



**Recommendations for the Use of Antiretroviral Drugs in
Pregnant Women with HIV Infection and Interventions to Reduce
Perinatal HIV Transmission in the United States**

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Entry and Attachment Inhibitors

Glossary of Terms for Supplement

Carcinogenic: Producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

Clastogenic: Causing disruption of or breakages in chromosomes

Genotoxic: Damaging to genetic material such as DNA and chromosomes

Mutagenic: Inducing or capable of inducing genetic mutation

Teratogenic: Interfering with fetal development and resulting in birth defects

The antiretroviral (ARV) drugs in the entry inhibitor class inhibit viral binding or fusion of HIV to host target cells. When the viral envelope glycoprotein (gp) 120 binds to the CD4 receptor, it induces conformational changes that enable gp120 to interact with a chemokine receptor such as CCR5 or CXCR4 on the host cell. After gp120 binds to the co-receptor, subsequent conformational changes expose the fusion peptide of viral transmembrane gp41. The fusion peptide then inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41. The two helices zip together and mediate the fusion of cellular and viral membranes. Enfuvirtide, which requires subcutaneous (SQ) administration, is a synthetic 36-amino-acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41. The drug binds to the HR1 region, preventing the HR1-HR2 interaction and the correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Maraviroc is a CCR5 co-receptor antagonist that interferes with viral entry at the chemokine co-receptor level.

Ibalizumab-uiyk, a recombinant humanized monoclonal antibody, is a CD4-directed post-attachment HIV-1 inhibitor. Ibalizumab-uiyk blocks HIV from infecting CD4+ T cells by binding to domain 2 of CD4, thereby interfering with post-attachment steps required for viral entry and preventing viral transmission that occurs via cell-cell fusion.

Enfuvirtide (Fuzeon, T-20)

(Last updated December 7, 2018; last reviewed December 7, 2018)

Enfuvirtide is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Reproduction/Fertility

Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on the fertility of male or female rats at doses up to 30 mg/kg/day administered SQ (a dose that is 1.6 times the maximum recommended adult human daily dose on a body surface area basis).

Teratogenicity/Adverse Pregnancy Outcomes

Studies in rats and rabbits have shown no evidence of teratogenicity and no effect on reproductive function with enfuvirtide.¹

Placental and Breast Milk Passage

A study in rats revealed no evidence of harm to the fetus when enfuvirtide was administered in doses up to 27 times the adult human daily dose on a body surface area basis. A separate study in rabbits likewise

revealed no harm to the fetus from enfuvirtide doses that were up to 3.2 times the adult human daily dose. Studies of radiolabeled enfuvirtide administered to lactating rats indicated radioactivity in the milk; however, it is not known if this reflected radiolabeled enfuvirtide or metabolites (amino acid and peptide fragments) of enfuvirtide.¹

Human Studies in Pregnancy

Pharmacokinetics

Data on the use of enfuvirtide during human pregnancy are limited to case reports of a small number of women treated with the drug.²⁻⁹

Placental and Breast Milk Passage

In vitro and *in vivo* studies suggest that enfuvirtide does not readily cross the human placenta. Minimal placental passage of enfuvirtide was reported in published studies that included a total of eight peripartum patients and their neonates. These findings were supported by data from an *ex vivo* human placental cotyledon perfusion model.^{2,5,10-12}

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry and in a national cohort of pregnant women with HIV infection in Italy, insufficient numbers of first-trimester exposures to enfuvirtide in humans have been monitored to be able to make a risk determination.^{13,14}

Excerpt from Table 10^a

Generic Name (Abbreviation) Trade Name.	Formulation	Dosing Recommendations	Use in Pregnancy
Enfuvirtide (T-20) Fuzeon	<u>T-20 (Fuzeon)</u> <i>Injectible:</i> <ul style="list-style-type: none"> Supplied as lyophilized powder. Each vial contains 108 mg of T-20; reconstitute with 1 mL of sterile water for injection for SQ delivery of approximately 90 mg/1 mL. 	T-20 is indicated for advanced HIV disease and must be used in combination with other ARV drugs to which the patient's virus is susceptible, as determined by resistance testing. <u>Standard Adult Dose:</u> <ul style="list-style-type: none"> T-20 90 mg (1 mL) twice daily without regard to meals <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> No PK data in human pregnancy. <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> Insufficient data to make dosing recommendation. 	Minimal to low placental transfer to fetus. ^b No data on human teratogenicity.

^a Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Guidelines, Appendix B, Table 8](#)).

^b Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; PK = pharmacokinetic; SQ = subcutaneous; T-20 = enfuvirtide

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