Tenofovir: The First Nucleotide Analog for HIV-1
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The FDA approval of tenofovir disoproxil fumarate (Viread) occurred on October 26, 2001, only six months after Gilead Sciences Inc. submitted the new drug application (NDA). It is indicated for the treatment of HIV-1 infection when used in combination with other antiretroviral medicines. The approval was based on clinical trials involving patients who were previously treated with antiretrovirals, but who showed signs of resistance and continued HIV replication despite drug therapy.

**Indication**
Tenofovir disoproxil fumarate is the first nucleotide analog approved for HIV-1 treatment. Nucleotides are phosphorylated nucleosides. As a nucleotide, tenofovir disoproxil fumarate remains in cells for longer periods of time than many other antiretroviral drugs, thereby allowing for once-daily dosing.

**Pharmacology**
Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/ml in distilled water at 25°C. Its chemical name is 9-[(R)-2-isopropoxyoxy]pentyl[2-[(isopropoxyxy]oxy]methoxy]phosphinyl]methoxy]phosphate (1:1). It has a molecular formula of C_{19}H_{30}N_{5}O_{10}P • C_{4}H_{4}O_{4} and a molecular weight of 635.52. Figure 1 shows the structure of tenofovir disoproxil fumarate.

**Mechanism of Action**
Tenofovir disoproxil fumarate is a prodrug of tenofovir.1 In vivo, it is converted to an acyclic nucleoside monophosphate called tenofovir monophosphate (TP). Nucleotide reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs) work in the same manner to block HIV replication. This is accomplished by competing with the natural DNA substrates to inhibit reverse transcriptase and subsequently decreasing or preventing HIV replication in infected cells.

**Clinical Trials**
There are different subtypes of the HIV-1 strains including A, B, C, D, E, F, G, and O. Most of the antiretroviral drugs are manufactured in the countries where subtype B is predominant. The anti-HIV activities of newly discovered drugs are usually determined against local subtype B strains. In a study done by Palmer et al.,2 the susceptibility of tenofovir to primary HIV-1 isolates was compared along with adefovir (Gilead Sciences Inc.) and zidovudine (Retrovir, GlaxoSmithKline). Adefovir is a nucleotide analog that is no longer being developed for HIV-1 treatment. The study concluded that tenofovir, adefovir, and zidovudine has equal potency against subtypes A, B, C, D, E, F, G, and O strains of HIV-1. The study also proved that there was minimal or no cross-resistance to the nucleotide analogs tenofovir and adefovir even in the presence of nucleoside-resistant strains.

**Efficacy**
A phase I/II randomized, dose-escalation study evaluated the safety, pharmacokinetics, and antiviral activity of tenofovir DF in HIV-infected adults with CD4 cell counts of 200 cells/mm³ or more and plasma HIV-1 RNA counts of 10,000 copies/ml or greater.4 Participants received one of...
four doses of tenofovir DF (75, 150, 300, or 600 mg) monotherapy as a single dose, followed by a seven-day observation period.

After 28 days of continuous treatment, HIV RNA reduction was significantly greater for all tenofovir DF-treated groups than for the placebo group. The tenofovir DF 300 mg group demonstrated a median –1.22 log₁₀ copies/ml decrease in HIV RNA from baseline. Within the tenofovir 300 mg group, the median decrease in HIV-1 RNA in the treatment-naïve participants was –1.57 log₁₀ copies/ml, whereas the median decrease in the treatment-experienced participants was –0.97 log₁₀ copies/ml. HIV RNA levels decreased by –0.08 log₁₀ copies/ml in the tenofovir DF 600 mg group. Increases in the CD4 cell counts in tenofovir DF-treated patients were not statistically significantly different than those treated with placebo.

Study 907 was a double-blind, placebo-controlled study of the safety and efficacy of tenofovir DF administered to HIV-1 patients with plasma HIV-1 RNA levels of 400 copies/ml or greater and 10,000 copies/mL or less. At baseline, patients had median HIV RNA levels of 2,340 copies/ml and mean CD4 cell counts of 426 cells/mm³. Baseline genotypic analysis of HIV isolates from these patients revealed that 94% of patients had evidence of NRTI mutations, 58% had protease inhibitor (PI)-resistant mutations, and 48% had non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant mutations.

Reductions below 400 copies/ml were achieved by 40% of patients treated with tenofovir DF at 24 weeks, compared to 11% in the placebo group (P < 0.0001). Reductions in HIV RNA to less than 50 copies/ml were achieved by 19% of patients in the tenofovir DF group compared to 1% in the placebo group (P < 0.0001). Mean change in absolute CD4 counts by week 24 was +11 cells/mm³ for the tenofovir group and –5 cells/mm³ for the placebo group.

**Adverse Reactions**

Mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence occurred in these clinical trials. Less than 1% of patients discontinued participation in the clinical studies because of adverse events. Laboratory abnormalities occurred with correlated frequency in the tenofovir DF- and placebo-treated groups. The percentages of occurrence are reported in Table 1.

Lactic acidosis and severe hepatomegaly with severe steatosis (including fatal cases) have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. Many of the patients reporting these side effects have been women. Obesity and prolonged exposure to nucleosides might also be risk factors. Caution should be used in administering tenofovir DF to patients with these risk factors. If a patient develops lactic acidosis or pronounce hepatotoxicity, treatment with tenofovir DF should be suspended.

**Pharmacokinetics**

Tenofovir is eliminated primarily through the kidneys by a combination of glomerular filtration and active tubular secretion. Renal clearance is approximately two times glomerular filtration rate. Tenofovir DF should not be administered to patients with renal insufficiency (CrCl < 60 ml/min) at this time. The co-administration of tenofovir DF with drugs that are eliminated by active tubular secretion might increase the serum concentrations of either tenofovir DF or the other drug, because of competition for the elimination pathway. Drugs that decrease renal function might increase serum concentrations of tenofovir.

The administration of tenofovir DF immediately after a high-fat meal (approximately 700–1000 KCal, 40%–50% fat) enhances bioavailability, with an increase in tenofovir area under the curve concentration (AUC) of approximately 40% and an increase in maximum concentration (Cmax) of 14%. Food also delayed time to maximum concentration (Tmax) by approximately one hour. In vitro protein binding of tenofovir to human plasma or serum protein was less than 0.7% and 7.2%, respectively. The terminal elimination half-life of tenofovir is approximately 17 hours in both healthy adults and patients. In vitro studies have determined that neither tenofovir DF nor tenofovir is a substrate for the cytochrome P-450 (CYP-450) enzymes. Although a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed with tenofovir DF, the potential for CYP-450-mediated interactions involving tenofovir with other medicinal products is low.

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**Table 1 Treatment-Related Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir 300 mg</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Number of Patients Treated</td>
<td>443</td>
<td>210</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Source: Adapted from Viread Prescribing Information.

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**Figure 1** The chemical structure of tenofovir disoproxil fumarate.

Source: Adapted from Viread Prescribing Information.

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**Source:** Adapted from Viread Prescribing Information.
The tablets are almond-shaped and imprinted with “GILEAD” and “4331” on one side and with “300” on the other side. They are packaged in bottles of 30 tablets. Table 2 shows the cost of one-month supply of reverse transcriptase inhibitors.15

**Conclusion**

Tenofovir DF demonstrates a significant antiviral response, even in treatment-resistant patients. It is slightly more expensive than other reverse transcriptase inhibitors, but the benefits gained by having another option for these patients, along with the convenient dosing, enable it to be cost-effective. So far, this powerful and convenient new option has demonstrated safety in clinical trials by exhibiting only mild gastrointestinal disturbances and minimal drug interactions. It will likely have an indispensable place in antiretroviral therapy.

**REFERENCES**