HIV/AIDS is a worldwide epidemic; an estimated 37.8 million people are currently living with HIV/AIDS. Of that number, approximately 850,000 to 950,000 U.S. residents are living with HIV; 180,000 to 280,000 of these persons do not know that they are infected.

Because of the continuing rise in HIV cases, researchers are continuing to develop strategies for preventing infection, with an emphasis on testing; to identify infected persons; and to ensure access to appropriate medical care.

On August 2, 2004, the Food and Drug Administration (FDA) approved Gilead’s fixed-dose combination drug (Truvada™), composed of emtricitabine (Emtriva®) and tenofovir disoproxil fumarate (Viread®). Truvada™ is indicated for the treatment of HIV-1 infection in adults and for use with other antiretroviral agents such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).

Both Viread® and Emtriva® are already available and have been studied individually. They exhibit inhibitory activity against HIV-1 reverse transcriptase and have been found to be safe and effective. Therefore, their resistance profiles, efficacy, and safety as part of multi-drug regimens have been extrapolated to support the use of Truvada™.

**PHARMACOLOGY**

The goal of antiretroviral therapy is to preserve the immune system by disrupting the viral cell cycle. The two agents in Truvada™ prevent HIV from replicating and, as a result, help protect the immune system. One tablet is bio-equivalent to one 200-mg Emtriva® capsule plus one 300-mg Viread® tablet (equivalent to 245 mg of tenofovir disoproxil fumarate) as active ingredients.

Emtricitabine, a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5′-triphosphate, which inhibits HIV-1 reverse transcriptase by competing with the natural substrate deoxy-cytidine 5′-triphosphate and by being incorporated into nascent viral DNA. These steps, caused by the action of this nucleoside reverse transcriptase inhibitor (NRTI), result in chain termination.

Tenofovir, an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate, was the first nucleotide analogue approved for HIV-1 treatment. As a nucleotide reverse transcriptase inhibitor (NtRTI), it remains in the cells for longer periods of time than many other antiretroviral drugs, thereby allowing for once-daily dosing.

Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir disphosphate. Tenofovir inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5′-triphosphate. Tenofovir also interferes with HIV-1 activity after its incorporation into DNA by causing chain termination.

**PHARMACOKINETICS**

**Emtricitabine**

Emtricitabine is rapidly absorbed after oral administration. Peak plasma concentrations occur in one to two hours. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. The plasma half-life, after administration, is approximately 10 hours.

In vitro binding of emtricitabine to human plasma proteins is less than 4% and is independent of the concentration over the range of 0.02 to 200 mcg/ml. Its maximum concentration (C_max) is 1.8 ± 0.72.
Following administration of radio-labeled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. These metabolites include 3′-sulfoxide diastereomers and their glucuronic acid conjugate.⁷

**Tenofovir Disoproxil Fumarate**

After oral administration of tenofovir disoproxil fumarate, the Cₘₙₙₙₙ is achieved in 1.0 ± 0.4 hour.

**Tenofovir**

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. The elimination half-life of tenofovir, after oral administration, is approximately 17 hours.

Patients with renal insufficiency (a creatinine clearance of less than 60 ml/minute) should not take tenofovir. The administration of tenofovir with drugs that are eliminated by active tubular secretion might increase the serum concentrations of either tenofovir or the other drug because of competition for the elimination pathway. Drugs that decrease renal function have the potential to cause elevated serum tenofovir concentrations.

The administration of tenofovir immediately after a high-fat meal enhances its bioavailability; the area-under-the-curve (AUC) concentration increases by approximately 40%, and the Cₘₙₙₙₙ increases by 14%. Food also delays the time to maximum concentration (Tₘₙₙₙₙ) by approximately one hour. In vitro binding of tenofovir to human plasma proteins is below 0.7% and is independent of concentrations over the range of 0.01 to 25 mcg/ml.

The Cₘₙₙₙₙ of tenofovir is 0.30 ± 0.09 mcg/ml. Approximately 70% to 80% of the intravenous (IV) dose of tenofovir is recovered as unchanged drug in the urine.⁶

**Special Populations**

The pharmacokinetic properties of emtricitabine and tenofovir are altered in patients with renal impairment. In patients with a creatinine clearance of less than 50 ml/minute, the Cₘₙₙₙₙ and AUC concentration of emtricitabine and tenofovir are increased.

The dosing interval for Truvada™ should be modified in patients with a creatinine clearance of 30 to 49 ml/minute. Truvada™ should not be used in patients with a creatinine clearance below 30 ml/minute or in patients with end-stage renal disease who need dialysis.⁵

**CLINICAL TRIALS**

The safety and efficacy of emtricitabine and tenofovir as combination therapy have not been extensively covered in the literature. As monotherapy, however, each agent has been shown to be effective in the treatment of HIV infection.

**Study GS-0172**

GS-0172 was a randomized, open-label, crossover study conducted to evaluate the pharmacokinetics, bioequivalence, and safety of the investigational fixed-dose combination of emtricitabine 200 mg plus tenofovir 300 mg compared with the coadministration of the individual 200-mg emtricitabine capsule and a 300-mg tenofovir tablet in healthy subjects. Forty-four healthy volunteers were enrolled, and 39 completed the study. Blood samples were obtained over 48 hours after each participant received a dose of the study drug following an overnight fast on two occasions, separated by a one-week washout period.⁵,⁸

Results showed that the fixed-dose combination tablet was bioequivalent to the coadministration of the emtricitabine capsule and the tenofovir tablet. Formulation bioequivalence was confirmed if the 90% confidence interval (CI) for the ratio of geometric means for the Cₘₙₙₙₙ and the AUC concentration fell within the range of 80% to 125%.⁵,⁸ Pharmacokinetic parameters of emtricitabine and tenofovir were also similar as the fixed-combination tablet and as the emtricitabine capsule plus tenofovir tablet.

Both regimens were well tolerated, and no serious adverse drug events (ADEs) were reported. Eight subjects (18%) experienced a total of 13 treatment-emergent ADEs, with grade 1 headache being most common (n = 3). Two subjects discontinued the study; one withdrew because of a treatment-related mild rash, and another withdrew because of grade 2 hypertension that was present at baseline but was not considered to be related to the study drug.

**Study FTC-303**

FTC-303 was a phase 3, 48-week, randomized, open-label, multicenter study comparing emtricitabine 200 mg once daily with the NRTI lamivudine (3TC, Epivir®, GlaxoSmithKline) 150 mg twice daily, in combination with the NRTI stavudine (d4T, Zerit®, Bristol-Myers Squibb Immunology) 40 mg twice daily or the NRTI zidovudine (ZDV, AZT, Retrovir®, GlaxoSmithKline) 300 mg twice daily plus a PI or an NNRTI in 440 patients. The patients were following a lamivudine-containing triple-antiretroviral regimen for at least 12 weeks before entry into the study, and their HIV RNA levels were below 400 copies/ml. The patients were randomly selected, in a 1:2 ratio, to either continue therapy with lamivudine or to switch to emtricitabine.⁵,⁸

At the time of enrollment into the study, the median duration of prior antiretroviral and lamivudine therapies had been 27.6 and 18 months, respectively. The median HIV RNA level was 1.7 log₁₀ copies/ml, and the mean CD4 cell count was 527 cells/µm³. There were no statistically significant differences between the treatment arms.

**Study GS-99-903**

GS-99-903 is an ongoing, phase 3, three-year, randomized, double-blind, active-controlled, multicenter clinical trial designed to compare the efficacy and safety of tenofovir 300 mg once daily with stavudine (d4T) 40 mg twice daily with a background regimen of emtricitabine (150 mg twice daily) and the NNRTI efavirenz (Sustiva®, Bristol-Myers Squibb Virology) 600 mg once daily in 600 treatment-naïve HIV-infected individuals. At the baseline evaluation, the mean HIV RNA level for the intention-to-treat population was 4.9 log₁₀ copies/ml, and the mean CD4 cell count was 279 cells/µm³. At 48 weeks, similar numbers of patients in both regimens experienced reductions in HIV RNA levels to below 50 and below 400 copies/ml, respectively.⁵,¹⁰,¹¹

**DRUG RESISTANCE**

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in vitro. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral reverse transcriptase.

Cross-resistance among certain NRTIs
Drug Forecast

has been recognized. The M184V/I and/or K65R substitutions selected in vitro by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects not responding to treatment with tenofovir in combination with either lamivudine or emtricitabine with either the NRTI abacavir sulfate (Ziagen®, GlaxoSmithKline) or the NRTI didanosine (ddI, Videx®, Bristol-Myers Squibb Immunology). Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

ADVERSE DRUG EFFECTS

Safety and efficacy studies of Truvada™ tablets (Emtriva®/Viread®) are ongoing. Two hundred eighty-three HIV-1 infected patients have received combination therapy with Emtriva® or Viread® with either an NNRTI or a PI for 24 to 48 weeks in ongoing clinical studies. According to these limited data, no new patterns of ADEs were identified. There was no increased frequency of established toxicities.

ADEs associated with emtricitabine in more than 5% of patients include abdominal pain, asthenia, headache, diarrhea, nausea, vomiting, dizziness, and rash. ADEs associated with tenofovir in more than 5% of patients include headache, nausea, vomiting, diarrhea, rash, and depression. Truvada™ therapy can result in severe lactic acidosis, osteopenia, elevated serum cholesterol and triglyceride levels, lipodystrophy, and diabetes.5

CONTRAINDICATIONS

Truvada™ is contraindicated in those patients with a hypersensitivity to any of the components of the product. It is a pregnancy category B drug.5

DRUG INTERACTIONS

Administering Truvada™ with the NRTI didanosine (ddI) should be undertaken with caution. Patients receiving this combination should be monitored closely for didanosine-associated ADEs, including pancreatitis and neuropathy. Patients receiving the PIs atazanavir (Reyataz®, Bristol-Myers Squibb Virology) and lopinavir/ritonavir (Kaletra®, Abbott) and Truvada™ should be monitored for any associated ADEs because of the resulting elevated tenofovir concentrations with these combinations.5

Truvada™ should be discontinued if associated ADEs occur. Atazanavir without the PI ritonavir (Norvir®, Abbott) should not be administered with Truvada™.

Because emtricitabine and tenofovir are eliminated primarily by the kidneys, taking Truvada™ with drugs that reduce renal function or that compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, or other renally eliminated drugs. Examples include, but are not limited to, adefovir dipivoxil (Hepsera®, Gilead), cidofovir injection (Vistide®, Gilead), acyclovir (Zovirax®, GlaxoSmithKline), ganciclovir (Cytovene®, Roche), and valganciclovir (Valcyte®, Roche).

Truvada™ should not be taken with Emtriva® or Viread® when either is used alone. Because of the similarities between emtricitabine and lamivudine, patients should not take Truvada™ with other drugs containing lamivudine, such as Combivir® (lamivudine/zidovudine), Epivir® (lamivudine), Epi-HBV® (lamivudine), Epzicom® (EpiVir®/Ziagen®), or Trizivir® (abacavir/lamivudine/zidovudine). Truvada™ should not be used as a component of a triple-nucleoside regimen.5

DOSAGE AND ADMINISTRATION

Truvada™ is given as one tablet containing 200 mg of emtricitabine and 300 mg of tenofovir. It can be taken orally with or without food once a day. Each tablet is film-coated for oral administration.

CONCLUSION

The use of highly active antiretroviral therapy (HAART) has been associated with decreased morbidity and mortality. HAART is indicated to prevent immune deterioration leading to immunodeficiency (a CD4 count below 200 cells/mm³). Because of the pill count burden and the frequency of administration, adherence to HAART therapy has been low. New combination medications such as Truvada™ offer alternatives that should increase patient compliance. This drug prevents HIV from altering the genetic material of healthy T cells, thus preventing the cells from producing new viral cells and reducing the amount of the virus in the body.

Truvada™ should be considered for patients who are treatment-naïve or who might benefit from a once-daily regimen.11 No results have yet demonstrated the effect of this agent on the clinical progression of HIV-1, and no drug–drug interaction studies of Truvada™ tablets have been conducted.

REFERENCES