

saquinavir (1200 mg TID) was not sufficient to produce adequate drug levels in the first four pregnant HIV-infected women enrolled in the study compared to those obtained with standard dosing in non-pregnant adults. Thus, the study was modified to evaluate the combination of saquinavir (800 mg) plus ritonavir (100 mg), both administered BID. This regimen was well-tolerated and achieved adequate saquinavir levels in the women [85, 86].

## FUSION INHIBITORS

Enfuvirtide, which requires subcutaneous administration, is the first of the fusion inhibitor class of antiretroviral drugs; these drugs inhibit binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein gp120 to the CD4<sup>+</sup> receptor induces conformational changes that enable gp120 to interact with a chemokine receptor on the host cell; binding of gp120 to the coreceptor causes subsequent conformational changes in the viral transmembrane glycoprotein gp41, exposing the “fusion peptide” of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a “zipping” together of the two helices and mediating the fusion of cellular and viral membranes. Enfuvirtide is a synthetic 36 amino acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41. As a molecular mimic of the HR2 region, the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Enfuvirtide was approved for use in combination with other antiretroviral drugs to treat advanced HIV infection in adults and children aged 6 years or older.

**Enfuvirtide (Fuzeon™, T-20)** is classified as FDA pregnancy category B.

- Animal carcinogenicity studies  
Long-term animal carcinogenicity studies of enfuvirtide have not been conducted. Enfuvirtide was neither mutagenic or clastogenic in a series of *in vitro* and animal *in vivo* screening tests.
- Reproduction/fertility animal studies  
Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on fertility of male or female rats at doses up to 30 mg/kg/day administered subcutaneously (1.6 times the maximum recommended adult human daily dose on a m<sup>2</sup> basis).

- Teratogenicity/developmental toxicity animal studies  
Studies in rats and rabbits revealed no evidence of harm to the fetus from enfuvirtide administered in doses up to 27 times and 3.7 times, respectively, the adult human daily dose on a m<sup>2</sup> basis.
- Placental and breast milk passage  
Studies of radio-labeled enfuvirtide administered to lactating rats indicated radioactivity was present in the milk; however, it is not known if this reflected radio-labeled enfuvirtide or from radio-labeled metabolites (e.g., amino acid and peptide fragments) of enfuvirtide. It is not known if enfuvirtide is crossed the human placenta or is excreted in human milk.
- Human studies in pregnancy  
No studies of enfuvirtide have been conducted in pregnant women or neonates.

## MISCELLANEOUS AGENTS

**Hydroxyurea** is classified as FDA pregnancy category D.

Hydroxyurea is a cytotoxic and antimitotic agent that inhibits DNA synthesis and has been used for treatment of myeloproliferative disorders and sickle cell anemia. It has recently been studied for treatment of HIV disease in combination with nucleoside analogue antiretroviral agents. By inhibiting ribonucleotide reductase, it depletes the pool of deoxynucleoside triphosphates, particularly dATP, thereby potentiating the incorporation of the nucleoside analogue drugs into viral DNA and increasing their antiretroviral effect. However, the drug has significant toxicities and its role in HIV therapy is not well defined.

- Animal carcinogenicity studies and human data  
Hydroxyurea is genotoxic in a wide range of *in vitro* and *in vivo* animal test systems, causes cellular transformation to a tumorigenic phenotype, and is a transspecies carcinogen, which implies a potential carcinogenic risk to humans. Conventional long-term animal carcinogenicity studies have not been performed. However, intraperitoneal administration of 125 to 250 mg/kg of hydroxyurea (approximately 0.6 to 1.2 times the maximum recommended human oral dose on a mg/m<sup>2</sup> basis) three times weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to controls.