4'-C-Ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) has attracted much attention due to its extremely excellent anti-HIV activity, for example, EFdA prevents the emergence of resistant HIV mutants, and is over 400 times more active than AZT and several orders of magnitude more active than the other clinical reverse-transcriptase inhibitory 2', 3'-dideoxy-nucleoside drugs, very low toxic, very long acting, very useful for the prevention of HIV-infection. EFdA is now under clinical investigation by Merck & Co. as MK-8591. In the beginning, a general idea for the development of anti-viral modified nucleosides will be presented, and then the development of EFdA will be discussed and the clinical results by Merck will be also presented. For the design of the modified nucleoside which could solve the problems that the clinical drugs have (emergence of drug-resistant HIV mutants, adverse effect by drugs, necessity to take quite a few amount of drugs), the following working hypotheses were proposed. They are: The way to prevent the emergence of drug-resistant HIV mutants, the way to decrease the toxicity of modified nucleosides, the way to provide the modified nucleoside with stability to both enzymatic and acidic glycolysis for long acting. 4'-C-substituted-2'-deoxynucleoside (4'SdN) was designed to meet the hypotheses (1), (3), and the additional modification of 4'SdN was performed to meet the hypothesis. The details of the hypotheses and the reasons for the design of 4'SdN will be discussed. To prevent the deamination of adenine base by adenosine deaminase, a fluorine atom was introduced at the 2-position of adenine. Finally, EFdA, modified at the two position (2 and 4') of the physiologic 2'-deoxyadenosine and has extremely excellent anti-HIV activity, was successfully developed.