Table 237.4. Major AIDS clinical trials group (ACTG) studies of delavirdine.

Name of study	Design	No. of subjects	Comments	Reference
ACTG 260	Open label dose-ranging phase 1B. Delavirdine vs zidovudine vs didanosine	113	Early reduction in HIV viral load was not sustained	Para *et al.* (1999)
ACTG 261	Phase II randomized, double-blind, multicenter comparison of delavirdine plus zidovudine plus didanosine vs. dual NRTIs	544 (CD4 100–500, < 6 months before NRTI monotherapy)	Modest antiviral advantage of triple therapy vs. dual therapy over 48 weeks of followup	Friedland *et al.* (1999)

Abbreviation: NRTI: nucleoside reverse transcriptase inhibitor.

in HDL, has not been assessed. No other study of blood lipids in response to delavirdine has been reported.

7. CLINICAL USES OF THE DRUG

Delavirdine is approved in many countries for treatment of HIV infection in combination with other antiretroviral drugs (e.g. zidovudine and lamivudine, or tenofovir and emtricitabine). It is now rarely used. There are insufficient clinical data comparing antiretroviral drug combinations including delavirdine with currently recommended combinations containing logical comparator drugs (e.g. nevirapine, efavirenz, or a ritonavir-boosted protease inhibitor). Further, most of the prospective clinical trials of delavirdine compared treatment with two nucleoside reverse transcriptase inhibitors (e.g. zidovudine plus lamivudine) with the same nucleoside analog combination plus delavirdine (Table 237.4).

The lack of clinical trials with delavirdine conducted to the current standard, coupled with unfavorable pharmacokinetics (a large total dose and the need for three-times daily therapy), a high incidence of skin rash, and multiple and complex drug interactions has meant that delavirdine is not recommended for first- or second-line therapy and is very rarely used in the clinic.

7a. HIV-1 infection

DOSE-RANGING, EARLY EFFICACY STUDIES

Para *et al.* (1999) conducted an open-label, phase Ib dose-ranging study of delavirdine monotherapy compared with either zidovudine or didanosine for patients with HIV-1 infection under the aegis of the AIDS Clinical Trials Group (ACTG Trial 260; Table 237.4). Delavirdine doses were adjusted weekly in the 113 subjects in the trial to achieve three different trough concentrations: 3–10, 11–30, or 31–50 μM. Two weeks after starting therapy, the decreases in mean HIV load (as $\log_{10}$ RNA copies/ml) in the three delavirdine arms were similar (0.87, 1.08, and 1.02 $\log_{10}$ for the low-, middle-, and high-target arms, respectively); however, by week 8, pooled results from all three delavirdine arms showed only a 0.10 $\log_{10}$ reduction. In contrast, for the subjects treated with zidovudine or didanosine, the mean HIV viral load reductions at weeks 2 and 8 were 0.67 and 0.55 $\log_{10}$, respectively. The trial was stopped early, owing to the poor sustainability of delavirdine monotherapy (undoubtedly because of development of delavirdine-resistant HIV-1 strains, but not studied at the time). Another study combining zidovudine with three different doses of delavirdine also found that there was an early reduction in HIV viral load that was gone by 12 weeks after the start of treatment, and by 12 weeks over 70% of viral strains were resistant to delavirdine, whereas none were resistant to zidovudine (Been-Tiktak *et al.*, 1999).

Two phase I/II dose escalation studies have been performed. Triple therapy with delavirdine (100–300 mg four times daily), didanosine, and zidovudine was compared with didanosine and zidovudine in HIV-infected patients with CD4 counts of 100–300 cells/μl (mean: 212/μl at baseline) for 24 weeks. The patients were a heavily pretreated group, with > 90% of participants having received prior zidovudine therapy for a mean duration of 23 months, and > 70% receiving prior didanosine or zalcitabine for a mean duration of 10 months. Within 1 week, those randomized to receive triple therapy had a significant increase in CD4 counts and decline in plasma HIV RNA levels (HIV viral load). In retrospect, of course, it is likely that many of these patients were already infected with zidovudine- and didanosine-resistant strains of HIV, and hence the addition of delavirdine was effectively monotherapy. As a consequence, strains of HIV resistant to delavirdine appeared in some patients within 12 weeks of starting therapy (because, like other nonnucleoside reverse transcriptase inhibitors, the genetic barrier to development of delavirdine resistance is very low), and this was reflected by the HIV viral load returning toward baseline. However, at week 24, a greater proportion of patients randomized to receive triple therapy than double therapy had a fivefold or greater decline in plasma HIV RNA (44% vs. 13%, respectively) and a greater than 1.0 $\log_{10}$ decline in HIV viral load (77% vs. 25%, respectively) (Freimuth, 1996).

In a second study of 34 HIV-1-infected patients with 200–500 CD4 cells/μl (mean 390/μl) and a mean of 17 months of prior zidovudine treatment were given different doses of delavirdine (from 100 mg four times daily to 400 mg three times daily) in combination with zidovudine for 12 weeks. A CD4 count increase of > 50 cells/μl occurred in about half the participants; a decline in plasma p24 antigen occurred in approximately one quarter of enrolled patients (Freimuth, 1996).