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Commentary

Nucleotide Reverse Transcriptase Inhibitors for Antiretroviral Therapy

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DESCRIPTION

The first class of antiretroviral medications to receive FDA approval was the NUcleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs). NRTIs are administered as prodrugs and must enter the host cell where they must be phosphorylated in order to function. Upon entering the host cell, the medication will be activated by cellular kinases.

Reverse transcriptase enzyme activity is inhibited by nucleoside reverse transcriptase inhibitors, which are nucleoside analogues. Viral propagation is slowed or stopped by this enzyme inhibition. The majority of NRTIs need to be taken numerous times per day, do not interfere with other medications, and may be taken either with or without meals. Didanosine, however, must be taken on an empty stomach since it can reduce the absorption of other Antiretrovirals when administered concurrently. All NRTIs have been linked, albeit seldom, to a deadly lactic acidosis and hepatic steatosis syndrome.

Tenofovir Disoproxil Fumarate (TDF), a nucleotide analogue reverse-transcriptase inhibitor, is frequently used to treat Hepatitis B Virus (HBV) and Human Immunodeficiency Virus infection (HIV). Long-term TDF use, however, is linked to a higher incidence of bone loss, osteoporosis, fractures, and other negative effects. On bone homeostasis and defect repair in mice, we looked at the impact of prolonged TDF usage. TDF prevented MC3T3-E1 cells from differentiating into osteoblasts and mineralizing *in vitro*. TDF was administered to 8-week-old C57BL/6 female mice for 38 days *in vivo* to mimic a chronic treatment. Reduced bone microarchitecture and four-point bending test results were seen in long bones.

Tenofovir is a nucleotide reverse transcriptase inhibitor, a subclass defined by fewer chemical steps required for intracellular action and a negative charge that effectively prolongs the compound's activity in the cell and permits once-daily delivery. The cornerstone of modern HIV multidrug regimens, NRTIs was the first antiretroviral medications to be administered.

HIV continues to be a global burden more than 40 years after the pandemic began, and a treatment is currently not in the cards. To treat and suppress HIV infection, Highly Active Antiretroviral Therapy (HAART) has thankfully been created. The mainstay of HIV treatment has evolved into combinations of two to three medications that target important viral proteins, including those that block HIV Reverse Transcriptase (RT). The history, mechanism of action, resistance, and current clinical application of Nucleoside Reverse Transcriptase Inhibitors (NRTIs), such as chain terminators, delayed chain terminators, Nucleoside Reverse Transcriptase Translocation Inhibitors (NRTTIs), and Nucleotide competing RT Inhibitors (NcRTIs), including long-acting regimens, are covered all together. A multi-gram synthesis of a nucleotide-competing reverse transcriptase inhibitor that is efficient. A chiral auxiliary-assisted alcohol resolution, a Mitsunobu reaction using a carbamate, and a lithium-iodide exchange/Weinreb ketone synthesis tandem are used in the synthesis. These chemical transitions were improved in order to boost synthesis yield. The pathway is completed by a late-stage palladium-catalyzed cyanation followed by the production of a pyrimidine-2-one ring.

Three decades ago, the nucleoside analogue 3-Azidothymidine (AZT) was found to effectively inhibit HIV replication in cell culture. Subsequent research revealed that AZT works by selectively inhibiting HIV Reverse Transcriptase (RT) *via* its triphosphate metabolite. These discoveries led to the development of the first antiretroviral class: nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs). Over time, NRTIs developed into the primary component of antiretroviral medication combinations that are currently used to treat all groups of HIV-infected people. Eight individual NRTIs, four fixed-dose combinations of two or three NRTIs, and one comprehensive fixed-dose regimen combining two NRTIs and one non-nucleoside RT inhibitor are currently available for clinical use.

Several NRTIs or their prodrugs are at various phases of clinical development, and additional powerful NRTIs are continually being discovered *via* drug discovery activities. The fundamental concepts of NRTI *in vitro* and *in vivo* pharmacology, examine their clinical usage, including the constraints of long-term NRTI therapy, and detail newly found NRTIs with promising pharmacological profiles, with a focus on those in the research pathway.

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