

## Advances in Development of Integrase inhibitors as anti HIV1 Regimen

Bechan Sharma

University of Allahabad, India

**Corresponding author:** Bechan Sharma

✉ bechansharma@gmail.com

Department of Biochemistry University of Allahabad, India

### Introducción

Since the discovery of human immunodeficiency virus type I (HIV1) in 1982 for which French virologists, Drs. Luc Antoine Montagnier and Françoise Barre-Sinoussi were awarded with the Nobel Prize in Physiology or Medicine for the year 2008, about 35 million people worldwide were reported to be living with HIV/AIDS in 2013. Of these, 3.2 million were children (<15 years old). Many of them (about 19 million) did not know that they have HIV-1 infections. About 39 million people have died since the first cases were reported in 1981 and 1.5 million people died of AIDS-related causes in 2013. The resource limiting countries like India with a very fast rate of growth in population needs to take special and effective measures to control new infections and the disease. HIV 1 is a slow growing virus, called as a lentivirus, and it selectively destroys the CD4+ve T lymphocytes helper cells which are involved in imparting immunity to the human systems. HIV 1 infection drastically reduce the CD4+ve T-lymphocytes number from 1200/ $\mu$ l in males and 1000/ $\mu$ l in females to about 200/ $\mu$ l or even below which leads to a clinical condition called as AIDS. In this condition the infected individual has total collapse of immunity with almost zero tolerance to any pathogenic invasion. Ultimately the patients die due to any of such opportunistic infections (1).

The antiHIV-1 regimens designed and developed so far have targeted three main enzymes of HIV-1 such as reverse transcriptase (RT), protease and integrase. Out of these, HIV-1 RT has been exhaustively exploited for development of antiHIV-1 drugs. The compounds against other two enzymes have also been developed and approved by FDA to be included in AIDS therapy (2). However, the emergence of drug resistance due to mutations in HIV-1 proteins and drug toxicities has always been a key issue in chemotherapy (3). Other possible targets for drug design and development could be the key steps involved in channelling the HIV-1 replication cycle such as binding of virus to the CD4 receptor and co-receptors; fusion with the host cell membrane; internalisation and uncoating of virus, formation of the pre-integration complex (PIC) and translocation into the nucleus; integration of viral cDNA into the host nucleus; processing of viral proteins and translocation to the cell surface to assemble into new immature virus forms; budding and release of new infectious virions. HIV can also infect multiple non dividing cells in the body such as brain cells (dendritic cells) and macrophages (4).

HIV 1 integrase (IN) is an enzyme protein comprised of 288 amino acid residues with a molecular weight of 32 kDa involved in catalysis of the integration reaction between the viral cDNA and the host genome in the infected cell's nucleus (5). Structurally,

HIV-1 integrase contains three independent functional domains: such as (1) N-terminal domain (NTD) containing 1-50 amino acids residues responsible for chelation with  $Zn^{2+}$  with the help of His12 and His16 as well as Cys40 and Cys43 amino acids (commonly known as HHCC Zinc finger motif) and multimerization. The HHCC zinc-finger motif chelates one zinc atom per IN monomer. (2) C-terminal domain (CTD) consisting of 213–288 amino acids is responsible for non-specific DNA binding, and (3) catalytic core domain (CCD) comprised of 51-212 amino acid residues is involved in  $Mg^{2+}/Mn^{2+}$  chelation, catalysis and DNA binding. CCD domain has a motif with catalytic triad comprising two aspartate and one glutamate residues (DDE) located at DDE motif on the positions 64, 116 and 152, respectively, and acts as the active site of integrase. CCD has a mixed  $\beta$  and  $\alpha$  structure with five  $\beta$ -sheets and six  $\alpha$  helices that are linked by flexible loops which allow conformational changes required for 3'-processing of the viral DNA and strand transfer reactions. The interaction of CTD is with NTD and CCD is essential for 3'-processing and strand-transfer activities of IN. IN acts as a multimer and dimerization is required for the 3'-processing step, with tetrameric IN catalyzing the strand-transfer reaction.

The multistep process of integration of proviral DNA into the host genome involves mainly two catalytic reactions: (1) 3'-endonucleolytic processing of proviral DNA ends (termed 3'-processing) and (2) integration of 3'-processed viral DNA into cellular DNA (referred to as strand transfer) (6). The inhibition of integrase activity at this stage may stop integration of viral genetic material into host's genome. Therefore, this enzyme hold promises to be exploited as a key target for design and development of new anti-HIV drugs. It also includes those compounds which may interfere in the PIC formation or integrase mediated strand transfer reactions. Competitive inhibitors compete directly with viral DNA for binding to integrase in order to inhibit 3'-end processing (7). Integrase inhibitors may therefore be designed and developed taking into consideration the active site make up of the enzyme, though the crystal structure of integrase-DNA complex is not yet available (8).

With the FDA approval in 2007 of the first integrase inhibitor (INI), raltegravir (first integrase strand transfer inhibitor, brand name Isentress), was found to effectively suppress virus replication in HIV-1 infected individuals (9). Raltegravir is more potent than other previously known integrase inhibitors with minimum toxicity. Two additional INIs such as elvitegravir (a novel quinolone HIV-1 integrase strand transfer inhibitor of low molecular weight, approved by FDA in 2012) and S/GSK1349572 is in advanced clinical development. Dolutegravir was another antiintegrase approved by FDA in 2013. MK-2048, a second generation integrase inhibitor appeared to have duration of

action up to four times longer than raltegravir. However, certain mutants for example R263A/K264A appearing in the integrase due to drug pressure drastically reduce the susceptibility of the enzyme to these inhibitors (10-12). Integrase inhibitors may be taken in combination with other types of HIV drugs to minimize adaptation by the virus. These antiintegrases are also effective against drug resistant virions. Since there have been problems with resistance to raltegravir and elvitegravir, more of newer drugs (second generation IN inhibitors such as MK2048) are therefore warranted to overcome the pharmacological disadvantage and to target antiIntegrase-resistant viruses keeping in view their bioavailability, efficacy, safety and cost etc.

## References

- 1 Singh S, Sharma B (2015) Immunodeficiency and microbial infections. *J. Microscopic Creatures* 1 (1): (In Press)
- 2 Sharma B (2014) Oxidative stress in patients receiving antiretroviral therapy. *Current HIV Research* 12: 13-21.
- 3 Sharma B (2011) the antiHIV-1 drugs toxicity and management strategies. *Neurobehavioural HIV Medicine* 3: 1-14.
- 4 Barré-Sinoussi F, Ross AL, Jean-François Delfraissy J-F (2013) Past, present and future: 30 years of HIV research. *Nature Reviews Microbiology* 11: 877-11,883.
- 5 Cocohoba J, Dong BJ (2008) Raltegravir: the first HIV integrase inhibitor. *Clinical therapeutics* 30: 1747-1765.
- 6 Fan X, Zhang FH, Al-Safi RI, Zeng LF, Shabaik Y, et al. (2011) "Design of HIV-1 integrase inhibitors targeting the catalytic domain as well as its interaction with LEDGF/p75: a scaffold hopping approach using salicylate and catechol groups". *Bioorganic & Medicinal Chemistry* 19: 4935-4952.
- 7 Chen X, Tsiang M, Yu F, Hung M, Jones GS, et al. (2008) Modeling, analysis, and validation of a novel HIV integrase structure provide insights into the binding modes of potent integrase inhibitors. *Journal of Molecular Biology* 380: 504-519.
- 8 Ribeiro AJM, Ramos MJ, Fernandes PA (2012) The Catalytic Mechanism of HIV-1 Integrase for DNA 3'-End Processing Established by QM/MM Calculations. *J Am Chem* 134: 13436-13447.
- 9 Steigbigel RT, Cooper DA, Kumar PN, Joseph E, Mauro Schechter, et al. (2008) "Raltegravir with Optimized background therapy for resistant HIV-1 infection". *N Engl J Med* 359: 339-354.
- 10 Blanco J-L, Varghese V, Rhee S-Y, Gatell JM, Shafer RW (2011) HIV-1 Integrase Inhibitor Resistance and Its Clinical Implications. *The Journal of Infectious Diseases* 203: 1204-1214.
- 11 Quashie PK, Sloan RD, Wainberg MA (2012) Novel therapeutic strategies targeting HIV integrase. *BMC Medicine* 10:34.
- 12 Houwer SD, Demeulemeester J, Thys W, Rocha S, Dirix L, et al. (2014) HIV-1 integrase mutant R263A/K264A is two-fold defective for TRN-SR2 binding and viral nuclear import. *J Biol Chem* 289: 25351-25361.