Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from http://aidsinfo.nih.gov/guidelines on 3/18/2013

Entry 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

Two drugs have been approved in this new class of antiretroviral (ARV) drugs aimed at inhibiting viral binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein (gp)120 to the CD4 receptor induces conformational changes that enable gp120 to interact with a chemokine receptor such as CCR5 or CXCR4 on the host cell; binding of gp120 to the coreceptor causes subsequent conformational changes in the viral transmembrane 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, 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, and 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 ARV drugs to treat advanced HIV infection in adults and children 6 years of age or older. Maraviroc interferes with viral entry at the chemokine coreceptor level; it is a CCR5 coreceptor antagonist approved for combination therapy for HIV infection in adults infected with CCR5-tropic virus.

Enfuvirtide (Fuzeon, T-20) is classified as Food and Drug Administration (FDA) Pregnancy Category B.
(Last updated July 31, 2012; last reviewed July 31, 2012)

- Animal carcinogenicity studies
  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 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 SQ (1.6 times the maximum recommended adult human daily dose on an m^2 body surface area 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 3.2 times, respectively, the adult human daily dose on an m^2 basis.

- Placental and breast milk passage
  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 (such as amino acid and peptide fragments) of enfuvirtide. It is not known if enfuvirtide crosses the human placenta or is excreted in human milk. A published case report of two peripartum pregnant patients and their neonates and data from an *ex vivo* human placental cotyledon perfusion model suggest that enfuvirtide does not cross the placenta.[1, 2]

- Human studies in pregnancy
  Very limited data exist on the use of enfuvirtide in pregnant women.[1, 3-5] There is a single case report detecting no placental transfer of drug based on cord blood measurements.[5]

References

1. Brennan-Benson P, Pakianathan M, Rice P, et al. Enfurvitide prevents vertical transmission of multidrug-resistant HIV-1 in pregnancy but does not cross the placenta. *AIDS*. Jan 9 2006;20(2):297-299. Available at http://www.ncbi.nlm.nih.gov/pubmed/16511429.
2. Ceccaldi PF, Ferreira C, Gavard L, Gil S, Peytavin G, Mandelbrot L. Placental transfer of enfuvirtide in the ex vivo human placenta perfusion model. *Am J Obstet Gynecol*. Apr 2008;198(4):433 e431-432. Available at http://www.ncbi.nlm.nih.gov/pubmed/18241815.
3. Cohan D, Feakins C, Wara D, et al. Perinatal transmission of multidrug-resistant HIV-1 despite viral suppression on an enfuvirtide-based treatment regimen. *AIDS*. Jun 10 2005;19(9):989-990. Available at http://www.ncbi.nlm.nih.gov/pubmed/15905684.
4. Meyohas MC, Lacombe K, Carbonne B, Morand-Joubert L, Girard PM. Enfuvirtide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. *AIDS*. Sep 24 2004;18(14):1966-1968. Available at http://www.ncbi.nlm.nih.gov/pubmed/15353987.
5. Weizsaecker K, Kurowski M, Hoffmeister B, Schurmann D, Feiterna-Sperling C. Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS*. May 2011;22(5):294-295. Available at http://www.ncbi.nlm.nih.gov/pubmed/21571982.

Maraviroc (Selzentry, MVC) is classified as FDA Pregnancy Category B.

(Last updated September 14, 2011; last reviewed July 31, 2012)

- Animal carcinogenicity studies
  Maraviroc was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies found no increase in tumor incidence in mice (transgenic rasH2 mice) and rats at exposures up to 11-fold higher than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).

- Reproduction/fertility animal studies
  Reproductive toxicity has been evaluated in rats. Maraviroc produced no adverse effects on fertility of male or female rats or sperm of male rats at exposures up to 20-fold higher than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).

- Teratogenicity/developmental toxicity animal studies
  Studies in rats and rabbits revealed no evidence of harm to the fetus from maraviroc administered in doses up to 20-fold higher in rats and 5-fold higher in rabbits than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).

- Placental and breast milk passage
  It is unknown if maraviroc crosses the placenta in humans. In a study of four macaques, a single oral

dose of 60 mg/kg or 100 mg/kg was given 2 hours before cesarean delivery. Median maternal concentration at delivery was 974 ng/mL (range 86–2830 ng/mL) and median infant concentration was 22 ng/mL (range 4–99 ng/mL) for a cord/maternal ratio of .023.[1] Maternal levels were detectable for 48 hours after a single dose, whereas infant levels were detectable for only 3.5 hours after birth. Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.

- Human studies in pregnancy
  No studies of maraviroc have been conducted in pregnant women or neonates.

- Additional concerns
  Although no increase in cancer has been observed with maraviroc, the drug has the potential to increase risk because of its mechanism of action and possible effects on immune surveillance.

Reference

1. Winters MA, Van Rompay KK, Kashuba AD, Shulman NS, Holodniy M. Maternal-fetal pharmacokinetics and dynamics of a single intrapartum dose of maraviroc in rhesus macaques. *Antimicrob Agents Chemother*. Oct 2010;54(10):4059-4063. Available at http://www.ncbi.nlm.nih.gov/pubmed/20696881.