an inverse relationship between the degree of nevirapine and efavirenz resistance and the impairment of viral replication in viruses with substitutions at G190 (Huang *et al*., 2003).

Uhlmann *et al*. (2004) assessed the effect of the specific G190A mutation on susceptibility to delavirdine. They studied 15 patients who after treatment with either nevirapine or efavirenz (median exposure of 20 months) developed an isolated G190A mutation, or G190A in combination with K103N, or K103N alone. Phenotypic and genotypic analyses of stored plasma specimens were performed before and after the mutations occurred to assess susceptibility. All isolates that developed only the G190A substitution became markedly less susceptible to nevirapine (125-fold median change) and efavirenz (10-fold median change) but were 2.5-fold more susceptible to delavirdine (Wilcoxon $p = 0.06$), consistent with the data of Huang *et al*. (2003). Strains with only K103N substitutions were resistant to all nonnucleoside reverse transcriptase inhibitors, including delavirdine. In the group with the double substitution, G190A and K103N, delavirdine susceptibility decreased 13-fold, whereas susceptibility to nevirapine and efavirenz increased by 239- and 154-fold, respectively (Kruskal-Wallis $p= 0.009$). The authors concluded that the presence of a G190A mutation attenuates the phenotypic resistance associated with a K103N substitution, although resistance was still present. The *in vivo* significance of the increased phenotypic susceptibility to delavirdine is unknown.

2c. *In vitro* synergy and antagonism

Delavirdine was synergistic against HIV-1 replication when tested in combination with the protease inhibitor U-75,875 or interferon-alpha (Pagano and Chong, 1995). Both delavirdine and atevirdine showed additive to synergistic effects with zidovudine against zidovudine-sensitive and -resistant strains of HIV-1 (Campbell *et al*., 1993; Chong *et al*., 1994). Didanosine was additive with atevirdine against didanosine-sensitive and -resistant strains of HIV-1 (Campbell *et al*., 1993). Three-drug combinations of delavirdine and zidovudine with either didanosine or zalcitabine synergistically inhibited HIV-1 replication (Chong and Pagano, 1997). The combination of delavirdine and nevirapine was antagonistic in inhibiting HIV reverse transcriptase activity (Gu *et al*., 1995). There was synergistic activity between lamivudine and delavirdine (ViiV Healthcare, product information, 2012).

3. MECHANISM OF DRUG ACTION

Delavirdine has a mechanism of action similar to other nonnucleoside reverse transcriptase inhibitors, including nevirapine (see Chapter 235, Nevirapine).

Similar to nevirapine, delavirdine inhibits the HIV-1 reverse transcriptase in a noncompetitive fashion through binding to the enzyme at a site distinct from the nucleic acid binding site and the site at which nucleoside and nucleotide reverse transcriptase inhibitors bind; nonnucleoside inhibitors do not cause chain termination and hence their inhibitory effects reverse rapidly when the drugs are withdrawn (Dueweke *et al*., 1992; Althaus *et al*., 1993; Gu *et al*., 1995).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

Delavirdine is administered orally in a dose of 400 mg three times daily. The drug may be administered with or without food, but if the patient is taking simple antacids, the two medications should be separated by at least 1 hour. Although no information is available about delavirdine absorption or dosing in patients taking H2R antagonists or proton pump inhibitors, co-administration with delavirdine is not recommended becasue absorption is diminished in the absence of gastric acid (ViiV Healthcare, product information, 2012).

4b. Newborn infants and children

There are no data available for dosing in the pediatric population. The drug has not been studied in subjects younger than 16 years.

4c. Pregnant and lactating mothers

Delavirdine is a category 3 drug, causing teratogenicity in rats, with development of ventricular septal defects. It is excreted in breast milk at concentrations significantly higher than in plasma. Breastfeeding women should not take delavirdine.

4d. Those requiring altered dosages

The pharmacokinetics of delavirdine has not been studied in patients with any degree of hepatic or renal insufficiency, or in subjects > 65 years. Because delavirdine is metabolized mainly by the liver, the drug should be used with caution in patients with hepatic dysfunction (ViiV Healthcare, product information, 2012).

5. PHARMACOKINETICS AND PHARMACODYNAMICS

5a. Bioavailability

Delavirdine was rapidly absorbed after oral administration, with a single-dose mean bioavailability of 85%. The peak in plasma concentration (C_{max}) occurs in 1 hour. In patients receiving 400 mg three times daily, the mean steady-state peak plasma concentration (C_{max})was 35 ± 20 μM, the trough concentration (C_{min}) was 15 ± 10 μM, and the area-under-the-concentration-time curve (AUC) was 180 μM·h/ml. Plasma concentrations tended to be higher in females than males, but the differences are not considered to be clinically significant (ViiV Healthcare, product information, 2012).

In HIV-infected subjects in the steady-state situation, taking delavirdine with food reduced the C_{max} by 25% but had no effect on the AUC or C_{min} (Morse *et al*., 2003a; ViiV Healthcare, product information, 2012).

Delavirdine is best absorbed in an acidic environment (it is a weak base with low solubility at pH > 3). Simple antacids,