

Adefovir dipivoxil

A Viewpoint by Arnold Fridland

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Nucleoside compounds remain important components of current therapeutic strategies aimed at controlling HIV infection. Unfortunately, the efficacy of currently approved agents is limited, particularly due to cross resistance to different drugs, nonadherence and unfavourable pharmacokinetics.

Adefovir dipivoxil is the oral form of adefovir (ADV, PMEA). Compounds such as ADV can be considered as monophosphates in which the first phosphate group has already been added as a phosphonate group. The initial kinase phosphorylation is a crucial step in the intracellular metabolism of most anti-HIV nucleoside compounds and, together with the intracellular half-life of the active triphosphate in target cells, can determine the efficacy of such agents. Compounds such as ADV enter cells by endocytosis and only require addition of 2 phosphate groups by ubiquitous cellular nucleotide kinases to be anabolised to the diphosphate derivative. ADV diphosphate, the active form of the drug, has an extremely long intracellular half-life in both

activated and resting lymphocytes, making this drug an excellent candidate for once-daily dosing. ADV has shown excellent activity against HIV isolates with zidovudine resistance mutations and the M184V lamivudine resistance mutation both *in vitro* and clinically. Given these attributes, adefovir dipivoxil may be effective in limiting the outgrowth of drug-escape HIV mutants and for use in combination with other antiretroviral agents. ADV also shows a broad antiviral spectrum against herpesviruses and human hepatitis B virus (HBV) and is currently being evaluated clinically for the treatment of HBV infection.

The most prominent adverse effect of adefovir dipivoxil is nephrotoxicity, mainly proximal renal tubular dysfunction. This toxicity seems to start at around 24 weeks of therapy and appears to abate upon drug discontinuation. Elevated serum creatinine and reduced phosphate levels appear to be good predictors of the renal toxicity.

In summary, adefovir dipivoxil is a novel nucleotide compound with unique pharmacological and antiviral properties. However, further studies may be needed to identify the most effective and safe regimens for the clinical use of this and related phosphonate compounds. ▲