Acquired immune deficiency syndrome (AIDS) is an infectious disease provoked by human immunodeficiency virus [1] and responsible for more than 34 million affected people according to the reports of UNAIDS [2]. This disease is one of the most dangerous and serious pandemic diseases of nowadays being the fourth cause of death worldwide. The disease interferes with the immune system and prevents its functioning, making people with AIDS more likely to get infections, such as opportunistic infections and tumors that usually do not affect people with functional immune systems.

Thus the aim of scientific community was to find agents possible to treat this disease and it should be mentioned that the development of the antiretroviral therapy has been of the most dramatic evolution.

In order to fight against HIV virus it is necessary to know its replication cycle. Based on it have been identified four targets for the development of effective anti-HIV drugs and they are:

1. Fusion and entrance into the cells
2. The reverse transcriptase
3. The integrase
4. Finally the protease

The first antiretroviral drug entered the battle against AIDS was Zidovudine (or AZT) in 1987 and belongs to the class of reverse transcriptase inhibitors.

It is a highly toxic drug, and the patient would take 12 tablets a day. Nevertheless, for some patients meant a slight prolongation of life.

Soon, however, the use of a single drug led to the development of resistant virus and, therefore, is the 1995 "erupted" the idea of combined drug therapy, i.e. Using three or more drugs in combination. Thus, current antiretroviral therapy (HAART) against HIV-1 infections is based on the combination of multiple drugs acting on different viral targets. Essential components of this combinatorial chemotherapy are the viral reverse transcriptase (RT) inhibitors.

Since appearance of the HIV virus only twenty five drugs were approved for treatment of AIDS.

The major target for antiviral chemotherapy of AIDS is reverse transcriptase (RT) since it is a key enzyme in HIV replication cycle [3-7]. Two classes of RT inhibitors are known: nucleoside RT inhibitors(NRTIs) and non-nucleoside RT inhibitors (NNRTIs).

The nucleoside Reverse Transcriptase Inhibitors (NRTIs), as already mentioned, were between the first drugs approved for AIDS therapy. Some examples of the drugs of this category are: Abacavir (Ziagen), Emtricitabine (Emtriva), Tenofovir (Viread), Zidovudine (Retrovir), Lamivudine (Epivir), Stavudine (Zerit) with the first approve being Zidovudine (AZT). They bind to the active site of the enzyme wherein the physiologically dideoxy-triphosphate nucleotides bind preventing further elongation after incorporation in the developing DNA strand .Despite the large number of NRTIs they have a disadvantage, since they cause serious side effects. First of all they are toxic to mitochondria. Furthermore, they are responsible for cardiotoxicity [8] and hepatotoxicity [9,10], lipodystrophy [11,12], renal disfunction [13,14], lactic acidosis [15], neurological and psychiatric disorders [16-18], dyslipidemia [19], oxidative stress [20].

Non-nucleoside Reverse transcriptase inhibitors (NNRTIs) are structurally diverse able to initiate conformational changes in HIV-RT due to the binding to the allosteric center of enzyme [21]. Actually they are compounds with a variety of heterocyclic rings in their molecules. For example, benzoxazin-2-one (Efavirenz), dipyrirdo[1,4]diazepin-6-one (Nevirapine), pyrimidine (Etravirine), piperazine and indolyl moieties (Delavirdine).The potency of reverse transcriptase inhibitor differs among the inhibitors. These drugs exhibited good potency with low toxicity but due to development of resistant strains with mutation the
first line drugs appeared to be problematic. The next generation FDA approved drugs etravirin [22] and rilpivirin [23] showed completely different profile regarding mutants, displaying very good activity against wild-type as well as the most frequent mutant HIV strains. Thus, they are more safe.

Except of the molecules approved by FDA, many other compounds have been found as potent RT inhibitors. [24-29] Among them are benzothiazine dioxides [26], 6-arylmethyl-substituted S-DABOs [27], 2-adamantyl-substituted thiazolidin-4-ones [28] lectines [29] and many others.

Despite the diversity in structure all NNRTIs approved, bind to the same site of RT. A mutation providing resistance to one NNRTI, also provides resistance to all other preparations of this class (\textit{\textquotedbl}cross resistance\textit{\textquotedbl}).

This is one reason why it is important to synthesize new NNRTIs, trying to find new compounds which will preferentially interact with another part of the enzyme.

REFERENCES