INTRODUCTION

The nucleotide analogs are agents with proven in vitro and in vivo efficacy against a wide variety of DNA viruses and retroviruses. Structurally, nucleotide analogs are acyclic nucleoside phosphonates (nucleoside monophosphates) that are designed to circumvent the first phosphorylation step necessary for the activation of nucleoside analogs, such as zidovudine, stavudine, didanosine, lamivudine, and abacavir (1).

To date, three nucleotide analogs have received Food and Drug Administration (FDA) approval in the United States: cidofovir, adefovir dipivoxil, and tenofovir disoproxil fumarate (tenofovir DF). Cidofovir ([S]-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine; Vistide™) is an intravenous drug approved for treatment of retinitis caused by cytomegalovirus infection. Adefovir dipivoxil (9-[2-\{(bis)pivaloylmethoxymethyl\}phosphonylmethoxyethyl]adenine; Hepsera™) is an oral prodrug of adefovir (phosphonylmethoxyethyl adenine [PMEA]) and is approved for the treatment of chronic active hepatitis B virus (HBV) infection in adults. Tenofovir DF (Viread™) is the oral prodrug of tenofovir (9-\{(R)-(2-phosphonylmethoxy)propyl\}adenine [PMPA]) and is approved for the treatment of HIV infection in combination with other antiretroviral infections. The chemical formulae of adefovir dipivoxil and tenofovir DF are shown in Figs. 1 and 2, respectively.

This chapter will provide an overview of the in vitro activity, pharmacological properties, clinical efficacy data, and toxicity profiles of tenofovir DF, and, to a lesser extent, adefovir dipivoxil. Although both of these drugs are HIV reverse transcriptase inhibitors, only tenofovir DF has received FDA approval for the treatment of HIV-1 infection. Conversely, the clinical development of adefovir dipivoxil for the treatment of HIV infection was limited by adverse events (specifically, reversible proximal renal tubular dysfunction) and is not approved for use in HIV infection, but, at lower doses than previously used in
HIV clinical trials, adefovir dipivoxil is efficacious and safe in the treatment of chronic HBV infection.

**MECHANISM OF ACTION AND IN VITRO ACTIVITY**

Adefovir dipivoxil and tenofovir DF are lipophilic ester derivatives of adefovir and tenofovir, respectively, and were designed as prodrugs in effort to improve oral bioavailability. After oral administration and adsorption, adefovir dipivoxil and tenofovir DF are rapidly cleaved by nonspecific carboxylesterases into adefovir and tenofovir, respectively. Once inside cells, these compounds are metabolized by adenylate cyclase to adefovir monophosphate and tenofovir monophosphate, and, subsequently, by nucleoside diphosphate kinase to adefovir diphosphate (PMEApp) and tenofovir diphosphate (PMPApp), the active moieties. The antiviral effect of the drugs is the result of selective interaction of the diphosphate metabolite (PMEApp and PMPApp) with the viral DNA polymerase. Based on the structural resemblance to natural deoxyadenine triphosphates (dATP), PMEApp and PMPApp may act as both a competitive inhibitor and an