J. Enzyme Inhibition, 1992, Vol. 6, pp. 1–8
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OVERVIEW

DEVELOPMENT OF INHIBITORS OF REVERSE TRANSCRIPTASE AND PROTEASE AS THERAPEUTICS AGAINST HIV INFECTION

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(*Received January 3, 1992*)

When efforts to develop antiviral drugs for therapy of acquired immunodeficiency syndrome (AIDS) were initiated in 1983, one of the central questions was whether antiretroviral therapy would ever be feasible. In the past 8 years since then, a number of potentially useful strategies for the antiviral therapy of human immunodeficiency virus (HIV: for its genetic structure see Figure 1) infection have emerged.[1–3] One such approach is the use of the broad family of 2′,3′-dideoxynucleosides,[4,5] which includes two prescription drugs, 3′-azido-2′,3′-dideoxythymidine (AZT or zidovudine) and 2′.3′-dideoxyinosine (ddI or didanosine) (Figure 2). AZT has been shown to reduce the replication of HIV-1 *in vivo* and to confer significant clinical benefits in patients in both early and advanced stages of infection.[6–8] ddI has also been shown to bring about certain benefits to some patiens with AIDS and its related diseases.[9–12] ddI has recently been conditionally approved for treatment of both adult and pediatric patients with AIDS who do not tolerate AZT therapy or whose clinical status is deteriorating despite AZT therapy. Other members of the dideoxynucleoside family, 2′,3′-dideoxycytidine (ddC)[13,14] and 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T)[15] (Figure 1), have also been shown to be active against HIV-1 in short-term clinical trials. A permuted version of dideoxynucleoside analogues, 2′,3′-dideoxy-3′-thiacytidine (3TC)[16] (Figure 1), is also in a phase 1 clinical trial. Today, the central question is no longer whether antiretroviral therapy will be feasible, but rather, how to use the emerging knowledge of the replicative cycle of HIV to create new opportunities for therapy of HIV infection.

Successful antiviral drugs, in theory, exert their effects by interacting with viral receptors, virally encoded enzymes, viral structural components, viral genes or their transcripts, or cellular factors required for viral replication.[1–3] However, at present, no antiretroviral drug or agent is likely to be devoid of at least some toxicity or side effects, in particular in the therapy of AIDS, since patients with AIDS and its related diseases would have to receive antiretroviral therapy for a long period of time, perhaps for the rest of their lives. Nevertheless, it is possible to make considerable clinical progress by carefully titrating dose and schedule to achieve optimal antiviral activity while minimizing the risk or serious toxicities.

The armamentarium of antiretroviral agents is rapidly growing. We now have a

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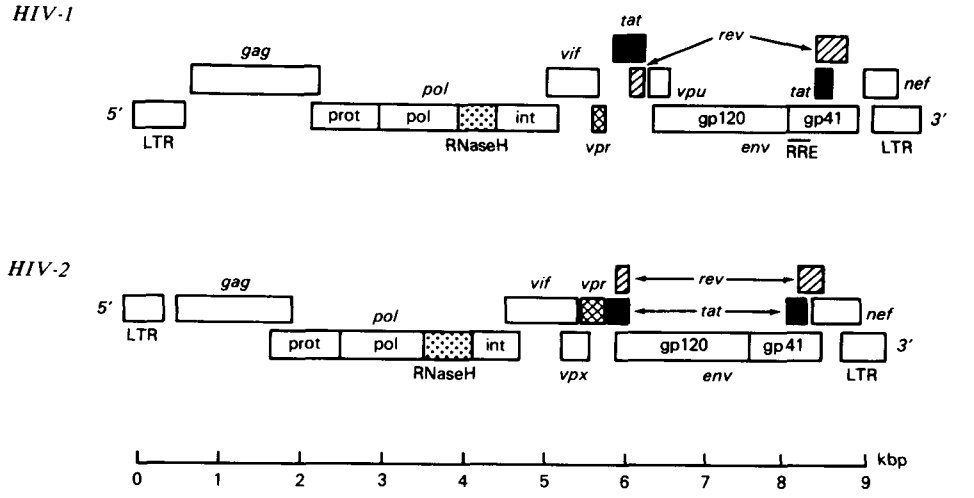

FIGURE 1 Genetic organization of HIV-1 and HIV-2. Three lanes in each panel represent three different reading frames where each gene is located. LTR, long terminal repeat; *gag*, group-specific antigen; *pol*, reverse transcriptase; prot, protease; int, integrase (endonuclease); *vif*, viral infectivity factor; *vpr*, viral protein R; *vpu*, viral protein U; *tat*, transactivating protein; *rev*, regulator of expression of virion proteins; *nef*, negative regulator factor; *vpx*, viral protein X. Within the LTR are three elements, U5, R, and U3 (not shown). Some sequences upstream of R in the transcript appear to be required for efficient polyadenylation; therefore polyadenylation is brought about by only the 3'LTR. The *rev*-responsive element (RRE) is located in the *env* of HIV-1.

number of drugs with different antiretroviral mechanisms. Efforts to optimize antiretroviral activities of certain compounds have also been made. For example, we have learned that substitution of an atom at a certain position in the base or ribose moiety can drastically alter the antiviral activities or other properties of a given nucleoside.[1-3,17-22] Although ddI became available for certain populations of patients with AIDS, the lipophilicity of dideoxypurine nucleosides is relatively low. This may limit the penetration of ddI into the central nervous system (CNS) where HIV replicates and probably causes a variety of neurological dysfunction, particularly in children with HIV infection. In fact, ddI appears to be less efficacious in improving HIV-related encephalopathy under the current dosing schedules.[11] In this regard, 6-halogen-substitution in dideoxypurine nucleosides has been shown to increase the lipophilicity.[22] This sort of modification may increase the penetration of dideoxypurine nucleoside analogues into the CNS, although further in-depth preclinical studies are required.

A number of non-nucleoside reverse transcriptase inhibitors have recently been reported.[23-26] These compounds include tetrahydro-imidazo [4,5,1,*jk*][1,4]-benzodiazepin-2-(1H)-one and -thione (TIBO) derivatives,[23] dipyridodiazepinone analogues,[24] pyridinone derivatives,[25] and certain bis(heteroaryl)piperazines[26] (Figure 3). Although these compounds are not structurally related, they appear to be related to each other in that they are active only against HIV-1 and inert against other retroviruses tested including HIV, simian immunodeficiency viruses and certain animal retroviruses. In this regard, a series of antiretroviral nucleosides, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT) and its analogues,[27] appear to fall

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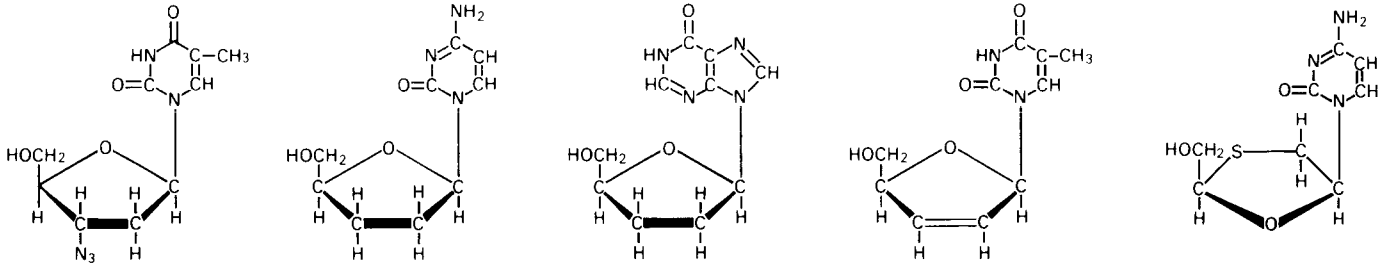

FIGURE 2 Selected nucleoside analogs active against HIV under preclinical and clinical development. Structures of 3′-azido-2′,3′-dideoxyinosine (ddI or didanosine), 2′,3′-didehydro-2′,3′,-dideoxythymidine (2′,3′-dideoxythymidinene or d4T), and the (−) enantiomer of 2′,3′-dideoxy-3′-thiacytidine (3TC) are shown.

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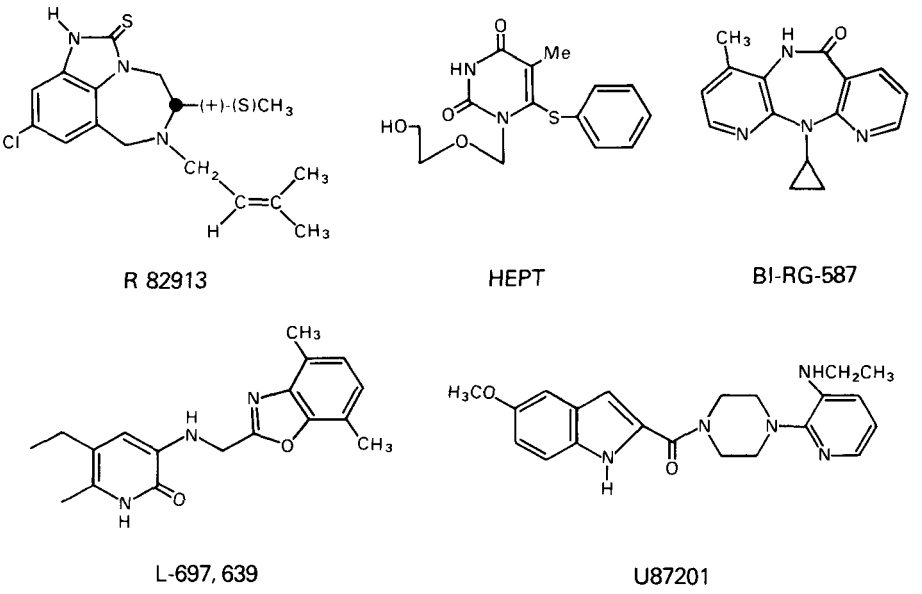

FIGURE 3 Selected non nucleoside HIV reverse transcriptase inhibitors. Structures of a TIBO analogue, R 82913; HEPT; a dipyridodiazepinone derivative, BI-RG-587; a pyridinone derivative, L-697, 639; and a bis(heteroaryl)piperazine derivative, U87201, are shown. HEPT is listed here since it shares individual properties with other non-nucleoside inhibitors (see text).

into the same category of non-nucleoside reverse transcriptase inhibitors. HEPT analogues resemble other non-nucleoside reverse transcriptase inhibitors in that they exert antiviral activity against HIV-1 but not against HIV-2 or animal retroviruses.[28] Furthermore, HEPT analogues do not require phosphorylation to exert antiretroviral effect. Very recently, it was reported that HIV-1 developed an extremely high level of resistance after serial passages in the presence of a pyridinone inhibitor *in vitro*.[29] Furthermore, such HIV variants resistant to pyridinone were cross-resistant to a TIBO compound (R82150) and a dipyridodiazepinone derivative (BI-RG-587) *in vitro*.[29] This observation may pose a serious problem for clinical application of some non-nucleoside reverse transcriptase inhibitors. Further careful studies are required to elucidate the mechanisms of resistance to these non-nucleoside compounds and to prevent emergence of such resistant HIV strains. In this Special Issue, De Clercq and his colleagues discuss prospects of some of these non-nucleoside reverse transcriptase inhibitors.

In the past 8 years, reverse transcriptase remained a prime target for antiretroviral therapy both because a number of inhibitors were known to discriminate reverse transcriptase and mammalian DNA polymerases, thus possibly avoiding toxicities or side effects, and because a great deal of knowledge regarding this enzyme had been accumulated since 1970, as will be discussed by DeVico and Sarngadharan in this Special Issue. Abbots and Wilson also discuss some interesting aspects of this enzyme. However, HIV has nine known genes (Figure 1) and has a strikingly complex system of genetic regulation. The very complexity of this virus could contribute to its defeat. Indeed, many steps in the replicative cycle of HIV have been considered as potential

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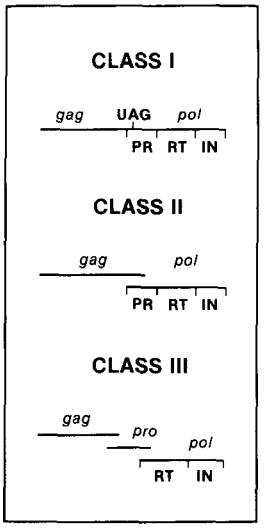

FIGURE 1 The genetic arrangement of *gag* and *pol* genes of various retroviruses. Class I: *gag* and *pol* genes in the same translational reading frame separated by a single termination codon. Class II: *pol* overlapping *gag* in the −1 reading frame. Class III: *gag* and *pol* separated by a third gene (*pro*) encoding the viral protease. Representative members of each class are given in the text.

encodes viral structural proteins, and is followed by the *env* gene, which encodes the viral surface glycoproteins. In addition to RT, the *pol* gene also encodes two other enzymes required for replication, the viral endonuclease/integrase (IN)[11–15] and in most cases the viral protease (PR).[16–19] Both mammalian and avian retroviral genomes encode these enzymes in the sequence PR–RT–IN.[14,15,17–20]

RT is expressed through the translation of a full length mRNA.[21] It is never synthesized as an individual protein, but is instead translated as part of a large polyprotein precursor[13,15,18,22–24] that contains the sequences of *gag* and *pol* gene products. The precursor, called gag-pol, is cleaved post-translationally to generate RT, along with the PR and IN enzymes.[16,24]

Despite the fact that gag and pol proteins are derived from a common precursor protein the retroviral genes are never arranged in the mRNA in a manner that allows uninterrupted translation of the precursor mRNA. A number of experiments have revealed that the expression of retroviral *pol* genes in fact depends upon several different mechanisms of translational suppression. Retroviruses can be divided into different classes based on which mechanism of suppression is used (Figure 1). The murine and feline leukemia viruses represent Class I, in which both the *gag* and *pol* genes are situated in the same translational reading frame in the mRNA, but are separated by a single amber UAG termination codon.[25,26] As a result, translation most frequently stops at this codon to produce the gag precursor polypeptide. Between 2% and 5% of the time, however, a translational read through event occurs and the gag-pol precursor is synthesized.[25–28] With the murine leukemia viruses, a glutamine residue is inserted at the position of the amber codon[25,27] and thus becomes the fifth residue in the amino acid sequence of the protease.[25]

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plasma half-life and poor oral bioavailability. In this Special Issue, Meek Discusses the role of HIV-1 protease in the viral replicative cycle and the strategy to use retroviral protease inhibitors as therapeutics for the treatment of AIDS.

As described at the outset, a variety of potentially useful strategies for the treatment of HIV infection have been considered and a number of antiretroviral agents are now in various stages of preclinical and clinical development. However, in the past several years, a number of formidable challenging issues have emerged. They include (i) the long-term drug related toxicities, (ii) the partial, limited restoration of immunological dysfunctions, and (iii) the development of various cancers, in particular, as improved therapies result in prolonged survival.[35] Because of the chronic nature of HIV infection and the inherent limitations of the current antiretroviral therapies in terms of relatively lower therapeutic ratios, it is most likely that future improved antiviral therapy would include the combined use of multiple antiretroviral drugs and, if available, certain immunopotentiating measures, as will be discussed below. Other formidable challenges involve, (iv) the emergence of drug-resistant HIV variants. Notable accomplishments on the study of AZT-resistant HIV variants have been made by Richman, Larder, and several other pioneering investigators.[36–39] Recently, HIV variants with a mutation associated with reduced *in vitro* sensitivity to ddI have also been isolated from patients with AIDS who received long-term ddI therapy,[40] although a consensus has not been reached as yet.[41] Richman discusses what has been learned and the prospect of drug resistance in this Special Issue. Finally, (v) the lack of methodologies to quantitate and monitor the effect of antiviral therapy has also posed a serious problem in assessing prognosis of patients with HIV infection and evaluating effects of antiretroviral therapy. Although certain state-of-the-art technologies such as the polymerase chain reaction or PCR have been exploited to establish new methods for quantification of viral load and possible monitoring of *in vivo* antiviral activity of therapy,[42,43] much more effort is urgently required in this area.

A variety of drugs are now undergoing clinical testing. However, many drugs may have serious dose-limiting side effects. A logical extension of current approaches for therapy of HIV infection would be the use of combinations of multiple antiviral agents which have different antiretroviral mechanisms or use different metabolic pathways for conversion to their corresponding active moieties.[44–47] For example, the antiretroviral effect of ddI is potentiated with ribavirin in a synergistic manner. This potentiation is caused at least in part because ribavirin stimulates the conversion of ddI to its putative active moiety, ddATP.[48–49] As such, combined use of drugs may enhance the antiretroviral activity of each drug but also reduce the adverse effects of each individual drug. The development of drug-resistant HIV variants may also be blocked or delayed in a combined use of multiple drugs. The issue of combination therapy and future drug development will be discussed by Yarchoan and Broder in this Special Issue.

Although we now have two prescription drugs, AZT and ddI, in our hands for treatment of AIDS and its related diseases, antiretroviral therapy is still in its early developmental stage. In the future, a number of effective strategies affecting multiple steps in viral replication will be available, and therapies with multiple drugs, combined with means for restoring immunoligic activity and preventing and treating AIDS-associated malignancies, will provide a major impact against the morbidity and mortality associated with infection with HIV-1. However, further progress in this area

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will require further understanding of the replicative cycle of HIV and clinical trials using the principles of the scientific method tightly coupled with basic research efforts.

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