Review paper

CURRENT APPROACHES TO ANTI-HIV-1 THERAPY

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SUMMARY

The acronym AIDS ("acquired immunodeficiency syndrome") has become the symbol for one of the biggest challenges to medicine in the 20th century. Already 2 years after the first reports on patients suffering from Kaposi's sarcoma or Pneumocystis carinii pneumonia a human retrovirus was identified as the infectious cause for AIDS. This retrovirus, now known as human immunodeficiency virus type 1 (HIV-1), has been the target of a combined effort of biological, medical and pharmacological research over the past decade. Whereas many different antiretroviral therapeutic strategies are currently still tested in laboratories or in clinical trials, some anti-HIV-1 drugs have already made their way to clinical routine application.

KEY WORDS

HIV-1, AIDS, antiretroviral treatment, nucleoside analogs

INTRODUCTION

All possible approaches to anti-HIV-1 therapy have to take into account the complex life cycle of lentiviruses as depicted in the figure 1. Every single step of the HIV-1 life cycle, from attachment of the virion to the membrane of target cells to the budding and release of new infectious virus, represents a possible target for therapeutic intervention. Whereas avian and lower vertebrate retroviruses produce only structural proteins, HIV-1 possesses also transregulating proteins which are able to modulate expression of the virus (1).

ANTIRETROVIRAL STRATEGIES

Of all conceivable antiretroviral strategies, the most successful will fight the virus before it reaches the nucleus of the infected cell. Besides blocking of receptor binding and virus uptake, the disturbance of the synthesis of the DNA provirus by the reverse transcriptase (RT) is still one of the most promising approaches. Because the RT is not a cellular enzyme, it is conceivable to target it without impairing vital functions within the cell. Two types of substances have emerged over the past decade as most promising candidates: nucleoside analogs and non-nucleoside RT inhibitors (2,3).

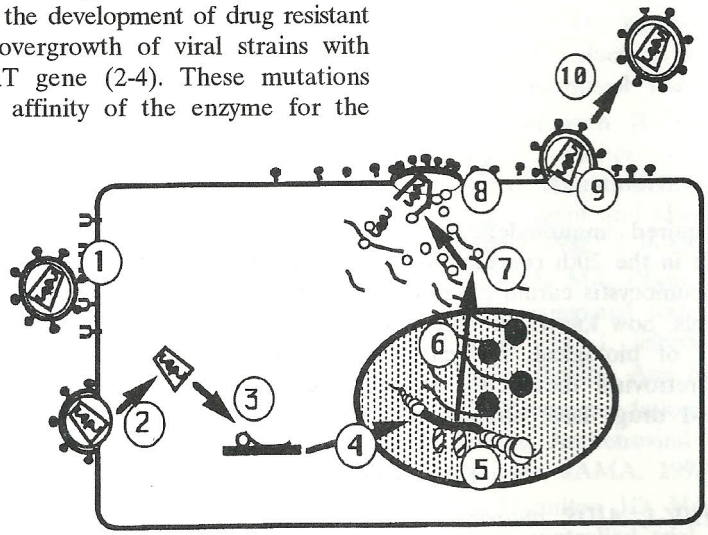
a. Nucleoside analogs.

Dideoxynucleosides are identical to deoxynucleosides, except for a critical side chain. Like deoxynucleosides they are taken up into the cells and are phosphorylated

at the 5'position by cellular kinases. However, after they are included into a growing DNA strand, further DNA synthesis is inhibited because the substitution of the -OH group at position 3' of the pentose ring does not allow the formation of a phosphodiester. This process is called chain termination. Since the HIV-1 RT is far more susceptible to the inhibition by dideoxynucleotides than the polymerase-α which is responsible for the synthesis of cellular DNA, inhibition of the RT occurs at concentrations where no impairment of the cellular enzyme is noticeable. The fact that the mitochondrial polymerase-γ and the polymerase-ß are also inhibited at relatively low concentrations might be an explanation for some of the side effects of the therapy with dideoxynucleotides, like myopathy and peripheral neuropathy (3). A limiting factor in the use of dideoxynucleosides is the development of drug resistant HIV-1 due to the overgrowth of viral strains with mutations in the RT gene (2-4). These mutations result in a reduced affinity of the enzyme for the respective dideoxynucleoside. In vitro, dideoxynucleoside-resistance manifests as virus replication in the presence of the drug, clinically, progression of HIV disease is observed.

b. Non-nucleoside RT inhibitors.

These substances comprise benzodiazepines (e.g TIBO derivatives, Nevirapine), pyridinone (e.g. L-compounds) and piperazine (e.g. U-90152, U-87201E) derivatives which, unlike nucleoside analogs, bind to a site distant from the nucleoside binding site of the HIV-1 RT (2). Although development of drug resistant viral strains has been observed more rapidly than with nucleoside analogs, some of these substances have entered clinical trials as monotherapy or in combination with other RT inhibitors.



steps of viral replication	potential therapeutics
1. virus-binding	soluble CD4, monoclonal antibodies
2. uncoating	hypericin
3. reverse transcription	nucleoside-analogs (AZT, ddC, ddI, d4T, 3TC, MEA) non-nucleoside RT inhibitors (Tibo, piperazine- and pyridinone-derivatives)
4. Migration of the provirus to the nucleus, integration	currently no potential drug available
5. viral transcription	HIV-1-tat antagonists, Ro24-7429, TAR decoys
6. transport of the viral mRNA to the cytoplasm	RRE decoys, transdominant HIV-1-rev mutants
7. protein synthesis	ribozymes, antisense molecules, inhibitors of glycosylation
8. RNA packaging, virus assembly	transdominant gag mutants, ribozymes, antisense RNA/DNA
9. virus budding	interferon α
10. virus maturation	protease inhibitors (U-81749, A77003, Ro 31-8959)

Fig. 1. The HIV-1 life cycle and possible antiretroviral strategies.

Of all antiretroviral drugs which have undergone clinical testing, the three nucleoside-analogs 3'-azido-3'deoxythymidin, *(AZT, zidovudine)*, 2',3'-dideoxyinosine *(ddI, didanosine)* and 2',3'-dideoxycytidin *(ddC, zalcitabine)* are currently used by most clinicians to treat HIV-1 infected patients.

Zidovudine was initially given successfully to patients with AIDS and AIDS related complex at 1500 mg daily (5). More recent studies showed that a reduced dose of 600 mg daily has the same therapeutic effect but is associated with less toxicity (6,7). Zidovudine side effects like headache, nausea, fatigue and disturbances of the hemopoietic system including macrocytosis with and without anemia (75% of patients) and neutropenia (50% of patients) as well as hyperpigmentation of nails are seen within 4-12 weeks after initiation of therapy whereas zidovudine-associated myopathy is only seen after 24 weeks (8,9). Side effects are fully reversible after discontinuation of therapy. *Didanosine,* an adenine-analog, like zidovudine is able to increase the CD4+ T cell-numbers and slow down disease progression (10,11). Bioavailability of didanosine is not as good as that of zidovudine due to poor resorption and degradation of the drug at acidic pH (12). The main side effects of didanosine are the occurrence of pancreatitis (acute fatal pancreatitis is seen in 0.4% of all cases) and a reversible sensorimotoric peripheral neuropathy. The cytidineanalog *zalcitabine* is inferior to zidovudine for initiation therapy, but is effective in combination with zidovudine and as monotherapy in patients after prior zidovudine therapy for several months (13,14). The main side effects of zalcitabine comprise reversible oral aphthae and sensorimotoric peripheral neuropathies (10%).

In agreement with the results of a State of the Art Conference on Anti-Retroviral Therapy for adult HIV-infected Patients at the NIAID in Bethesda, MD, USA (15), zidovudine at 600 mg (3 x 200 mg) daily is the antiretroviral therapy of first choice if there are no contraindications (e.g. manifest anemia or neutropenia). Although didanosin (500 mg and 750 mg/d) has been shown to be equally effective it is apparently less well tolerated by the patients.

As to the question when to initiate antiretroviral therapy, the logical approach would be to start therapy immediately after infection. Indeed, several studies have shown in the past that zidovudine therapy during asymptomatic HIV-1 infection may result in an improved quality of life and in a delayed progression to AIDS (16, 17). However, a European multicenter study ("Concorde", 18) could demonstrate no survival benefit of a group of patients receiving antiretroviral therapy over a study group receiving placebo. Although the discussion about the latter study is not finished yet, the bottom line of current wisdom is that early antiretroviral therapy, with the currently available drugs, does not have a dramatic clinical benefit.

There is general agreement that initiation of antiretroviral therapy is not necessary when numbers of CD4+ T cells are above 500/µl. When CD4+ T cell numbers drop below 500 but remain at a stable level, it is up to the individual physician to decide whether or not to start antiretroviral treatment - support for both decisions is in the literature. In this context it is important to remember that a therapy decision should be based on at least two independent CD4+ T cell counts because of daily and circadian fluctuations in T cell numbers. If a steady decline of CD4+ T cells ranging from 500-200/µl is observed, therapy should be initiated with zidovudine 3 x 200 mg as first choice drug. Such a therapy is strongly recommended, if a clinical deterioration with weight loss, oral thrush, oral hairy leucoplakia etc. is observed. Similarly, a decline of CD4+ T cells below 200/µl should lead to the initiation of therapy. If zidovudine side effects are observed, antiretroviral therapy should be switched to didanosine or zalcitabine. Such a change should also be considered.

(1) if laboratory data are indicative of a progression of immunodeficiency (quick decline of CD4+ T cells and rise of serum p24 antigen, ß2-microglobulin and neopterine) under zidovudine monotherapy, even in the absence of clinical progression,
(2) if therapy failure of zidovudine as defined by clinical progression and appearance of HIV-1-associated symptoms becomes evident even in the absence of laboratory changes.

Alternative antiretroviral treatment consists of didanosine (2 x 200 mg/d for patients above 60 kg, 2 x 125 mg/d for patients < 60 kg) or zalcitabine 3 x 0.75 mg/d. Both regimens yielded good results in clinical studies in patients with 50 - 500 CD4+ T cells/µl.

ZIDOVUDINE THERAPY IN PREGNANCY

In April 1994 the results of a placebo controlled double blind study of zidovudine treatment during pregnancy and birth, and of the newborn during the first 6 weeks after birth, were released. Only 8% of children in the study group, but 23% in the control group, were infected by HIV-1.

FUTURE DIRECTION

Similarly to tuberculosis therapy and chemotherapy for internal malignancies, a combination of several antiretroviral drugs is a promising approach for the near future. Encouraging results are already emerging from clinical studies involving different combinations of nucleoside and non-nucleoside RT inhibitors, but also drugs directed against other steps of the retroviral life cycle will join the antiretroviral armentarium in the foreseeable future.

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