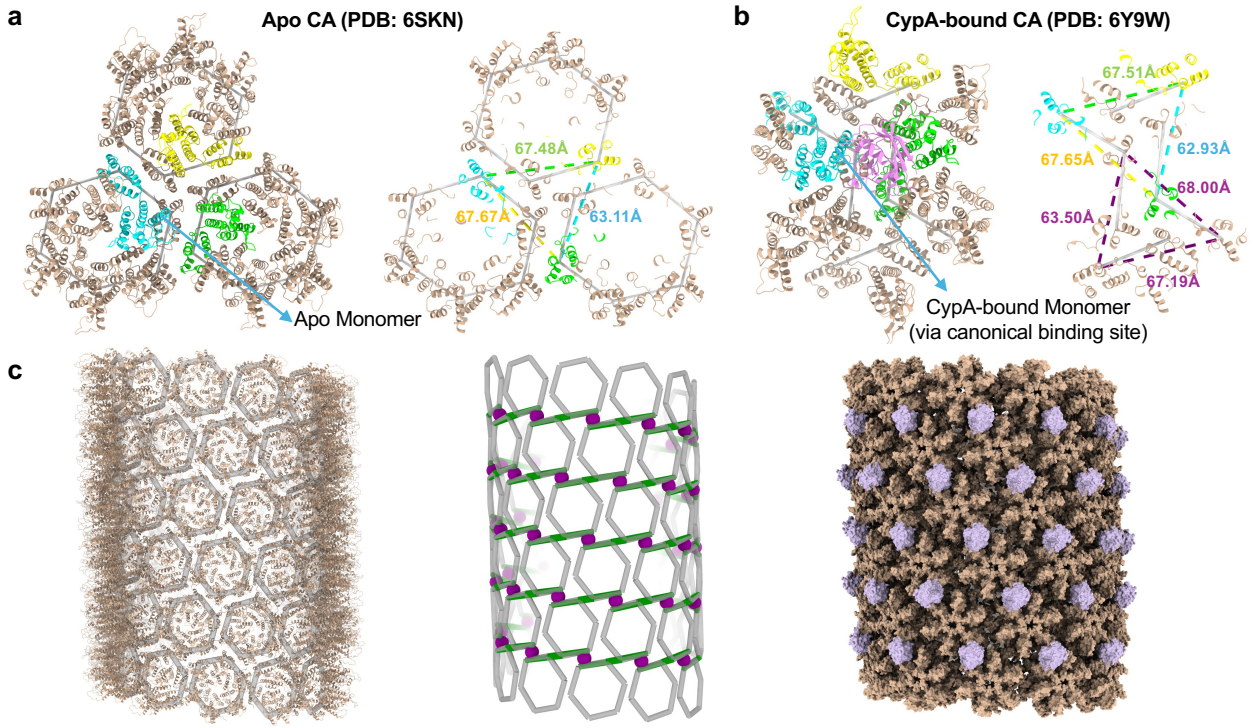

Fig. 7 | The geometric index as an indicator of co-factor (CypA) binding. a, The Apo CA complex in a tubular structure with helical symmetry (-13, 8) (PDB: 6SKN), where the monomer coloured in cyan is matched to the corresponding CypA-binding monomer (cyan) in **b** by the Needleman-Wunsch algorithm. Right: the three dashed lines indicate the characteristic triangle, with numbers denoting their lengths in the corresponding colours. **b**, A CypA-CA complex in a tubular structure with helical symmetry (-13, 8) (PBD: 6Y9W), where CypA is coloured in magenta. Right: six dashed lines construct two characteristic triangles at two neighbouring local three-fold axes. **c**, CypA-binding site prediction based on the features revealed in **a** and **b**. Left: an HIV-1 capsid tube (PDB: 6X63) in brown with the data-derived profile of CA hexamers in light grey. Middle: the data-derived geometric model, with green lines representing the geometric indices. Purple spheres predict CypA-binding sites. Right: CypAs in light purple are mapped onto the predicted binding sites of the capsid tube (PDB: 6X63), by aligning the CypA-binding monomer in the complex in Supplementary Fig. 10e to the corresponding CypA-binding monomers in the capsid tube.

Mapping the geometric indices onto the surface of a CA tubular assembly[53] (PDB: 6X63, helical symmetry -12, 11) further supports this interpretation (Fig. 7c, left and middle). Only parallel configurations (type 1-3) are present, with no distorted (type 4-5) arrangements, indicating a continuous sheet-like topology without seam lines. When CypA-binding sites are overlaid as purple spheres at the type 2 interfaces, the smaller geometric index identifies the

canonical CypA-binding monomer. Alignment of the CypA-CA complex (PDB: 6ZDJ, symmetry -13, 10) onto these positions yields a model (Fig. 7c, right, and Movie 5) in which bound CypAs follow one of the three characteristic orientations in the hexameric surface lattice.

Earlier work[29] suggested that CypA selectively binds the CA hexamer array direction with the highest curvature. However, their more recent high-resolution data[31] combining cryo-EM density and atomic models indicate that CypA instead bridges two CA hexamers along the direction of lowest curvature, with additional CypA molecules occasionally bound adjacent to these at the trimer interfaces. The Apo and CypA-CA complexes analysed here (Figs. 7a,b; Supplementary Fig. 10) derive from these updated data[31], and our predicted CypA-binding sites in the CA tubular assembly[53] (PDB: 6X63) are consistent with the hexamer array orientation with the lowest curvature.

In tubular assemblies, the three hexamer array orientations can be described as most curved, least curved, and intermediate, depending on the helical symmetry. However, absolute curvature varies between different helical symmetries, making it difficult to determine whether these three relative directions are directly comparable across different tubes – particularly considering capsomer tilt, twist[30], and internal curvature[31]. We therefore further quantified the curvature patterns along the three hexamer array orientations (ori1-ori3) in tubular assemblies with helical symmetry (-13, 8; PDB: 6SKN) and (-12, 11; PDB: 6X63) using a covariance matrix analysis (see Methods). As illustrated in Supplementary Figs. 10 and quantified in Supplementary Fig. 12, curvature strengths differ between symmetries. However, their relative geometric patterns remain conserved, with the three relative curvature directions consistently aligning with the geometric index configurations of types 1-3 (Fig. 6d),

respectively. These results suggest that the geometric index captures relative local curvature patterns across different protein assemblies, as revealed by the covariance matrix approach, thereby refining our understanding beyond merely absolute curvature values alone.

Ligand-specific curvature responses revealed by the geometric index. To examine how ligand binding influences local geometry, we compared Apo and CypA-bound CA complexes with identical helical symmetry (Apo CA, Fig. 7a, PDB: 6SKN; CypA-CA, Fig. 7b, PDB: 6Y9W). Alignment of the corresponding monomers revealed a decrease in geometric index upon CypA binding, consistent with a local curvature increase. This agrees with experimental findings showing that CypA concentration modulates curvature as follows. In the absence of CypA, long tubes form; at intermediate concentration, short tubes and cones appear; and at high concentrations, small cones and spheres dominate, all consistent with enhanced curvature upon CypA binding[29].

Equivalent analyses for LEN- and CPSF6-peptide-bound CA complexes (Supplementary Fig. 13), derived from CA lattice structures, showed the opposite trend – an increase in geometric index, suggesting local flattening of the lattice. Although studies on CPSF6-induced geometric changes are limited, recent reports[38,54] indicate that LEN binding causes lattice flattening, defective capsid closure, and loss of essential pliability, in agreement with our results.

While these observations revealed by the geometric index highlight opposing geometric effects at the two primary binding sites – curvature enhancement upon CypA binding versus surface flattening upon FG-motif or LEN binding – they should be interpreted cautiously. The CypA complexes originate from tubular assemblies, whereas the LEN and CPSF6 complexes

are derived from CA lattices; thus, part of the observed differences may arise from the structural context rather than ligand binding alone. Moreover, cofactor binding is likely to affect not only local geometry but also biochemical and mechanical properties of the lattice.

Nevertheless, the alignment of our geometric findings and experimental observations supports a genuine site-specific coupling between ligand binding and local geometric modulation. These results suggest that cofactors and inhibitors may regulate capsid function by exploiting local geometric flexibility along distinct structural axes. The geometric index thereby provides a quantitative framework to relate surface topology, curvature changes, and molecular interactions, offering a route to disentangling biologically meaningful effects from model-dependent variations.

Discussion

The geometric index acts like a mathematical microscope, providing a quantitative link between the local surface lattice architecture of an HIV-1 capsid and its biophysical properties. By capturing both the size and orientation of local lattice distortions, it connects atomic-scale geometry with macroscopic features such as curvature, molecular frustration, and cofactor binding, revealing a deep coupling of capsid geometry and function. A surprising conclusion from our study is that the choice of surface lattice in an HIV capsid model is paramount for capturing essential aspects of its biology. In contrast to the conventionally used fullerene lattice, only the data-derived surface lattice links potential seam-line locations with local frustration patterns. In addition to this, the geometric index can be used to identify curvature-dependent binding of cofactors and small molecules consistent with those observed in the experimental literature.

Beyond these structural insights revealed by our study, the geometric index opens up new avenues for the study of capsid assembly and evolution. The distinct geometric signatures observed across capsids reconstructed via different reconstruction protocols suggest that the assembly methods used may leave characteristic imprints on capsid structure. Exploring the implications of this for the assembly kinetics of different cone structures through the lens of the geometric index may clarify how HIV-1 controls its final morphology. The role of the viral genome also warrants attention in this context. While capsid proteins can assemble into cones or tubes *in vitro* in the absence of RNA[55], *in vivo* data show that cylindrical shells rarely encapsulate genomes, whereas conical ones consistently do[21,56]. This observation implies that genome-capsid coupling could influence cone geometry, potentially guiding the formation of functionally competent cores. Our geometric index can be used to quantify any curvature effects that may occur in the presence and absence of the genomic RNA, providing a platform for studying how interactions with viral genomes may bias assembly outcomes.

The geometric principles uncovered here may shed new light also on antiviral and synthetic design strategies. In analogy to Capsid Assembly Modulators (CAMs) developed for Hepatitis B virus[57,58], geometric features derived from our criterion could guide the development of HIV-1 assembly inhibitors that destabilise or misdirect core formation at pivotal locations in the capsid surface revealed by the geometric index. For example, modulating the sizes or orientations of characteristic triangles might bias assembly toward non-productive or malformed structures. Conversely, the same insights could be harnessed in gene therapy, where HIV-1 cores serve as lentiviral vectors for payload delivery. Tailoring assembly conditions to favour desired geometric configurations may improve vector stability or cargo

capacity. Finally, integrating this geometric framework with AI-driven molecular design offers a promising avenue for geometry-informed antiviral and vector engineering.

Overall, our results establish geometry as a central organising principle of HIV-1 capsid structure and function. The geometric index provides a unifying descriptor that connects local geometric organisation with curvature, assembly, and molecular interactions. Extending this framework to other retroviruses and to artificial capsid systems may uncover universal geometric rules of viral architecture, guiding both antiviral development and the design of bioengineered protein nano-containers.

Methods

Computational Fullerene and Quantum Mechanical Methodology

Fullerene: Following a previous publication[20], the Fullerene[42–45] program was used to create multiple fullerenic models of the HIV-1 capsid. Specifically, the ring spiral pentagon indices (RSPIs)[59,60] corresponding to the broader end (the last seven indices) were systematically altered by increments of ±1, ±2, and higher values. For this purpose, input files for the geometry search were generated outside of the program Fullerene using a template input text file modified with sed. Each modified RSPI was then tested within Fullerene to determine whether it produced a valid closed fullerene. This validation was performed without attempting to generate a three-dimensional geometry, relying instead on the program's ability to verify consistency of the candidate RSPI with the specified number of carbons and the canonical RSPI rules. The majority of RSPI variations proved invalid. Therefore, searches were conducted in parallel to efficiently identify the small subset of valid candidates. A valid

RSPI indicates the existence of a closed three-dimensional geometry consistent with the indices.

Candidate RSPIs that passed validation were used as input for three-dimensional embedding procedures available in Fullerene, including the 3D Tutte[61] embedding method. Multiple embedding algorithms were tested because some methods yielded less deformed geometries than others; we found that 3D Tutte was more consistent at producing closed geometries than the adjacency matrix eigenvector (AME) method[62]. To improve reproducibility and reduce bias, the embedding process was automated and repeated with different methods. For each candidate RSPI, embedding parameters were optimised to obtain satisfactory initial three-dimensional structures. Although log files provided preliminary indicators of structural quality, visual inspection was used to confirm the adequacy of the resulting geometries during parameter optimisation.

Subsequent structural optimisation was carried out using semi-empirical quantum mechanical methods implemented in MOPAC[65] with Parametric Method 3 (PM3)[63], PM6[63], and PM7[63] Hamiltonians. Final refinement of carbon fullerene geometries was performed with higher-level quantum mechanical approaches based on density functional theory (DFT) as described below. As a result, there are three different topological classes of vertices 352, 452, and 524. These structures correspond to fullerenes with 352 (C_{352}), 452 (C_{452}), and 524 (C_{524}) carbon atoms, which contain 166, 216, and 240 hexagonal faces, respectively, in addition to the 12 pentagonal faces required by topology. Each fullerene has multiple possible isomers that arise from different arrangements of the pentagonal and hexagonal rings on the carbon cage. The full data set contains 654 fullerene structures divided into 325 of C_{352}, 39 of C_{452}, and 290 of C_{524}.

Optimisation: To investigate the energy landscape of the preferential shape of fullerene-based capsid topologies we treated the vertices of the generated fullerene cones as carbon atoms and subjected them to tight-binding (TB) density functional theory (DFT) optimizations and final energy evaluations. This allowed us to estimate the optimal fullerenic shape-per-discrete vertices count. In order to optimise the fullerene structures, we employed the Orca 6.0[64] quantum chemistry package. To determine the minimum energetics of each fullerene cone we used the GFN2-xTB DFT tight binding approach of the Grimme group[65]. While more accurate energies would likely be obtained through more sophisticated wavefunction approaches, or even through canonical DFT, given the size of the dataset and atomic count of each fullerene cone, the GFN2-xTB approach provides an efficient and sufficiently accurate metric for ranking[65].

The binding energy per atom derived from the quantum mechanical calculations is defined through the following equation

$$E_b = \frac{1}{N}(E_{tot} - NE_1), \qquad (3)$$

where E_{tot} is the total energy of the fullerenic cone from GFN2-xTB calculations, E_1 is the energy of a single carbon atom, E_b is the binding energy, and N is the number of carbon atoms in the fullerene.

Capsid Structures: To determine topologically favourable capsid structures based on the analysed fullerene cones we have introduced two criteria for characterisation of cone structures. The first criterion is related to the binding energy, see (1), and the second characterizes the spherical asymmetry of the structures, as presented by Diaz-Tendero et al[66].

The binding energy of a fullerene cone is closely related to the geometrical distortion of its surface. This has been revealed by Solov'yov et al[67] by demonstrating that the binding energy of a single wall carbon nanotube of arbitrary chirality can be calculated with a 99 % accuracy as a sum of surface, curvature and edge energy terms. Because of the similarity of their model and those used to study liquid droplets, nuclei and clusters, they adopted the name liquid surface model (LSM)[67].

One can generalize the LSM to the energetics of the fullerene cones studied here. In the fullerene case the dominant contributions to energy arise due to the surface area of the cone and the curvature of its surface. According to the LSM the lower values of the binding energy defined in (1) suggest the corresponding fullerene structures have fewer surface distortions, i.e., the overall shape is smoother, and the surface is less curved. Following this argument, in the present analysis we have chosen the structures with the lower E_b value as those being more compact, and, therefore, topologically favourable.

Binding energy provides a natural means to characterize the quality of the fullerene cones. We have introduced a second parameter ξ which describes the asymmetrical components and is used in conjecture with the binding energy E_b to highlight favourable structures. We can define the cone asymmetry through the following equation, adapted from Díaz-Tendero et al[66]:

$$\xi = \frac{1}{\sqrt{2}}\left[\left(\frac{1}{a}-\frac{1}{b}\right)^2+\left(\frac{1}{a}-\frac{1}{c}\right)^2+\left(\frac{1}{b}-\frac{1}{c}\right)^2\right]^2, \quad (4)$$

where, a, b, and c are the normalised principal components I_{xx}, I_{yy}, and I_{zz} of the moment of inertia tensor of the cone, respectively, as defined by equations 3-5.

$$a = \frac{I_{xx}}{I_{zz}} \quad (5)$$

$$b = \frac{I_{yy}}{I_{zz}} \quad (6)$$

$$c = \frac{I_{zz}}{I_{zz}} = 1 \quad (7)$$

We orientate the axes, so that the z-component of the inertial tensor is the largest. Given the oblong cone shape of the resultant fullerenes, $a < c$ and $b < c$ hold for all configurations. The asymmetry parameter ξ in (2) describes the deformation deviation from the fullerene cone compared to a sphere of radius $R = a = b = c$ (corresponding to ξ = 0). For an axially symmetric ellipsoidal shape $a = b = R < c$, we have

$$\xi(ellipsoid) = \frac{1}{R} - 1. \quad (8)$$

From this equation, it follows that for $R = \frac{1}{2}$, ξ = 1. The correlation between the asymmetry parameter ξ and the energy E_b is illustrated in Supplementary Fig. 2.

The Construction and Comparison of Geometric Representations

To construct the data-derived geometric model, we use the N195 Cα in the CA_{CTD} of each monomer as a reference point. This site was chosen because the distance between diametrically opposed N195 Cα (orange dashed lines in Fig. 3d) correlates with the internal curvature of the CA hexamers[31]. As illustrated in Fig. 3d, profiles of three CA hexamers (grey hexagons) derived from the N195 Cα positions show that their hexagonal edges are not perfectly coincident, leaving distinct inter-hexamer gaps.

For comparative analysis, we generated fullerene and Kagome lattices (Supplementary Fig. 3). In these two lattices, the fullerene vertices (black dots) were defined as the centroids of triplets of the neighbouring hexamer vertices (light purple arrows), while the Kagome lattice

(grey dots) were defined as midpoints between corresponding vertices of adjacent hexamers located across the local twofold axes (brown arrows). Each Kagome vertex thus represents a pair of monomers connected through a dimer interface.

The three geometric representations – the data-derived, fullerene, and Kagome lattices – are compared in Supplementary Fig. 4. All models were constructed onto seven uniformly sized hexagons with different colours. The fullerene lattice produces slightly larger hexagons covering the small gaps between the coloured hexagons (Supplementary Fig. 4b), while the Kagome lattice reproduces the same hexagon size but rotated by approximately 30° around the hexagons' centres (Supplementary Fig. 4d&e). Comparisons of the data-derived lattice (represented by the coloured hexagons) with the fullerene and Kagome lattices are shown in Supplementary Figs. 4c&f, respectively.

To evaluate geometric discrepancies, we superimposed the three lattice types on representative regions of the HIV-1 capsid model *vlp23*. Supplementary Fig. 5 shows the corresponding overlays of the data-derived model (grey lines) with the fullerene (black dots), and Kagome (grey dots) lattices. The characteristic triangles that define different geometric indices were extracted from these overlays, allowing a direct comparison of the data-derived lattice (orange dashed lines) with the fullerene and Kagome lattices (purple dashed lines) in Supplementary Fig. 6.

Molecular Frustration

Local energetic frustration was quantified based on previous work[32,33], which evaluates the energetic contribution of native residue-residue contacts relative to an ensemble of alternative (decoy) interactions. For each pair of residues *i* and *j*, a frustration index (Z-score)

was computed to assess how favourable the native interaction energy is compared to randomised contacts, including electrostatic contributions. The frustration level here is defined as minus frustration index (or minus Z-score). Based on that, interactions were classified as highly frustrated (frustration level ≥ 1), neutral ($-0.78 <$ frustration level < 1), or minimally frustrated (frustration level ≤ -0.78).

To evaluate interface frustration, we extended the formalism to compute a local frustration parameter (γ_i) at each dimer interface, defined as:

$$\gamma_i = \frac{\sum_{q \epsilon Z_i} q}{|Z_i|}, \qquad (9)$$

where Z_i represents the set of frustration levels for all interactions involving the H9 helices at the ith dimer interface. To align with the dimer baseline structure (PDB: 2KOD), we selected residues 146-221 from each monomer (76 residues per monomer) at every dimer interface to compute frustration. These residues encompass the H9 helices and neighbouring regions that mediate inter-monomer contacts.

Monomer Alignment for CypA-binding site identification and Mapping

To identify and map CypA-binding monomers (via the canonical binding site), we applied the Needleman-Wunsch algorithm[68], a dynamic programming method for sequence alignment. It is used here to compare the CypA-binding monomer from the CypA-CA complex (PDB: 6Y9W, Fig. 7b) with the three potential CypA-binding monomers in the Apo CA complex (PDB: 6SKN, Fig. 7a). Structural similarity was evaluated by root mean square deviation (RMSD). The monomer with the lowest RMSD value (0.002 Å, compared with 0.779 Å and 0.952 Å for the other two candidates) was identified as the corresponding CypA-binding monomer and coloured in cyan, while the other two were coloured in lime and yellow, respectively.

The same alignment procedure was used to map CypA-binding monomers from the CypA-CA complex (PDB: 6ZDJ, Supplementary Fig. 10e) onto the predicted binding monomers on the surface of the CA tubular structure (PDB: 6X63, Fig. 7c).

Comparison of Local Curvature in Hexameric Surface lattices Using Covariance Matrices

To compare local curvature in different tubular hexameric surface lattices, we analysed data of CA hexamers from assemblies with distinct helical symmetries.

We first defined six triangles for each hexamer, as illustrated in Supplementary Fig. 11a (PDB: 4XFX). The centroid of each hexagon, determined from the N195 Cα atomic positions of the six CA monomers, was used as the central vertex. This point was then connected to each of its six outer vertices to form six triangles. In a planar hexamer without internal curvature (PDB: 4XFX), all six triangles are coplanar. By contrast, for curved hexamers (PDB: 6SKN and 6X63), they exhibit angular deviations, reflecting internal bending of the hexamer. In Supplementary Fig. 11b (PDB: 6SKN), six triangles are constructed for each hexamer and colour-coded according to the three monomers at the local threefold axis (as in Fig. 7a): hexagon 1 (yellow), hexagon 2 (cyan), and hexagon 3 (lime).

As illustrated in Supplementary Fig. 11b, here we define three hexamer array orientations[29] as:

- ori1, the most curved direction, based on the hexamer arrangement composed of hexagons 1 and 2;
- ori2, the intermediate curvature direction, based on hexagons 1 and 3;

- ori3, the least curved direction, based on hexagons 2 and 3. Experimentally determined and theory predicted CypA-binding sites are both located at the dimer interface between hexagons 2 and 3.

As shown in the top row of Supplementary Fig. 12, in each orientation, we labelled triangles (tri1-tri6) for each orientation, starting from the dimer interface and ordered counterclockwise. To quantify curvature patterns, we computed 6×6 covariance matrices for each orientation, with entries corresponding to the relative angles between the normal vectors of the triangles in the adjacent hexamers. Analyses were performed on tubular assemblies with helical symmetries (-13, 8) (PDB: 6SKN; Supplementary Fig. 12, middle row) and (-12, 11) (PDB: 6X63; Supplementary Fig. 12, bottom row). Colour depth of each entry in the covariance matrix encodes the size of the angle.

The covariance matrices were approximately symmetric along the diagonal, implying a degree of symmetry along the local 2-fold axis between the hexamers. Deviations from perfect symmetry indicate relative distortions from perfect rotational symmetry. Averages over all matrix entries were taken as a proxy for the absolute curvature for each lattice orientation. In the (-13, 8) symmetry, two orientations exhibited higher curvatures (29.5° and 25.4°) and one lower curvature (5.9°), whereas in the (-12, 11) symmetry, one high (31.4°) and two lower curvatures (18.4° and 13.4°) were observed. Despite differences in absolute curvature values between these symmetries, the relative curvature pattern – meaning the locations of high and low values in the matrix – was preserved. This suggests that the relative geometric organisation revealed by this provides refine information superseding absolute curvature values.

Interestingly, the three relative orientations (ori1-ori3) correspond to the type 1-3 configurations defined by the geometric index (Supplementary Fig. 12, top row), demonstrating that the index reliably captures intrinsic local geometric organisation across different helical symmetries.

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Author Contributions

W.L. & R.T. designed the study. W.L. developed the geometric index framework, lattice representations, and molecular frustration computations; performed the geometric and cofactor binding analyses; and created the figures. C.A.P., J.S.R., & J.R.P. carried out the

carbon fullerene structure generation and corresponding energy computations. W.L. & R.T. interpreted the results and wrote the manuscript with input from all authors.

Competing Interests

The authors declare no competing interests.

Materials & Correspondence

For the carbon-fullerene and capsid *vlp23* atomic structures, please contact J.R.P.. Correspondence regarding all other data and results should be addressed to W.L. and R.T..

References

1. Sharp, P. M. & Hahn, B. H. Origins of HIV and the AIDS pandemic. *Cold Spring Harb. Perspect. Med.* **1**, (2011).
2. Williams, A. *et al.* Geographic and Population Distributions of Human Immunodeficiency Virus (HIV)-1 and HIV-2 Circulating Subtypes: A Systematic Literature Review and Meta-Analysis (2010-2021). *J. Infect. Dis.* **228**,1583–1591 (2023).
3. Nyamweya, S. *et al.* Comparing HIV-1 and HIV-2 infection: Lessons for viral immunopathogenesis. *Rev. Med. Virol.* **23**, 221–240 (2013).
4. Morling, K. L., ElGhazaly, M., Milne, R. S. B. & Towers, G. J. HIV capsids: orchestrators of innate immune evasion, pathogenesis and pandemicity. *J. Gen. Virol.* **106**, 1-22 (2025).
5. Temple, J., Tripler, T. N., Shen, Q. & Xiong, Y. A snapshot of HIV-1 capsid–host interactions. *Curr. Res. Struct. Biol.* **2**, 222–228 (2020).
6. Zila, V., Müller, T. G., Müller, B. & Kräusslich, H. G. HIV-1 capsid is the key orchestrator of early viral replication. *PLoS Pathog.* **17**, 1-9 (2021).
7. Novikova, M., Zhang, Y., Freed, E. O. & Peng, K. Multiple Roles of HIV-1 Capsid during the Virus Replication Cycle. *Virol. Sin.* **34**, 119–134 (2019).

8. Link, J. O. *et al.* Clinical targeting of HIV capsid protein with a long-acting small molecule. *Nature* **584**, 614–618 (2020).

9. Bester, S. M. *et al.* Structural and mechanistic bases for a potent HIV-1 capsid inhibitor. *Science.* **370**, 360–364 (2020).

10. Naldini, L., Trono, D. & Verma, I. M. Lentiviral vectors, two decades later. *Science.* **353**, 1101–1102 (2016).

11. Wolff, J. H. & Mikkelsen, J. G. Delivering genes with human immunodeficiency virus-derived vehicles: still state-of-the-art after 25 years. *J. Biomed. Sci*. **29**, 1-22 (2022).

12. Poletti, V. & Mavilio, F. Designing lentiviral vectors for gene therapy of genetic diseases. *Viruses* **13**, 1-14 (2021).

13. Milone, M. C. & O'Doherty, U. Clinical use of lentiviral vectors. *Leukemia*. **32**, 1529–1541 (2018).

14. Caspar, D. L. & Klug, A. Physical principles in the construction of regular viruses. *Cold Spring Harb. Symp. Quant. Biol.* **27**, 1–24 (1962).

15. Carrillo-Tripp, M. *et al.* VIPERdb^2: An enhanced and web API enabled relational database for structural virology. *Nucleic Acids Res.* **37**, D436-D442 (2009).

16. Twarock, R. & Luque, A. Structural puzzles in virology solved with an overarching icosahedral design principle. *Nat. Commun.* **10**, 1-9 (2019).

17. Brunk, N. E. & Twarock, R. Percolation Theory Reveals Biophysical Properties of Virus-like Particles. *ACS Nano* **15**, 12988–12995 (2021).

18. Highland, C. M., Tan, A., Ricaña, C. L., Briggs, J. A. G. & Dick, R. A. Structural insights into HIV-1 polyanion-dependent capsid lattice formation revealed by single particle cryo-EM. *Proc. Natl. Acad. Sci. U.S.A.* **120**, 1-9 (2023).

19. Li, S., Hill, C. P., Sundquist, W. I. & Finch, J. T. Image reconstructions of helical assemblies of the HIV-1 CA protein. *Nature* **407**, 409-413 (2000).

20. Zhao, G. *et al.* Mature HIV-1 capsid structure by cryo-electron microscopy and all-atom molecular dynamics. *Nature* **497**, 643–646 (2013).

21. Erdemci-Tandogan, G., Wagner, J., Van Der Schoot, P. & Zandi, R. Role of Genome in the Formation of Conical Retroviral Shells. *J. Phys. Chem. B* **120**, 6298–6305 (2016).

22. Ni, T. *et al. Structure of Native HIV-1 Cores and Their Interactions with IP6 and CypA*. *Sci. Adv*. **7**, 1-12 (2021).

23. Perilla, J. R. & Schulten, K. Physical properties of the HIV-1 capsid from all-atom molecular dynamics simulations. *Nat. Commun.* **8**, 1-10 (2017).

24. Deshpande, A. *et al.* Elasticity of the HIV-1 core facilitates nuclear entry and infection. *PLoS Pathog.* **20**, 1-24 (2024).

25. Shen, Q. *et al.* The capsid lattice engages a bipartite NUP153 motif to mediate nuclear entry of HIV-1 cores. *Proc. Natl. Acad. Sci. U.S.A.* **120**, 1-11 (2023).

26. Levandovsky, A. & Zandi, R. Nonequilibirum assembly, retroviruses, and conical structures. *Phys. Rev. Lett.* **102**, 1-4 (2009).

27. Ning, J. *et al.* In vitro protease cleavage and computer simulations reveal the HIV-1 capsid maturation pathway. *Nat. Commun.* **7**, 1-12 (2016).

28. Yu, Z. *et al.* Unclosed HIV-1 Capsids Suggest a Curled Sheet Model of Assembly. *J. Mol. Biol.* **425**, 112–123 (2013).

29. Liu, C. *et al.* Cyclophilin A stabilizes the HIV-1 capsid through a novel non-canonical binding site. *Nat. Commun.* **7**, 1-10 (2016).

30. Mattei, S., Glass, B., Hagen, W. J. H., Kräusslich, H.-G. & Briggs, J. A. G. The structure and flexibility of conical HIV-1 capsids determined within intact virions. *Science.* **354**, 1434-1437 (2016).

31. Ni, T. *et al.* Intrinsic curvature of the HIV-1 CA hexamer underlies capsid topology and interaction with cyclophilin A. *Nat. Struct. Mol. Biol.* **27**, 855–862 (2020).

32. Parra, R. G. *et al.* Protein Frustratometer 2: a tool to localize energetic frustration in protein molecules, now with electrostatics. *Nucleic Acids Res.* **44**, W356–W360 (2016).

33. Rausch, A. O. *et al.* FrustratometeR: an R-package to compute local frustration in protein structures, point mutants and MD simulations. *Bioinformatics* **37**, 3038–3040 (2021).

34. Luban, J., Bossolt, K. L., Franke, E. K., Kalpana, G. V & Gofft, S. P. Human Immunodeficiency Virus Type 1 Gag Protein Binds to Cyclophilins A and B. *Cell* **73**, 1067-1078 (1993).

35. Gamble, T. R. *et al.* Crystal structure of human cyclophilin A bound to the amino-terminal domain of HIV-1 capsid. *Cell* **87**, 1285–1294 (1996).

36. Highland, C. M., Tan, A., Ricaña, C. L., Briggs, J. A. G. & Dick, R. A. Structural insights into HIV-1 polyanion-dependent capsid lattice formation revealed by single particle cryo-EM. *Proc. Natl. Acad. Sci. U.S.A.* **120**, 1-9 (2023).

37. Li, C. *et al.* Lenacapavir disrupts HIV-1 core integrity while stabilizing the capsid lattice. *Proc. Natl. Acad. Sci. U.S.A.* **122**, (2025).

38. Huang, S. W. *et al.* The primary mechanism for highly potent inhibition of HIV-1 maturation by lenacapavir. *PLoS Pathog.* **21**, (2025).

39. Stacey, J. C. V. *et al*. Two structural switches in HIV-1 capsid regulate capsid curvature and host factor binding. *Proc. Natl. Acad. Sci. U.S.A.* **120**, 1-11 (2023).

40. Twarock, R., Towers, G. J. & Stockley, P. G. Molecular frustration: a hypothesis for regulation of viral infections. *Trends Microbiol.* **32**, 17–26 (2024).

41. Saito, A. & Yamashita, M. HIV-1 capsid variability: viral exploitation and evasion of capsid-binding molecules. *Retrovirology* **18**, 1-26 (2021).

42. Schwerdtfeger, P., Wirz, L. N. & Avery, J. The topology of fullerenes. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **5**, 96–145 (2015).

43. Schwerdtfeger, P., Wirz, L. & Avery, J. Program fullerene: A software package for constructing and analyzing structures of regular fullerenes. *J. Comput. Chem.* **34**, 1508–1526 (2013).

44. Babic, D., Balaban, A. T. & Klein, D. J. *Nomenclature and Coding of Fullerenes*. *J. Chem. Inf. Comput. Sci*. **35**, 515-526 (1995).

45. Fowler, P. W. & Manolopoulos, D. E. *An Atlas of Fullerenes*. (Dover Publications Inc., Mineola, New York, 2006).

46. Schaller, T. *et al.* HIV-1 capsid-cyclophilin interactions determine nuclear import pathway, integration targeting and replication efficiency. *PLoS Pathog.* **7**, 1-15 (2011).

47. Di Nunzio, F. *et al.* Human Nucleoporins Promote HIV-1 Docking at the Nuclear Pore, Nuclear Import and Integration. *PLoS One* **7**, 1-15 (2012).

48. Bichel, K. *et al.* HIV-1 capsid undergoes coupled binding and isomerization by the nuclear pore protein NUP358. *Retrovirology* **10**, 1-12 (2013).

49. Lee, K. E. *et al.* Flexible Use of Nuclear Import Pathways by HIV-1. *Cell Host & Microbe* **7**, 221–233 (2010).

50. Price, A. J. *et al.* CPSF6 Defines a Conserved Capsid Interface that Modulates HIV-1 Replication. *PLoS Pathog.* **8**, 1-14 (2012).

51. Price, A. J. *et al.* Host Cofactors and Pharmacologic Ligands Share an Essential Interface in HIV-1 Capsid That Is Lost upon Disassembly. *PLoS Pathog.* **10**, 1-17 (2014).

52. Rebensburg, S. V. *et al.* Sec24C is an HIV-1 host dependency factor crucial for virus replication. *Nat. Microbiol.* **6**, 435–444 (2021).

53. Lu, M. *et al.* Atomic-resolution structure of HIV-1 capsid tubes by magic-angle spinning NMR. *Nat. Struct. Mol. Biol.* **27**, 863–869 (2020).

54. Faysal, K. R. *et al.* Pharmacologic hyperstabilisation of the HIV-1 capsid lattice induces capsid failure. *eLife* **13**, 1-27 (2024).

55. Meng, X. *et al.* Protease Cleavage Leads to Formation of Mature Trimer Interface in HIV-1 Capsid. *PLoS Pathog.* **8**, 1-9 (2012).

56. Woodward, C. L., Cheng, S. N. & Jensen, G. J. Electron Cryotomography Studies of Maturing HIV-1 Particles Reveal the Assembly Pathway of the Viral Core. *J. Virol.* **89**, 1267–1277 (2015).

57. Zlotnick, A., Nair, S. & Katen, S. P. New tricks for old molecules: A newly discovered modality for CAMs may yet lead to an HBV cure. *Hepatology* **78**, 1026–1028 (2023).

58. Hadden, J. A. *et al.* All-atom molecular dynamics of the HBV capsid reveals insights into biological function and cryo-EM resolution limits. *eLife* **7**, 1-27 (2018).

59. Goodson, A. L., Gladys, C. L. & Worst, D. E. *Numbering and Naming of Fullerenes by Chemical Abstracts Service*. *J. Chem. Inf. Comput. Sci.* **35**, 969-978 (1995).

60. Fowler, P. W. & Manolopoulos, D. E. Magic numbers and stable structures for fullerenes, fullerides and fullerenium ions. *Nature* **355**, 428–430 (1992).

61. Tutte, W. T. How to Draw a Graph. *Proc. Lond. Math. Soc.* **3**, 743–767 (1963).

62. Manolopoulos, D. E. & Fowler, P. W. Molecular Graphs, Point Groups, and Fullerenes. *J. Chem. Phys.* **96**, 7603–7614 (1992).

63. Stewart, J. J. P. Optimization of parameters for semiempirical methods VI: More modifications to the NDDO approximations and re-optimization of parameters. *J. Mol. Model* **19**, 1–32 (2013).

64. Neese, F. Software Update: The ORCA Program System—Version 6.0. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **15**, 1-10 (2025).

65. Bannwarth, C., Ehlert, S. & Grimme, S. GFN2-xTB - An Accurate and Broadly Parametrized Self-Consistent Tight-Binding Quantum Chemical Method with Multipole Electrostatics and Density-Dependent Dispersion Contributions. *J. Chem. Theory Comput.* **15**, 1652–1671 (2019).

66. Díaz-Tendero, S., Alcamí, M. & Martín, F. Fullerene C50: Sphericity takes over, not strain. *Chem. Phys. Lett.* **407**, 153–158 (2005).

67. Solov'yov, I. A., Mathew, M., Solov'Yov, A. V. & Greiner, W. Liquid surface model for carbon nanotube energetics. *Phys. Rev. E. Stat. Nonlin. Soft Matter. Phys.* **78**, 1-13 (2008).

68. Needleman, S. B. & Wunsch, C. D. A General Method Applicable to the Search for Similarities in the Amino Acid Sequence of Two Proteins. *J. Mol. Biol.* **48**, 443–453 (1970).

69. Goddard, T. D., Huang, C. C. *et al.* UCSF ChimeraX: Meeting modern challenges in visualization and analysis. *Protein Sci.* **27(1)**, 14–25 (2018).