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PREFACE

The book series, "***Frontiers in Clinical Drug Research-HIV***" presents important recent developments in the form of cutting edge reviews written by the authorities in the field. The chapters in this 3rd volume are mainly focused on Human papillomavirus (HPV) infections, different HIV-1 inhibitors (integrase inhibitors, protease inhibitors, entry inhibitors and reverse transcriptase inhibitors), Highly Active Antiretroviral Therapy (HAART) and blockage of HIV-1 replication.

Anna Rosa Garbuglia in Chapter 1 discusses a common sexually transmitted disease, Human papillomavirus (HPV) infection that leads to about 250,000 deaths each year. Ashton *et al*., in chapter 2 discuss the structure, function and mechanism of HIV-1 integrase inhibitors. Highly active antiretroviral therapy (HAART) uses multiple drugs that can act on special viral targets. Chapter 3 by Silpi Basak describes the importance of this therapy that stops the replication of HIV and reduces HIV related deaths, illness and hospitalization by 60-80%.

Chapters 4 to 8 by Liu & Kong provide novel insights into the design of individual anti-HIV strategies on treatments and minimizing side effects for clinical development. These chapters include current progress and challenges in the development of entry inhibitors, prospects of reverse transcriptase inhibitors, targets and clinical applications of integrase inhibitors, outlook of proteinase inhibitors and blocking HIV-1 replication by targeting the Tat-hijacked transcriptional machinery.

I am grateful to all the eminent scientists for their excellent contributions. I also express my gratitude to the editorial staff, particularly Mr. Mahmood Alam (Director Publication), Mr. Shehzad Naqvi (Senior Manager Publications) and Ms. Fariya Zulfiqar (Assistant Manager Publications) for their hard work and persistent efforts.

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CHAPTER 1

Human Papillomavirus in HIV Positive People

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Abstract: Human papillomavirus (HPV) infection is the most common sexually transmitted disease worldwide and most sexually active individuals of both sexes acquire HPV at least once during their life. This virus is associated with >90% of anal and cervical cancers. Human immunodeficiency virus (HIV) infection increases incidence of both invasive cervical cancer and anal cancer. The risk of anal HPV infection declines with age in women, whereas this is not the case in men. Prophylactic HPV vaccines represent a promise for cervical and anal cancer prevention in HIV-positive people. Still now, no data are available for prevention of HPV related cancers with anti-HPV vaccination in adult HIV-positive people, but several trials are on-going. Both vaccines are well tolerated and the adverse effects are comparable to those observed in HIV negative people. However, an implementation of secondary prevention would be useful to reduce cervical and anal cancer incidence and mortality after a much shorter interval in all infected people, even in aged subjects.

Keywords: Anal cancer, Cervical cancer, Human papillomavirus (HPV), Human Immunodeficiency virus (HIV), Prevention, Vaccine.

HUMAN PAPILLOMAVIRUSES, GENERALITIES

Papillomaviruses are a heterogeneous group with double strand circular DNA genome approximately 8,000 nucleotides long. All papillomaviruses are host-specific and strictly epitheliotropic. In HPV genome three general regions are present: an early region, which contains 1). Early open reading frames (ORF E1,

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E2, E4, E6, E7, E8); 2) Late region, which codes for L1 and L2 proteins, and 3) an upstream regulation region (URR) or long control region (LCR), where sequences with regulatory functions are located (Fig. **1**). E1 protein is essential for replication and amplification of the viral episome in the nucleus of infected cells. It is considered one of the best characterized helicases and provides unique insights on how HPVs use different host-cell machinery to replicate and amplify their genomes in a strictly controlled manner [1]. It is the only enzyme encoded by papillomaviruses and it is the most conserved protein encoded by HPV. E1 protein is required to increase the copy number of viral episome upon infection of basal keratinocytes, and then it is needed to maintain a constant level of episome in cells that are displaced upward in the epithelium and which begin to be differentiated. In the end it also promotes the amplification of viral genome during the productive phases of the viral cycle life, which takes place in the upper most differentiated epithelial layers. It must first recognize a specific segment of the viral genome known as "the origin of DNA replication" or ***ori***. E1 has the capacity to induce DNA damage with the subsequent possibility to participate in the early stages of cancer induced by high risk (HR) HPVs. A nuclear accumulation of E1 arrests cells in phase S and it triggers a DNA damage response. Moreover a complex formation with E2 attenuates the ability of E1 to induce DDR (DNA damage response). E2 regulates viral transcription, and it has multiple binding sites in the viral LCR. E2 also plays a role in the regulation of accurate genome partitioning during cell basal division [2].

The E4 coding region is located centrally within the E2 region, and its transcript is the most abundant among HPV coded mRNAs. In general E4 products become detectable at the onset of the vegetative viral genome amplification as the late stages of infection begin. E4 contributes to genome amplification success and virus synthesis because of its high level of expression; E4 is easily visualized in biopsies material by immunostaining, and it could be detected in lesions caused by diverse papillomavirus types. E4 can serve as a biomarker of active infection, and in the cases of high risk human types also for disease severity presence assessment [3 - 5]. In some cutaneous lesions, E4 can be expressed at a higher level than the virion coat proteins, and can account for as much as 30% of the viral proteins content in lesion sites [6, 7]. Historically, E4 ORF was considered to

be an "early" viral gene, however currently no obvious function for E4 during the early stages of virus life-cycle has yet been convincingly described. Both animal studies using CRPV [8] and HR HPV types [9, 10] have suggested a role for E4 in modulating genome amplification and virus synthesis. This activity is less pronounced in low risk (LR) HPV (*i.e.* HPV11). It is likely that its primary function is in some steps of virus release and transmission [11].

The difference between the E4 proteins of different papillomaviruses lies in the structures that they form in the infected cells, and in the timing at which these structures appear. Many cutaneous HPV types such as HPV1 and 63 (mu genus), HPV4 and 65 (gamma genus) and HPV5 and 8 (beta genus) form productive papillomas which are characterized by the appearance of inclusion granules. These inclusions are noticeable in the lower and mild epithelial layers and clearly visible in the haematoxylin and eosin stains. These results strengthen the argument to employ E4 protein production as a marker of disease severity. E5 proteins could contribute indirectly to genome amplification by modifying the cellular environment, with E5 also being involved in koilocytes formation [12], and it interferes with apoptosis process. E5 is also thought to make an important contribution to genome amplification success because of its ability to stabilize EGFR and to enhance EGF signalling and MAP kinase activity [13, 14]. However, it seems not to play an essential role in replication activity nor in neoplastic transformation, since some HPV genomes did not have E5 gene.

E6 protein is present both in HR and LR types; it is a basic protein, rich in cysteine and approximately 150 amino acids in size. Two zinc binding domains with the Cys-X-X-Cys are conserved in the E6 proteins of all HPV types. The HR E6 proteins are distributed to both the nucleus and the cytoplasm and have been reported to bind to over 12 different proteins [15].The transformation capacity of E6 protein has been demonstrated in NIH 3T3 cells (rodent fibroblast) [16] and in cancer derived cells, such as well SiHa and Cashy cell lines, which have E6 and E7 genes randomly integrated in their genome. They are constantly transcribed and carry out they oncogenic activity by inducing degradation of the tumor suppressor protein p53 *via* ubiquitin pathway. P53 protein is a well-characterized tumor suppressor that regulates the expression of proteins involved in cell cycle control, including the cyclin kinase inhibitor, p21. On exposure to DNA damage,

CHAPTER 2

Allosteric Integrase Inhibitors

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Abstract: In the recent years, integrase (IN) has emerged as an important new target for the development of anti-HIV-1 agents. The enzyme is involved in a key stage of the retroviral replicative cycle, and interacts with a range of cellular co-factors. Due to the absolute necessity of the enzyme for successful infection and the range of cellular co-factors employed by the enzyme, new ways of targeting both IN and its cofactors could yield agents with improved resistance profiles. Allosteric inhibitors are currently receiving a great deal of focus from both academia and industry alike and offer the possibility of a new class of anti-HIV-1 inhibitor.

Keywords: ALLINI, Allosteric, HIV-1, Integrase, LEDGIN, LEDGF/p75, Multimerization, PIC, Retrovirus, STI.

INTRODUCTION

Human immunodeficiency virus type-1 (HIV-1) and human immunodeficiency virus type-2 (HIV-2) are retroviruses [1, 2] that belong to the lentivirus genus and like a lot of retroviruses induce immunosuppression [3] in the host organism. How immunosuppression is achieved is not fully understood, but it involves HIV-1 evading both the innate [4 - 6] and adaptive [7] immune response. In addition, the virus is also able to establish latent reservoirs in specific immune cells, *e.g.* $CD4^+$ memory T cells [8] and other tissues, *e.g.* the CNS and the gut.

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Through the use of highly active antiretroviral therapy (HAART) [9, 10], the immunosuppression can be mitigated, but once treatment is withdrawn, there is a rapid viral rebound [11]. Also the poor fidelity [12, 13] shown by reverse transcriptase (RT) [14] when transcribing the viral genome into dsDNA also means that the viral populations can adapt very quickly to their environment and hence resistance is known for all classes of anti-HIV-1 agent [15, 16]. Therefore, until there is an effective way of dealing with both resistance and viral latency [17], there will be a need for new anti-HIV-1 agents.

Viral entry into host cells is a complex phenomenon [18] involving many steps operating in sequence. Initial contact with a host cell by the virus is mediated *via* heparin sulfate [19] and leads to the specific interaction between gp120 and the primary cellular receptor CD4 [20].

Gp120 is derived from the heavily glycosylated envelope protein Env gp160 and contains five conserved domains (C1-C5) and five variable loops (V1-V5) [21]. The binding of gp120 to CD4 induces a significant conformational change in gp120 that facilitates receptor engagement [22]. The binding to the chemokine co-receptor (CCR5 or CXCR4) [23, 24] by gp120 exposes the fusion peptide, gp41 which tethers the viral and host membrane together [25]. Following the fusion of the two membranes, the viral capsid is released into the cytosol of the cell, where the virus begins its replicative cycle.

Viral uncoating [26] and reverse transcription is initiated by a viral complex known as the reverse transcription complex (RTC) [27, 28]; the exact nature of the RTC is still to be elucidated but it is known to contain cellular factors and multiple viral proteins including RT, integrase (IN), matrix protein (MA), capsid protein (CA), nucleocapsid (NC), and the accessory protein, (viral protein, regulatory; Vpr) [29 - 31]. As the RTC transolcates towards the nucleus *via* elements of the cytoskeleton [32] (both the microtubule [27, 33] and microfilament [34] networks are used along with a range of associated proteins), it transforms into the preintegration complex (PIC) [35 - 38] and IN prepares the viral DNA for insertion.

IN catalyzes two processes *in vivo*; 3'-processing and strand transfer (ST) [39,

40]. Both processes are reliant upon the two magnesium ions (Mg^{2+}) in the active site of the enzyme in order to facilitate the chemistry; the 3'-processing process occurs in the cytoplasm as the PIC travels towards the nucleus. Many of the details of how HIV-1 gains entry into the nucleus are still unknown, but it is known to access the nucleus *via* the nuclear pore complex (NPC) [41, 42].

Once HIV-1 has gained entry to the nucleus of its target cell (HIV-1 infects both non-dividing primary cells and growth arrested cells [43, 44]), it selects an integration site in an active gene on the host chromatin [45] with the aid of the host protein, Lens epithelium-derived growth factor/p75 (LEDGF/p75) [46] and undertakes the ST reaction which results in permanent infection of the host cell.

A range of viral accessory proteins [4] help to orchestrate the translation by the host cell's machinery of the viral DNA in to the constituent parts of the HIV-1 virus and the newly synthesized proteins, gp120, gp41, Gag and Gag-Pro-Pol together with the viral RNA are transferred to the plasma membrane [47] where immature virus particles bud off from the cell. During budding, the viral enzyme protease [48, 49] is activated and it processes [50] the viral precursor proteins Gag and Gag-Pro-Pol into functional viral components [51] in a process known as maturation, resulting in infective viral particles.

The three Food and Drug Administration (FDA) approved IN inhibitors, raltegravir [52], elvitegravir [53] and dolutegravir [54] work by chelating to one or more of the Mg^{2+} ions inhibiting the strand transfer reaction and hence are known as strand transfer inhibitors (STI) [55, 56]. The introduction of ST IN inhibitors has added another point of attack in the replicative cycle of HIV-1, but due to the important multifunctional role that IN plays in the replicative cycle of the virus, modulation of its activity, particularly its interactions with other components of the PIC, offers the promise of developing a new class of IN inhibitors that are more resistant to the development of resistance. In the recent years, interest has grown in allosteric IN inhibitors that do disrupt the normal functioning of IN and this review will focus on the current state of the field.

CHAPTER 3

HAART: A Boon to Mankind

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Abstract: Human Immunodeficiency Virus (HIV) is a retrovirus which affects mainly the host's immune system along with other systems. Discovered in 1983, HIV created a havoc because of its high mortality due to opportunistic infections and AIDS related carcinoma. The pandemic caused by HIV was due to its easy transmission through blood, blood products, unprotected sex, sharing of needles among intravenous drug abusers and mother to foetus *etc*. Initially no drug or vaccine was available and the first antiretroviral drug zidovudine was approved for clinical use in 1987. Gradually different classes of antiretroviral drugs have been developed. With use of monotherapy, drug resistance in HIV developed fast due to mutation. In 1996, three studies reported that triple therapy effectively halted the replication of HIV and 60-80% reduction in HIV related deaths, illness and hospitalization, with this, the era of HAART (Highly Active Antiretroviral Therapy) began. HAART is actually Combination Antiretroviral Therapy (CART) and now has become the standard of care. Though HAART does not cure HIV, it stops HIV from replication and transmission to others. In September, 2015, Revised WHO Guidelines for global HIV treatment, has recommended the immediate initiation of ART at the time of diagnosis which has revolutionized HIV treatment. Now with HAART, the person infected with HIV can expect a normal to near normal life expectancy which is really a boon to mankind.

Keywords: Antiretroviral drugs, Combination therapy, Drug resistance, HAART, HIV replication cycle, Monotherapy, Pandemic of AIDS, Post exposure prophylaxis, Pre-exposure prophylaxis, Revised WHO Guidelines 2015.

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INTRODUCTION

The reporting of rare *Pneumocystis carinii* (now known as *Pneumocystis jiroveci*) pneumonia in 4 otherwise healthy homosexual individuals by a General Practioner Dr. Merle A.Sande in 1981, opened the Pandora's box, letting the World know about Acquired Immunodeficiency Syndrome (AIDS) and its devastating effects [1].

Dr. Sande was one of the first to recognize the inevitable public health crisis posed by this newly found disease. In 1983, Luc Antoine Montagnier, a French virologist who was the leader of the team that discovered Lymphaenopathy Associated Virus (LAV), a new type of Retrovirus, previously unknown in humans and the causative agent of AIDS [2]. Robert Charles Gallo, an American biomedical researcher and virologist along with his group isolated and characterized Human T lymphotropic virus-III (HTLV-III) in 1984 [3]. Gallo also reported that in HTLV-III infected persons, the lymph node follicles are the most important site for virus replication. It was also reported that HTLV-III were closely related to leukaemia viruses and was the causative agent of AIDS [3]. Both LAV and HTLV-III were known to cause AIDS and presently known as Human Immunodeficiency Virus-1 *i.e.* HIV-1 as per regulation of International Council for Taxonomy of Viruses (ICTV). Gallo was awarded his second Lasker Award in 1986 for determining that this retrovirus is the causative agent of Acquired Immunodeficiency Syndrome (AIDS) [4, 5]. Later on it was found that sera from prostitutes in Senegal, West Africa, did not react with HIV-1 but they were reacting with Simian Immunodeficiency Virus (SIV). In 1985, Montagnier also isolated a new virus from those sera, which is now known as HIV-2 [6]. In 2008, Luc Montagnier was awarded the Nobel Prize in Physiology and Medicine jointly with Francoise Barre-Sinoussi and Harald zur Hausen for the discovery of HIV, the causative agent of AIDS.

Then, whole world observed how man became the victim of AIDS, a multisystemic deadly disease without any treatment option. The HIV infected individuals were progressing to full blown AIDS and embracing death. WHO declared AIDS as Global Public Health Problem. Till date, HIV infections cause one of the most devastating disease that mankind is experiencing. No effective

vaccine could be developed. Presently, the anti-HIV drugs mainly target the viral enzymes to inhibit viral replication. Hence, a clear concept about the structure, genomic organization and replication of HIV should be there while discussing antiretroviral therapy (ART).

Morphology and Replication of HIV

Both HIV-1 and HIV-2 belongs to family Retroviridae and is a spherical enveloped virus having diameter 90-120 nm. The genome is composed of two identical copies of single stranded positive sense RNA. The Reverse transcriptase enzyme, which is characteristic of retroviruses, remain in association with Viral RNA. The genome is surrounded by an icosahedral capsid and then by matrix protein. The outermost layer is the envelope having glycoprotein spikes on the surface. The HIV genome contains three structural genes gag, pol and env which are characteristics of all Retroviruses. Along with that other nonstructural and regulatory genes specific for HIV are also present. The gag gene codes for a precursor protein p55 which cleave into p15, p18 and p24. The p24 is the most important core antigen which can be detected in patient's serum after HIV infection before seroconversion occurs. So, p24 is the earliest antigenic marker after HIV infection before antibody appears. Then p24 antibody appears and p24 antigen disappears. In full blown AIDS, the reappearance of p24 antigen indicates exacerbation of the disease and poor prognosis. The pol gene codes for reverse transcriptase enzyme and other viral enzymes such as protease, endonuclease *etc*. The env gene codes for a protein gp160, that is cleaved into gp120 and gp41.The gp120 remains as the projecting knob like spikes on viral surface and gp41 remains as transmembrane pedicle. The gp120 has the domains that binds to CD4 and coreceptors while gp41 anchors the transmembrane / surface complex in virus membrane and also causes fusion between host cell and viral membrane during viral entry. The gp120 is highly pleomorphic and contains five conserved domains (C1 to C5) and five highly variable domains that are stabilized by disulphide bond [7]. The gp120 is the major envelope antigen and antibody to gp120 is the earliest antibody to appear in patient's circulation after HIV infection and this stage is designated as seroconversion. The antibody to gp120 takes around 6 weeks to appear after HIV infection and remain in the circulation till the terminal stage of the disease.

CHAPTER 4

The Current Progress and Challenge in the Development of Entry Inhibitors of HIV-1

Chang Liu[*] and **Xiaohong Kong**[*]

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Abstract: The human immunodeficiency virus (HIV-1) enters cells through a series of molecular interactions between the envelope protein and cellular receptors, thus providing many opportunities to block infection. HIV-1 entry inhibitors are a complex group of drugs with multiple mechanisms of action depending on the stage of the viral entry process they target. Actually, entry inhibitors fall into three categories: attachment inhibitors, co-receptor inhibitors and fusion inhibitors. Maraviroc and Enfuvirtide–that target gp120-CCR5 interaction and gp41-mediated fusion are currently being used in the clinic. Meanwhile, a wide array of additional agents are in various stages of development. The small molecule attachment inhibitor BMS-663068 has shown potent antiviral activity in early phase studies, and phase II trials are underway. The post-attachment inhibitor ibalizumab has shown antiviral activity in phase I and II trials; further studies including subcutaneous delivery of drug to healthy individuals are anticipated. Cenicriviroc, a small-molecule CCR5 antagonist that also has activity as a CCR2 antagonist, has entered phase II studies. No CXCR4 antagonists are currently in clinical trials, but next-generation injectable peptide fusion inhibitors have been ongoing with human trials. These compounds should be used in drug combination regimens to achieve the highest possible benefit, tolerability and compliance and to diminish the risk of resistance development. Unfortunately, as is the case for other classes of antiretroviral drugs that target other steps in the viral life cycle, HIV-1 can also become resistant to entry inhibitors. In this part, we will summarize the current progress in the development of different class of entry inhibitors and the facing limitations in clinical use.

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Keywords: Attachment inhibitors, Co-receptor inhibitors, Entry inhibitors, Envelope glycoprotein, Fusion inhibitors, HIV, Resistance.

INTRODUCTION

Although vaccine is possible to prevent infections with some viruses, such as smallpox virus and hepatitis B virus (HBV), it is not for others: hepatitis C virus (HCV), human immunodeficiency virus (HIV), and so on [1]. Antiviral drugs are very important for those viruses without efficient vaccines. There are different strategies of antiviral drug designing, for HIV therapy is aimed at multiple drugs combination [2]. HIV, the causative agent of the acquired immunodeficiency syndrome (AIDS), belongs to the retrovirus family and targets the human immune system. Currently, the treatment of patients with antiviral drugs (ARVs), which has been the most advanced medical treatment of HIV-1 infection, can inhibit HIV-1 replication to undetectable levels. Today, more than twenty drugs representing antiretroviral classes that inhibit five different steps in the viral life cycle have been used in clinic, since zidovudine (AZT), the first drug for treating HIV infection, was approved in 1987. There are also new opportunities for exploitation of anti-HIV targets, and novel strategies of HIV eradication [3, 4].

The entry of HIV-1 into susceptible target cells is a complex, multi-stage process involving sequential attachment, CD4 binding, co-receptor binding, and membrane fusion. The first step in HIV-1 entry is that the surface subunit gp120 of the viral envelope binds to primary receptor CD4. The envelope glycoprotein of HIV-1 is a heterotrimer of three molecules of gp120 and three transmembrane subunits -- gp41 molecules, which remain being attached through non-covalent interactions [5, 6]. CD4 is on the surface of susceptible target cells, such as macrophages, T-helper lymphocytes. Conformation of the trimeric Env complex changes subsequently induced by specific interactions between CD4 and the viral envelope proteins (Env) including exposure of new epitopes in the gp120 surface subunit and undefined changes in non-covalent interactions between gp120 and the gp41 transmembrane subunit. These conformational changes are propitious to binding of gp120 to a chemokine co-receptor, either CCR5or CXCR4, depending on the Env sequence. The fusion peptide of the gp41 ectodomain inserts into the target cell membrane owing to co-receptor binding. Then, in the gp41 ectodomain,

the anti-parallel association of two helically coiled heptad repeats to form a six-helix bundle brings about the close approximation of the cell and virus membranes, leading to fusion [7 - 9]. Every stage in the process of entry affords a potential opportunity for developing antiretroviral drugs.

HIV-1 entry inhibitors are a complex group of drugs, which possess multiple mechanisms of action depending on the stage of the viral entry process that they target. Two entry inhibitors are approved for the treatment of HIV-1 infection currently. Maraviroc, a CCR5 antagonist, blocks interactions between Env and the CCR5 co-receptor [10]. Enfuvirtide, a fusion inhibitor, disrupts conformational changes in gp41 that drive membrane fusion [11]. Furthermore, the development of drugs targeting other stages in HIV-1 entry is ongoing.

In this part, we will summarize the current progress in the development of HIV-1 entry inhibitors and the facing limitations in clinical use.

ENTRY INHIBITOR

There are plenty of potential targets to impede the entry process as multiple sequential interactions within gp120 and gp41 and host surface proteins are involved in HIV-1 entry. As a result, entry inhibitors are a heterogeneous group of compounds which possess multiple mechanisms of action. Actually, There are three class antiretroviral agents targeting HV-1 entry: attachment inhibitor (inhibits HIV gp120 attachment to CD4), CCR5 inhibitor (inhibits HIV gp120 binding to CCR5, and suitable for R5 tropic virus) and fusion inhibitor (Table **4.1**). Entry inhibitors are currently being used in the clinical treatment, and some more are under development. Unfortunately, under normal circumstance, HIV can also become resistant to entry inhibitors when the existence of other classes of antiretroviral drugs that target other steps in the viral life cycle.

Here, we focus mainly on the drugs which are or have been tested in clinical trials.

Inhibitors of Interactions between Envelope Glycoprotein and CD4 Receptor

A number of strategies that can block interactions between CD4 and gp120 have been pursued since the identification of CD4 as the initial receptor for HIV-1. The

CHAPTER 5

Prospects of Reverse Transcriptase Inhibitors

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Abstract: Despite being the first anti-viral described to be effective against HIV, reverse transcriptase inhibitors remain the cornerstone of highly active antiretroviral therapy (HAART). There are two broad classes of reverse transcriptase inhibitor, the nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). In this part, we firstly introduce the approved reverse transcriptase inhibitors containing eight NRTIs (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine and tenofovir disoproxil fumarate) and five NNRTIs (nevirapine, efavirenz, delavirdine, etravirine and rilpivirine). As a dNTP analog, an NRTI is converted to a dNTP analog by a phosphorylation cascade performed by cellular kinases, and then RT catalytically incorporates the drug as an NRTI monophosphate at the 3'-end of the growing viral DNA primer. Upon incorporation, an NRTI inhibits the elongation of DNA primer because NRTIs lack a 3'-OH group that prevents addition of the next nucleotide. An NRTI-triphosphate does not block the activity of an RT molecule, however, certain RT mutations cause NRTI resistance by discriminating an NRTI-triphosphate from the analogous dNTP substrate. Unlike NRTIs that do not directly inhibit RT, an NNRTI drug binds to a hydrophobic pocket in the palm sub-domain adjacent to the base of the thumb sub-domain and allosterically inhibits DNA polymerization. The NNRTI pocket permits the design of highly specific inhibitors having low toxicities and minimal side effects. The NNRTI pocket is not required to be highly conserved for carrying out the enzymatic activity unlike the conserved active site or dNTP-binding site of RT. Therefore, HIV-1 has a relatively lower genetic barrier for developing NNRTI-resistance mutations than for NRTI-resistance mutations. Primary NNRTI-resistance mutations appear in and around the NNRTI pocket, that is, most of the pocket residues can mutate to confer NNRTI resistance. Then we will focus on six new drugs which are

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currently in preclinical or approved for second-line therapy and describe the patterns of resistance associated with their applications as well as the underlying mechanisms that have been described. Newer RTIs have greater anti-viral activity and less toxic than older. Some reverse transcriptase inhibitors with a low genetic barrier are more commonly used due to affordability and availability in resource-limited settings. While their application results in the emergence of specific patterns of antiviral resistance, useful strategies and new compounds are necessary for patients in such settings.

Keywords: Antiviral activity, Drug-resistant, Nonnucleoside reverse transcriptase inhibitors (NNRTIs), Nucleoside reverse transcriptase (NRTIs), Reverse transcriptase inhibitors (RTIs), Toxicity.

INTRODUCTION

During the HIV-1 life cycle, HIV-1 reverse transcriptase (RT) possesses the ability to convert its single-stranded RNA genome into double-stranded DNA [1]. Because of its unique association with retroviruses, RT has since long been considered as an attractive target, and pending elucidation of the role of the RT and retroviruses in any human pathology, numerous inhibitors of RT were described in 30 years. These inhibitors could be classified into nucleoside/ nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) two classes (Table **5.1**). NRTIs incorporate into nascent viral DNA and block further extension of DNA (Fig. **5.1**). NNRTIs stop HIV-1 replication by binding to the hydrophobic pocket within the p66 subunit of RT enzyme (Fig. **5.1**) [2]. NNRTIs are noncompetitive inhibitors of HIV-1 RT and do not require activation.

Table 5.1. Generic names and common abbreviations for FDA-approved reverse transcriptase inhibitors.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Zidovudine	AZT	Nevirapine	NEV
Didanosine	ddI	Efavirenz	EFV
Zalcitabine	ddC	Delavirdine	DLV
Stavudine	d4T	Etravirine	ETR
Lamivudine	3TC	Rilpivirine	RPV

(Table 5.1) contd.....

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**	
Abacavir	ABC		
Emtricitabine	FTC		
Tenofovir	TDF		

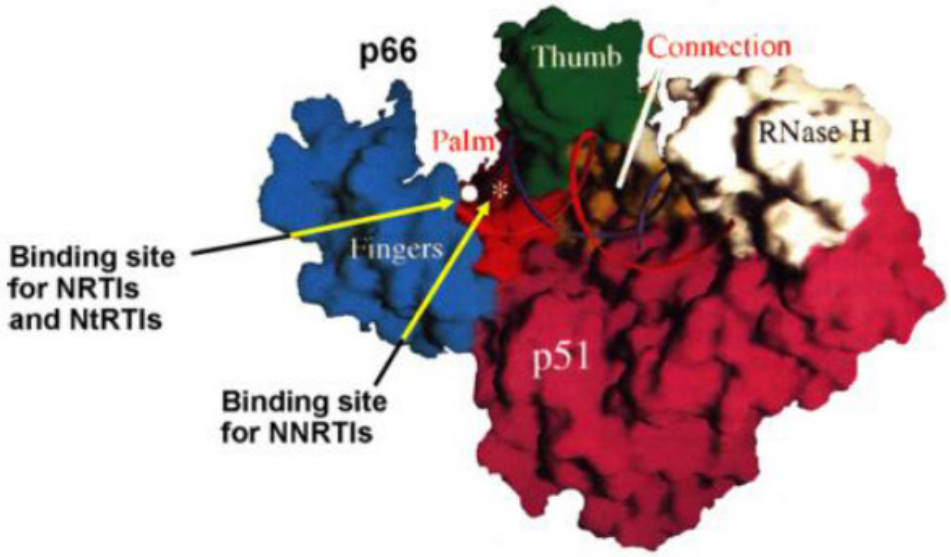

Fig. (5.1). Human immunodeficiency virus (HIV) reverse transcriptase with the binding site for NRTIs and NNRTIs.

NRTIs

In the Clinical Application of NRTIs

NRTIs are analogs of naturally occurring dNTPs that lack a 3'-hydroxyl group on theribose sugar/pseudosugar [3]. To exhibit antiviral activity, NRTIs must be metabolically converted by host-cell kinases to their corresponding triphosphate forms, which then inhibit viral DNA synthesis by acting as chain-terminators of DNA synthesis. So far, eight NRTIs-zidovudine (AZT, Retrovir®), didanosine (ddI, Videx®), zalcitabine (ddC, Hivid®), stavudine (d4T, Zerit®), lamivudine (3TC, Epivir®), abacavir (ABC, Ziagen®), emtricitabine ((-)FTC, Emtriva®) and tenofovir disoproxil fumarate (TDF, Viread®) have been approved by the US Food and Drug Administration (FDA) for the treatment of HIV (Fig. **5.2**) [4].

CHAPTER 6

HIV-1 Integrase Inhibitors: Targets and Clinical Application

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Abstract: Since the discovery of HIV as the etiology for AIDS 30 years ago, major progress has been made, including the discovery of drugs that now control the disease. Integration of the HIV-1 DNA is required and essential to maintain the viral DNA in the infected cell. Integration process occurs in several events, mainly in endonucleolytic processing of the 3' ends of the viral DNA and strand transfer or joining of the viral and cellular DNA. The design and discovery of integrase inhibitors were first focused on targeting the catalytic site of IN with a specific effect on strand transfer. Several integrase inhibitors were developed clinically. Here, we reviewed the integrase (IN) inhibitors from the discovery of the first compounds 20 years ago to the approval of two highly effective IN strand transfer inhibitors, raltegravir and elvitegravir, and the promising clinical activity of dolutegravir. We divide the development of integrase inhibitors into six parts, which are diketo acids, peptides, nucleotides, natural compounds and biological product, polyhydroxylated aromatic compounds and other inhibitors. After summarizing the molecular mechanism of integrase inhibitors, we discuss the remaining challenges. Those include: overcoming resistance to clinical drugs, long-term safety, cost of therapy, and the development of new classes of inhibitors.

Keywords: Diketo acids, HIV-1 integrase inhibitors, Natural compounds and biological product, Nucleotides, Peptides, Polyhydroxylated aromatic compounds.

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INTRODUCTION

Since the clinical identification of AIDS, There have emerged many extraordinary scientific efforts to find an effective therapeutic approach to combat with it, and highly active antiretroviral therapy (HAART) was an effective therapy applied in the clinical application [1]. HAART has had considerable success in controlling HIV infection. However, there are still two key issues: first, the emergence of extensively cross-resistant strains of HIV-1 (partly because of poor compliance), and second, the adverse effects (poor tolerability, drug−drug interactions, toxicities) of long-term use of these drug regimens, leading to poor patient compliance (namely, failure of patients to adhere to the drug regimen) [2]. Additional efforts to improve the current therapeutic approaches are needed. Among so many experimental inhibitors of HIV-1 replication, integrase inhibitors are considered to be a highly promising drug class. Insertion of the viral genome into host cell chromatin by the viral integrase (IN) is a necessary step for the propagation of retroviruses to allow the transcription of the viral genome and the production of viral proteins. When the virus enters the target cell, the viral RNA genome is reverse transcribed to form a linear, double-stranded DNA [3]. Integration is required for viral replication because the transcription of the viral genome and the production of viral proteins require the vDNA integrated into the host chromosome.

IN carries vDNA integration following two consecutive steps: 3'-processing (3'-P) in the cytoplasm and strand transfer (ST) in the nucleus (Fig. **6.1**). For 3'-P IN processing vDNA by cleaving its 3'-end immediately after a conserved CA dinucleotide, thereby releasing a GT dinucleotide from each long terminal repeats (LTRs) 3' ends. The pre-integration complex (PIC) then translocate to the nucleus where IN binds to the cellular target DNA. ST is carried out by IN tetramers, allowing the concerted integration of both extremities of the linear vDNA, five bases from each other on opposite strands, producing a 5-nucleotide sequence that is repeated at each side of the fully integrated proviral DNA. Thus, to complete the integration process, ST products need to be processed and fully sealed with the host genome. This "repair" step requires removal of the two mispaired nucleotides at the 5'-ends of the vDNA and gap filling. Once repaired, transcription, translation, and maturation of the different viral components lead to the assembly

of new particles budding out of the cell. Of note, a small but consistent fraction of PIC (around 1%) can undergo different processes after nuclear import [4]. Those include end-joining, homologous recombination, or auto integration (IN dependent) and produce circular forms of vDNA. Inhibition of IN markedly increases the proportion of those forms, raising the question of potential expression or DNA reservoirs for later integration [4, 5].

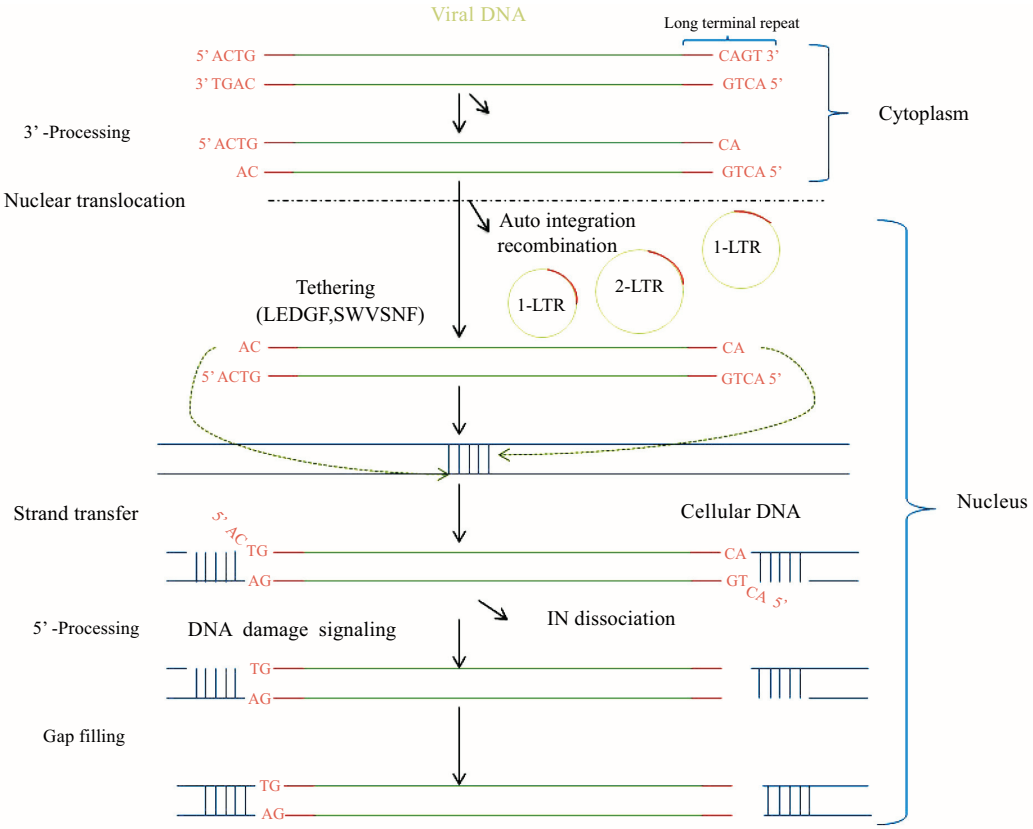

Fig. (6.1). Schematic steps for integration.

HIV-1 IN is a 32 kDa polypeptide of 288 amino acids, belonging to a family of proteins including RNase H, Ruv C, and other retroviral IN. IN contains three domains. The N-terminal domain (NTD, amino acids 1-49) contains a zinc-binding motif, HHCC, important for oligomerization. IN residues 50-212 correspond to the catalytic core domain (CCD), including a D-D35-X motif

CHAPTER 7

The Current Progress and Challenge in the Development of Protease Inhibitors of HIV-1

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Abstract: HIV protease plays a crucial role in the viral life cycle by processing the viral Gag and Gag-Pol polyproteins into structural and functional proteins essential for viral maturation. Inhibition of HIV-1 protease leads to the production of noninfectious virus particles and hence is an important therapeutic target for antiviral therapy in AIDS patients. It is a 99-residue protein belonging to the class of aspartic acid proteases, functioning as a catalytic dimer. The inclusion of protease inhibitors (PIs) in highly active antiretroviral therapy has significantly improved clinical outcomes in HIV-1 infected patients. The first HIV-1 protease inhibitors were developed in the mid-1990s and approved for clinical practice by 1995. So far ten such drugs have been approved for HIV treatment by the US Food and Drug Administration, including saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, fosamprenavir, atazanavir, tipranavir and darunavir, and broadly divided into first, second, and third generations. Expect for tipranavir, all of them are competitive peptidomimetic HIV protease inhibitors, which are able to mimic the transition state of HIV-1 protease substrates. However, the rapid emergence of drug-resistant HIV-1 strains and the appearance of cross-resistance are severely limiting the long-term treatment options, all of these make it urgent to develop new HIV protease inhibitors to combat the global disease. Thus, numerous efforts have been made in the design and synthesis of novel protease inhibitors with broad-spectrum activity against multidrug-resistant HIV-1 variants by medicinal chemists. Recently, considerable attention has been paid to the development of newer compounds capable of inhibiting wild-type and resistant HIV-1 protease. In this review, we have made an attempt to provide an overview on newly

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developing peptidomimetic and non-peptidomimetic PIs, and treatment of related recent patents in the development of novel PIs.

Keywords: Antiviral efficacy, Development, HIV, Modify, Peptidomimetic PIs, Non-peptidomimetic PIs, Toxicities, Treatment.

INTRODUCTION

Protease plays a vital role in the maturation of released virions. It is a 99-residue protein belonging to the class of aspartic acid proteases, functioning as a catalytic dimer [1 - 4]. It helps in processing Gag-Pol and Pol polyproteins into mature functional and structural proteins. In the absence of this enzyme, the nascent virions are non-infectious and hence the transmission of HIV-1 is prevented. Thus, protease seems to be an indispensable target in the treatment of HIV-1.

HIV-1 protease inhibitors are small molecules that inhibit HIV-1 replication by actively competing for the binding site of the viral protease enzyme [5]. The first HIV-1 protease inhibitors were developed in the mid-1990s and approved for clinical practice by 1995. So far ten such drugs have been approved for HIV treatment by the US Food and Drug Administration, broadly divided into first, second, and third generations, with progressive improvements in terms of potency and genetic barrier, dosing schedule, or toxic effects [6].

First-generation HIV-1 protease inhibitors: nelfinavir, indinavir, ritonavir, saquinavir (Fig. 7.1)

- High pill burden and low tolerance, mainly replaced by new protease inhibitors in clinical practice.
- Ritonavir mainly used as a component of boosted protease inhibitors.
- Nelfinavir not on the market.

Second-generation HIV-1 protease inhibitors: lopinavir, atazanavir, amprenavir, fosamprenavir (Fig. 7.2)

- Increased potency and tolerance.
- Lopinavir plus ritonavir: available as a heat-stable, fixed-dose combination; currently the only coformulated protease inhibitor; available and recommended

by WHO (since 2003) for second-line antiretroviral therapy in low-income and middle-income countries.

- Atazanavir plus ritonavir is recommended by WHO as an alternative for second-line antiretroviral therapy in low-income and middle-income countries.
- Fosamprenavir (prodrug of amprenavir) is preferred over amprenavir.

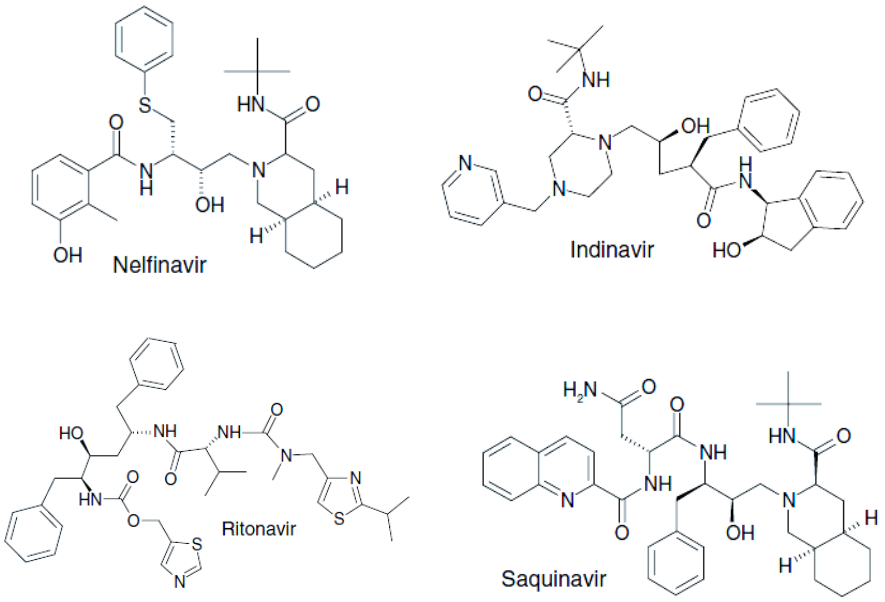

Fig. (7.1). Approved first-generation protease inhibitors.

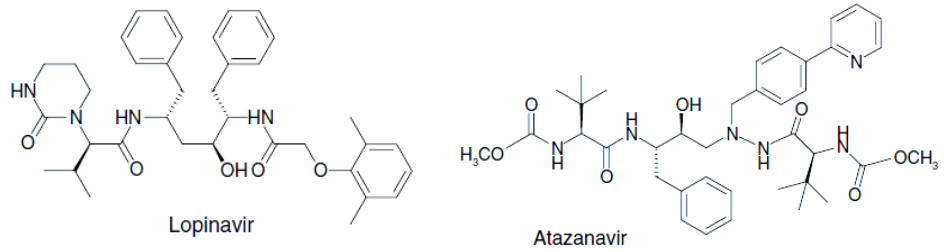

Fig. (7.2). Approved second -generation protease inhibitors.

CHAPTER 8

Blocking HIV-1 Replication *via* Targeting the Tat-mediated Transcriptional Machinery

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Abstract: HIV-1 infection can be effectively controlled by highly active antiretroviral therapy (HAART), which improves the quality of lives of infected individuals, but fails to completely eradicate the virus, even after decades of treatment. This issue, together with the emergence of multi-drug-resistant viruses, clearly underscores the continuing need to find novel agents able to target vulnerable steps in the viral replication cycle. HIV transcriptional regulation is a crucial step required to re-initiate viral replication from post-integration latency after interruption of therapy and to keep the virus in circulation. In this step, the viral protein Tat plays a central role by dramatically increasing the production of elongated transcripts through its unique interaction with the viral TAR RNA and the cellular cofactor P-TEFb, together with a myriad of other host factors which are recruited to the viral promoter to ensure efficient transcription. The transcriptional machinery, involving an intricate interplay of many viral and cellular components, offers a plethora of potential therapeutic targets that have not yet been exploited by any of the antiretroviral drugs used in therapy.

Keyword: HIV Tat, P-TEFb, TAR, Transcription inhibitors.

INTRODUCTION

The introduction of antiretroviral drugs (highly active antiretroviral therapy, HAART) has changed the infection of HIV-1 infection, leading to a significant reduction in AIDS-related morbidity and mortality, HIV treatment still faces

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many challenges. A major concern is the continued increase of virus variants resistant to more of the administered drugs [1, 2]. Therefore, continual endeavor should be identification of new targets for drug therapy characterized by being essential for viral replication and therefore less prone to mutational changes.

Within the HIV-1 life cycle, its gene transcription is an essential step and the only stage during which viral genome amplification occurs. Transcription or synthesis of HIV-1 protein coding genes by RNA polymerase is a complex and multistage process, which is regulated by the viral and cellular factors. It is well known that the virally encoded Tat protein is essential for efficient transcription and plays a central role in sustaining a high level viral replication [3]. In the absence of Tat, HIV only produces short completely spliced mRNAs encoding Tat and Rev, but cannot be efficiently elongated to produce full-length viral RNA genome [4]. Tat is a 86–101 residue regulatory protein, where N-terminal domain (residues 1-19), cystein (Cys)-rich domain (residue 20-39), core domain (residue 40-47), and basic domain (residue 48-56), are recognized to be essential for its transactivation function. Tat protein binds to the trans-activating response element (TAR), a highly stable secondary stem-loop structure located at the 5'-end of nascent viral RNA transcripts. This Tat/TAR complex can active the transcription. After Tat/TAR interaction, transcriptionally active complexes assembled at the LTR. The assembly of the Tat-TAR-P-TEFb complex to the HIV promoter activates Cdk9 kinase activities, which further auto-phosphorylates P-TEFb and hyper-phosphorylates the C-terminal domain of RNA polymerase II. Finally, these transcription elongation complexes lead to synthesize full-length HIV viral mRNA [5]. Some other cellular proteins have been reported to mediate or modulate Tat activity, such as Tat-associated kinases (TAKs), Tat-associated histone acetyl-tranferases (TAHs) and other many host factors. TAKs comprise RNApII carboxyl terminal domain (CTD) kinases TFIIH, PTEF-b, and CDK2/cyclin E, while TAHs include p300/CBP complex, the p300/CBP-associated factor (P/CAF) and GCN5 (Fig. **8.1**) [6].

Recent findings on the molecular mechanisms which control HIV-1 transcription and latency confirm the main role of the viral trans-activator protein Tat which acts like a molecular switch between productive transcription and latency [8]. Since Tat is required to sustain high level of HIV-1 active replication and is

essential for viruses to emerge from latency, Tat mediated transcription inhibitors could be a valid strategy that holds great potential in an attempt to eliminate viral latency. Considering that HIV-1 transcription regulation requires a complex interplay of both viral and cellular components, such inhibitors are expected to decrease the incidence of drug resistance. So further research efforts have focused on discovering and developing of selective HIV-1 replication inhibitors for Tat-mediated transcription. Accordingly, this part will report on the most recent and significant Tat mediated transcription inhibitors and molecules interfering with the well-consolidated Tat/TAR/P-TEFb axis, as well as novel therapeutics that interfere with other cellular cofactors which support the Tat trans-activating activity.

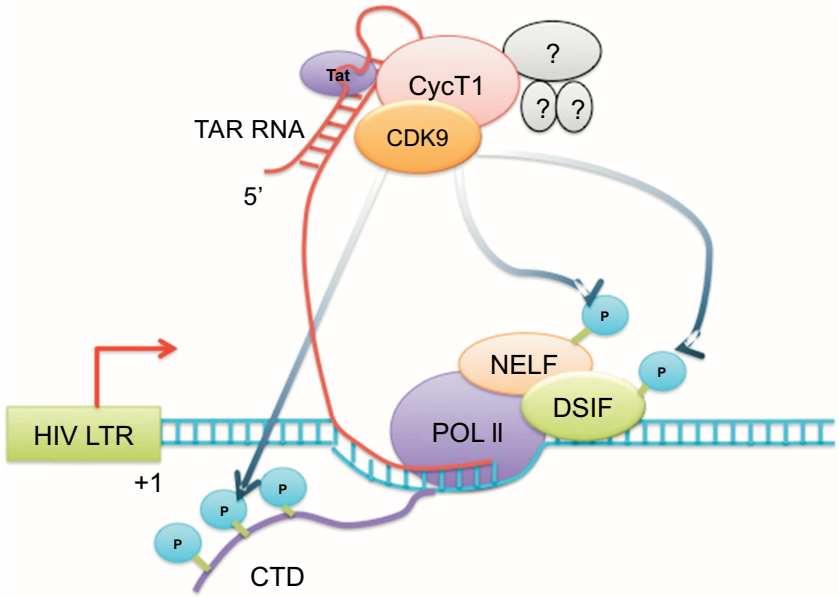

Fig. (8.1). The function of HIV Tat [7].

INHIBITORS OF TAT-MEDIATED TRANSCRIPTION

Inhibitors of TAR-Tat Interaction

TAR RNA forms a stable construction that includes a six-residue loop, a trinucleotide pyrimidine bulge, and extensive duplex structure. In particular, the pyrimidine bulge and adjacent duplex of TAR are specifically involved in Tat binding. It has been reported that disruption of this interaction between Tat and

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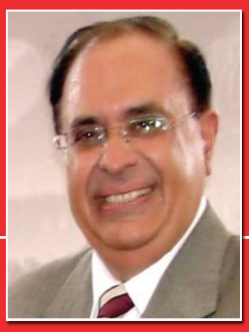

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