Structure of a HIV-1 IN-Allosteric Inhibitor Complex at 2.93 Å Resolution: Routes to Inhibitor Optimization

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HIV integrase (IN) inserts viral DNA into the host genome and is the target of the strand transfer inhibitors (STIs), a class of small molecules currently in clinical use. Another potent class of antivirals is the allosteric inhibitors of integrase, or ALLINIs. ALLINIs promote IN aggregation by stabilizing an interaction between the catalytic core domain (CCD) and carboxy-terminal domain (CTD) that undermines viral particle formation in late replication. Ongoing challenges with inhibitor potency, toxicity, and viral resistance motivate research to understand their mechanism. Here, we present a 2.93 Å resolution structure of a minimal ternary complex formed by the IN CCD, CTD, and the preclinical lead ALLINI BI-224436. The structure reveals side chain orientations and a more precise view of the molecular interactions that underlie ALLINI-induced aggregation of HIV IN. The complex has a pronounced asymmetry, with non-identical ALLINI binding interfaces that depend on the nature of the proximal CTD dimers formed in the crystal lattice. We identify several new interactions including a network of cation-π and π-π interactions at the protein-protein and protein-drug interfaces. An accessible pocket adjacent to the bound ALLINI is occupied by ethylene glycol, suggesting specific directions for drug design. The minimal CCD•ALLINI•CTD assembly, like the full-length protein complex, favors the formation of drug-induced polymers in solution via two modes of CTD dimerization, providing orthogonal evidence supporting a branched polymer mechanism of aggregation. From this improved atomic model, we can generalize the mode of action for first-generation molecules and current clinical leads, facilitating routes for improvement of existing ALLINI scaffolds. We have further extended these studies by determining the structure of another ALLINI, BI-D, and two additional ALLINI-resistant forms of intact IN that are found in replication-competent viruses (INW1C and INN222K), at 4.5 Å. These data reveal structural perturbations that would undermine the branched polymer network promoted by ALLINI binding. Together, these results provide important insights to help optimize ALLINI design.