HIV intgrease inhibitors

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Abstract

Each year, more than 4 million people get infected with HIV (Human immunodeficiency virus), and almost 2.5 million people die from AIDS, which has become the fourth biggest reason for mortality worldwide. The magnitude of this problem has led to the allocation of a lot of resources to the study of HIV, the major goals of this research being the development of anti-retroviral drugs and a vaccine. AIDS was discovered in 1981 and the responsible virus for this devastating disease is human immunodeficiency virus. This progressive, degenerative disease reduces the effectiveness of humans' immune system and leaves individuals more susceptible to opportunistic infections and tumors (Siegal F B, 1981).

Introduction:

HIV must take over a T helper cells machinery to form new progeny viruses. To do that, HIV genome first, must be converted from RNA to DNA by action of reverse transcriptase enzyme. After that, HIV's DNA incorporates into the CD4 cell's DNA by action of integrase enzyme. Therefore, to block this incorporation, integase inhibitors work on it. Integrase inhibitors are considered a remarkable addition to anti-HIV therapy. Raltegravir which has considered the first integrase inhibitors has many advantages including: a unique mechanism of action, powerful anti-HIV activity and mild side effect has become a necessary component of therapy for AIDS patients (Jessica L Adams, PharmD, 2012). Elvitergravir also has improved pharmacokinetic profiles and gives longer half- lives for once daily dosing (Jessica L Adams, PharmD, 2012).

There are many critical steps in the HIV replication cycle that are an important target for anti- AIDS drugs including entry steps

and post entry steps. To stop the entry steps, drugs target the surface subunit of the viral envelope (gp120) and attach to the CD4 receptor of the host cells. The interaction between gp120 and co receptors of host cells (CXCR4 or CCR5) and membrane fusion of HIV due to subsequent conformational changes within the envelop complex (Richmand DD, 2001). While post entry step targets include viral reverse transcriptase In the meantime, the preferred regimen for HIV-infected patients consists of a non-nucleoside reverse transcriptase inhibitor or protease inhibitor combined with two nucleoside reverse transcriptase inhibitors and this regimen is referred to as highly active anti-retroviral therapy (HAART) (Flexener C, 2007). In 2007 Merck and Co has developed a new drug Raltergravir, it is a integrase strand transfer inhibitor which is now commonly used for HIV patients (Anker M, 2008).

HIV-1 integrase is a 32-KDa protein which consists of three structural domains (see figure-1) including N-terminal domain, catalytic core domain and C-terminal domain which are determined by X-ray crystallography and solution NMR (Rice P A, 2001). Integration of HIV genome with host genome allows the infection to persist without symptoms within latent viral reservoirs (Anthony N J, 2004). The whole integration process involves 3’ processing in the cytoplasm and the strand transfer in the nucleus (See figure-2). After that, the integration process is finalized by the cell enzymes which cleave viral DNA 5’overhang and fill the space left between viral and cellular DNA (Pommeir Y, 2004).

which is responsible for conversion of single stranded viral RNA into double stranded proviral DNA, integrase which is responsible for integration of proviral DNA into host genome, and protease which responsible for cleaving newly synthesized poly protein to create the mature protein components of HIV virions (Flexener C, 2007).

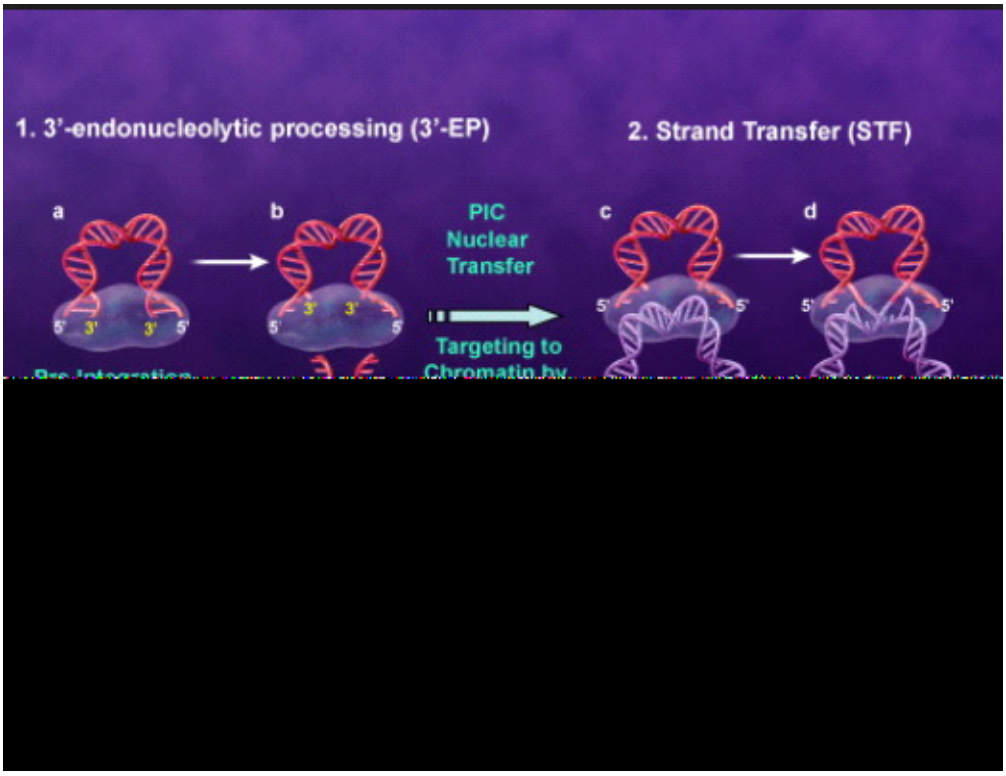

Figure 1: structure of intgrase enzyme of HIV

It was not easy to develop successful integrase inhibitors; it takes more than 20 years to develop intgrase inhibitors such as anti-retroviral HIV therapeutics (Marchand C, 2010). Many researchers have done projects to discover integrase

inhibitors, but only those acting on the strand transfer have developed useful anti-retroviral drugs. Those drugs were found to inhibit strand transfer more than 3’ prime processing, so they are referred to as integrase strand transfer inhibitors (Hazuda D J, 2000). The mechanism of action of strand transfer integrase inhibitors are by binding with the catalytic core domain of the viral enzyme and competing for binding with host DNA (Peter Messian, 2013). The first integrase inhibitor that was tested in human clinical trials was G-rich nucleotidic sequence that binds to viral integrase enzyme specifically (Field A K, 1999).

Raltergravir is the successful result of a long–term research effort by Merck and Co (Pace P, 2008). Raltegravir is given orally twice daily and has many advantages which include high efficacy, good tolerability by patients, a good safety profile and almost complete absence of significant negative drug to drug interactions (Department of Health and Human Services, 2012). For these reasonsRaltegravir was one of the first integrase inhibitors approved by the FDA to be used in patients suffering from AIDS. In 2008, combination use of Raltegravir with protease inhibitors darunavir and non-nucleoside reverse transcriptase inhibitors etravirine resulted in high levels of viral suppression in HIV patients. A Qd mark clinical trial revealed that qd use of raltegravir alone is more effective than use of raltegravir in combination with tenofovir and evavirenz at suppression of viral load to less than 50% copies viral RNA/ml in more than 83% of subjects over a period of 48 weeks (Eron J J Jr, 2011). Moreover, Qd mark reported that raltegravir does not need to be boosted by any pharmacological enhancer to be active.

Elvitegravir is another integrase inhibitor that has approved to be used to treat AIDS patients. Elvitegravir is a potent once-daily single tablet anti-HIV integrase strand transfer inhibitor. This drug targets HIV integrase enzyme through a selective effect on strand transfer (Francois Raffi, 2012). The mechanism of action of elvitegravir is by binding to specific complexes between integrase and viral DNA, resulting in displacement of the reactive 3’ end of the viral DNA and chelation of

the two essential magnesium ions present in the integrase active site (Malet I, 2012).

Anti-HIV integrase strand transfer inhibitors (INSTI) are active against many retroviruses, including lentiviruses and HIV-1 and HIV-2 (Koh Y, 2011). Elvitegravinis usually co-formulated with additional drug termed cobicistat for augmentation. Currently there is a potent once-daily single tablet anti-retroviral regimen (STR) termed as Stribild R and formed from four drugs which are elvitegravir, cobicistat , and two potent nucleoside reverse transcriptase inhibitors (NRTI) Conclusion

emtricitabie and tenofovir (Sax P E, 2012). This regimen is safer and more effective than other regimens such as AtripleR which are composed of emtricitabine, tenofovir and efavirenz.

Recent clinical studies suggested that new second generation integrase strand transfer inhibitor dolutegravir, which has not been approved yet by the FDA, is superior to elvitegravir over 48 weeks of therapy when both drugs are combined with a fixed dose of once-daily non-nucleoside reverse transcriptase inhibitors (Walmesly S, 2012).

Integration of the viral genome into host cell chromatin is a unique step in HIV replication cycle. Developing a novel drug that can block viral integrase enzyme that mediates this step will inhibit HIV replication. Better understanding of integrase function which, in turn, is leading to the development of new molecules that can block integrase function through novel mechanisms. Raltergravir and Elvitegravir are two drugs that are proved to block viral integrase enzyme. Therefore, it is important that integrase inhibitors used in the first-line therapy against HIV infection.

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