Effect of Allosteric Inhibitors on the Integrase Conformation Probed by All-Atom Simulations

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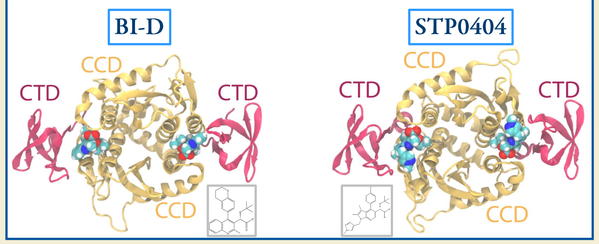
Abstract

One of the key steps in the retroviral replication process is the integration of viral DNA (vDNA) into the host cell chromosome. The integration of vDNA is catalyzed by a viral enzyme integrase (IN) which became an important retroviral target for therapeutic agents. A new distinct class of inhibitors binds at the dimer interface of IN and disrupts the catalytic activity of IN. Although the binding pocket of ALLINIs is well-characterized using experimental methods, the exact mechanism of inhibition is still unclear. In this work, we performed a set of all-atom molecular dynamics (MD) simulations to determine the effect of two ALLINIs on the HIV-1 IN dynamics. The MD simulations revealed that ALLINIs maintain the structural integrity of the IN dimer by mediating the interactions between the catalytic core and the C-terminal domains. Further analysis of the binding pockets revealed key interactions which were formed or ruptured between amino acids of the binding pockets and inhibitors.

Introduction

- IN catalyzes the integration process of vDNA into human cell chromosome.
- HIV-1 IN emerged as an important target for therapeutic agents.
- IN is comprised of three domains: NTD, CCD and CTD.
- Allosteric inhibitors bind at a second site of HIV-1 IN and inhibit the retroviral replication process.
- In this work, we determined the effect of two inhibitors on HIV-1 IN structure: BI-D and STP0404.



Research Goals

- The binding site of ALLINIs is well-characterized but the exact mechanism of inhibition remains unclear.
- How ALLINIs affect the structural integrity of HIV-1 IN?
- Which protein interface at the binding site has a greater contribution to the binding of the ALLINIs?
- Specifically, which amino acid side-chains play a key role in the recognition of the ALLINIs?

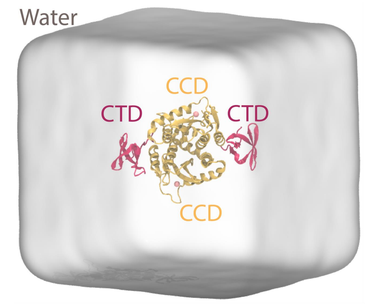
System Setup

All-atom molecular dynamics (MD) simulations were employed to probe the dynamics of HIV-1 IN in the presence and absence of two ALLINIs.
NAMD simulation software was utilized with CHARMM forcefield to conduct MD simulations.
BI-D and STP0404 were parameterized using QM calculations along with CGENFF software.

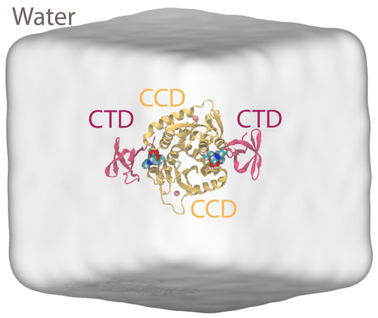
Simulation details

System	System Size (atoms)	Simulation Time (ns)
Apo HIV-1 IN	132,742	460
HIV-1 IN w/ BI-D	134,344	580
HIV-1 IN w/ STP0404	142,889	680

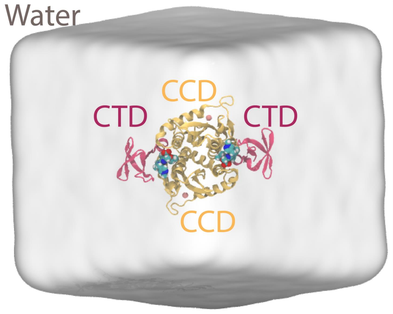
Apo HIV-1 IN simulation domain



HIV-1 IN w/ BI-D simulation domain

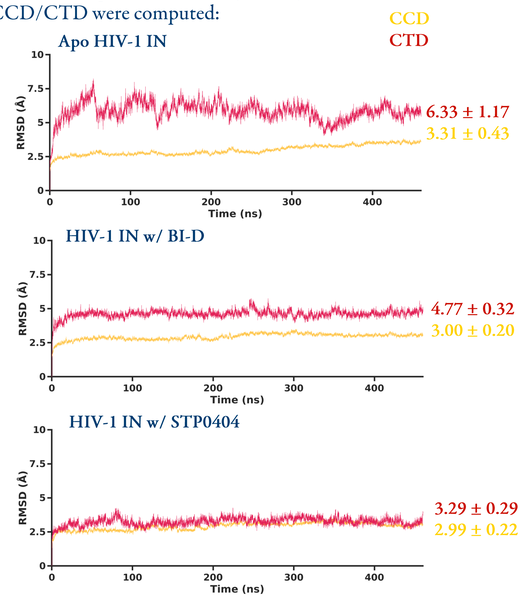


HIV-1 IN w/ STP0404 simulation domain



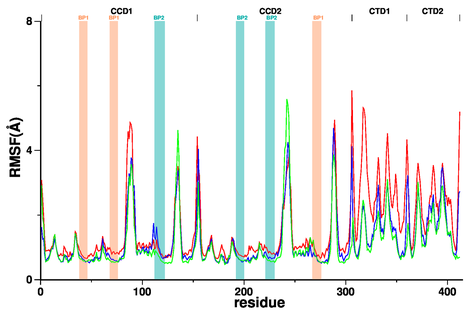
Flexibility of CTD

Root-mean-square deviation (RMSD) of CA atoms of the CCD/CTD were computed:

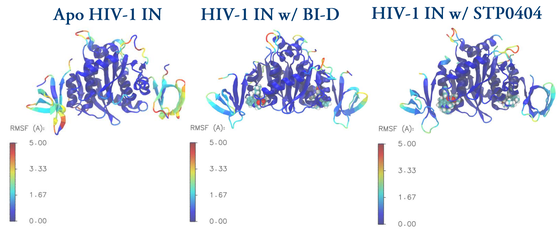


CTD is more **rigid** in the presence of ligands based on RMSD.

Root-mean-square fluctuations (RMSF) of CA atoms of individual IN amino acids were computed:

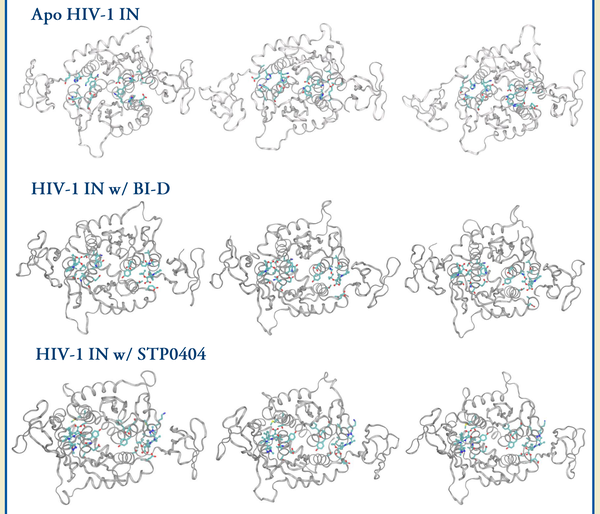


CTD is more **rigid** in the presence of ligands based on RMSD.



Binding Site Flexibility

Snapshots of the BI-D and STP0404 binding sites from MD simulations are shown



Conclusions and Next Steps

- BI-D and STP0404 maintain the structural integrity of the IN dimer by mediating the interactions between the CCD and CTD.
- Identified a list of amino acid side-chains in the binding site of BI-D and STP0404 which could be important for the recognition of the ALLNIs .
- As a next step, I plan to apply free energy perturbation (FEP) method to obtain the contribution of each amino acid side-chain and interface in the binding site of BI-D and STP0404 to the free energy of binding.

Acknowledgments

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