

CURRENT STATUS OF NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The nonnucleoside reverse transcriptase inhibitors (NNRTIs) were discussed at the Chicago course by John P. Phair, MD, from Northwestern University Medical School. Dr Phair reviewed the characteristics of this class of compounds, summarized available clinical trial data, and discussed the use of NNRTIs in combination with protease inhibitors.

The nonnucleoside reverse transcriptase inhibitors (NNRTIs) are the most recent class of antiretroviral drugs to become available for HIV treatment. The NNRTIs function by binding noncompetitively to the hydrophobic pocket close to the polymerase catalytic site of the reverse transcriptase (RT) and decreasing RT polymerizing activity. The NNRTIs are selectively active against HIV-1; these drugs are not effective for HIV-2 or for HIV-1 group O isolates, and they do not interfere with the function of human DNA polymerases.

The rapid development of viral resistance to the NNRTIs has historically been the significant obstacle to the development of these drugs. Resistance often

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develops within weeks of administration of these drugs. In most cases, less susceptible isolates contain amino acid substitutions in the region of codons 179, 181, 188, and 190, and 98, 100, 103, 106, and 108 of the RT. In general, resistance to

NNRTIs does not alter the susceptibility of the virus to nucleoside reverse transcriptase inhibitors (nRTIs), and, conversely, resistance to NNRTIs usually does not reduce susceptibility to nRTIs. Cross-resistance with the protease inhibitors is unlikely due to the different enzyme targets involved. Cross-resistance within the NNRTI class is extensive. Two NNRTI-associated alterations, substitutions at codons 188 and 181, appear to suppress resistance to zidovudine when co-expressed with zidovudine-resistance-conferring mutations.

This rapid appearance of virus with increased resistance precludes the use of NNRTIs as monotherapy. Clinical trials evaluating these drugs as part of double- and triple-combination regimens with nRTIs and protease inhibitors are ongoing.

Delavirdine

In vitro studies have demonstrated that delavirdine blocks HIV-1 replication, including replication in HIV-1 isolates that are resistant to nRTIs or protease inhibitors. In tissue culture, delavirdine is synergistic with nRTIs, protease inhibitors, and immunomodulators. Steady-state pharmacokinetics for delavirdine are nonlinear; increased doses result in increased blood levels and decreased clearance. Delavirdine is metabolized primarily by the hepatic cytochrome P450 system. There is high interpatient variability in steady-state delavirdine concentrations that cannot be explained by demographic factors. Trough blood levels of delavirdine greater than 10 μM are easily achieved with the recommended dose of 400 mg tid. A summary of selected drug interactions with delavirdine is presented in Table 1.

The majority of clinical trials with delavirdine were conducted before protease inhibitors were available. One clinical trial comparing didanosine/delavirdine with didanosine monotherapy was stopped when no significant differences were found between the two arms of the study. A clinical

Table 1. Selected Delavirdine Drug Interactions

- Delavirdine is a weak base with very low solubility at pH above 3.0
- Administration of an antacid reduced delavirdine absorption and area-under-the-curve by approximately one third
- Ingestion of delavirdine with a high-fat meal or simultaneously with didanosine does not significantly alter delavirdine pharmacokinetics
- Concurrent use of fluconazole, clarithromycin, zidovudine, or trimethoprim/sulfamethoxazole does not significantly alter delavirdine pharmacokinetics
- Concurrent use of rifampin or rifabutin (strong inducers of the cytochrome P450 system) significantly increases the clearance of delavirdine

trial evaluating zidovudine/delavirdine has been modified to include lamivudine, and results are not yet available.

However, a proportional hazard regression analysis combining results from 1740 patients enrolled in Pharmacia & Upjohn protocols 0017 and 0021 revealed that in patients taking delavirdine/zidovudine or delavirdine/didanosine a 0.5 log decrease in plasma HIV RNA following therapy was associated with a 56% reduction in the clinical progression rate. An initial increase of 25 CD4+ cells/ μL or more was not associated with a reduction in clinical progression rate; however, sustained increases in CD4+ cell count of 25/ μL or more appeared to be a better predictor of clinical progression.

The most frequent and usually the first genotypic mutation observed with delavirdine monotherapy and combination therapy is at K103N. The Y181C

mutation is observed during monotherapy and delavirdine/didanosine therapy; the P236L mutation, alone or in combination with the K103 mutation, is observed during delavirdine/zidovudine therapy. In general, delavirdine phenotypic susceptibility decreases in the presence of Y181C ± K103N/T mutations > P236L + K103N > P236L > K103T > K103N mutations. A stepwise increase in delavirdine IC₅₀ is often observed with the emergence of a second mutation, and double mutations correlate with poorer surrogate marker response.

The major side effect associated with delavirdine is a diffuse pruritic maculopapular rash that usually occurs in the first month of therapy in approximately 33% of patients. The rash is not related to blood levels or doses of delavirdine and appears to be more common in patients with CD4+ counts below 300 cells/μL who are taking other medications. More than 85% of patients who develop a rash can continue therapy.

Nevirapine

Nevirapine, the first NNRTI approved by the US Food and Drug Administration, is rapidly absorbed and is associated with a dramatic decrease in viral load after initiation of therapy. Plasma concentrations exceed the IC₅₀ after the first dose. In addition, nevirapine penetrates the blood-brain barrier with a ratio of 1:1 unbound nevirapine in plasma to nevirapine in the cerebrospinal fluid (CSF). Although clinical trial data are not available, nevirapine may prove to be a useful drug for the management of HIV encephalopathy.

Nevirapine in combination has been shown to maintain suppression of viral replication in naive and advanced patients. In one study (Boehringer Ingelheim protocol 1046), antiretroviral naive patients (mean CD4+ count 375 cells/μL and mean plasma HIV RNA 25,740 copies/mL) were randomized to zidovudine/ nevirapine/ didanosine, zidovudine/nevirapine, or zidovudine/didanosine. Figure 1 shows the difference between the treatment arms at 28 weeks. Two-thirds of patients on triple-combination therapy had a sustained reduction in plasma HIV RNA below the level of detection for more than 52 weeks. In this study, nevirapine-associated resistance developed whether or not the indi-

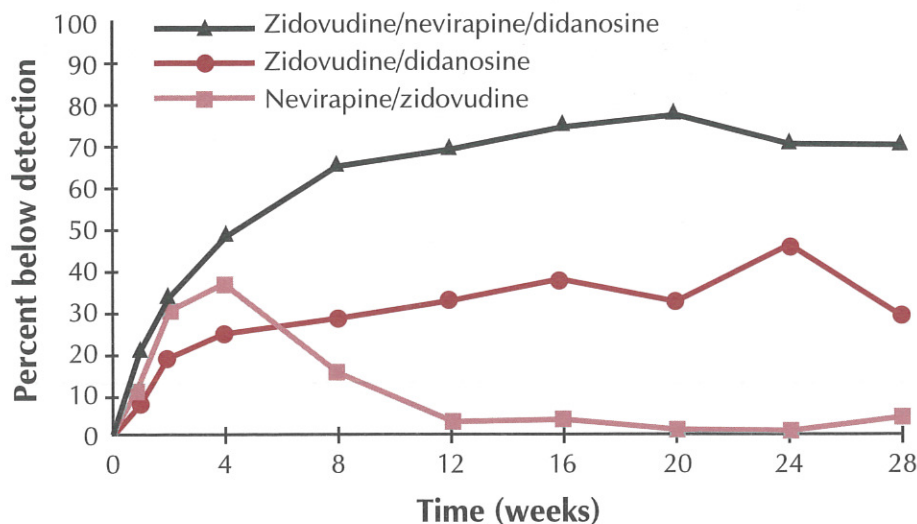


Figure 1. Percentage of patients below the limit of plasma HIV RNA detection (<200 copies/mL) through 28 weeks of treatment with nevirapine/zidovudine, zidovudine/didanosine, or zidovudine/didanosine/nevirapine. From the BI 1046 trial.

vidual adhered to the prescribed regimen as measured by pill counts, but individuals not adhering to the regimen were much more likely to develop resistance to nevirapine.

ACTG protocol 193A evaluated the nevirapine in patients with advanced HIV disease and extensive antiretroviral pretreatment (mean CD4+ 20 cells/μL; 18% of patients were antiretroviral naive). Patients were randomized to zidovudine/ alternating didanosine, zidovudine/ zalcitabine, zidovudine/didanosine, or zidovudine/didanosine/nevirapine. There

was a significant increase in median survival in patients taking the triple-combination regimen compared with patients taking zidovudine/alternating didanosine ($P = 0.012$) or zidovudine/ zalcitabine ($P = 0.009$).

As with delavirdine, rash is the most common side effect associated with the use of nevirapine. In an analysis combining patients from three comparative trials, rash occurred in 37% of 252 patients taking nevirapine, compared with 20% of 255 control patients ($P < 0.01$).

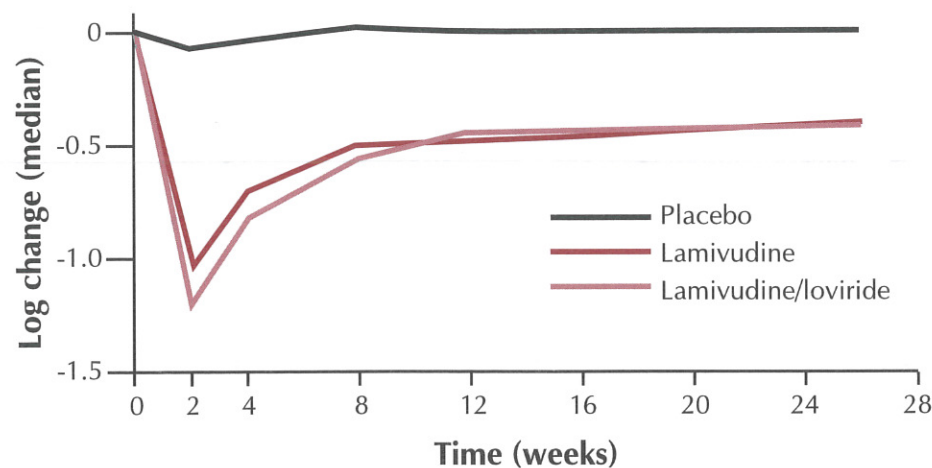


Figure 2. Median log change in plasma HIV RNA from baseline through 26 weeks in patients randomized to add placebo, lamivudine, or lamivudine/loviride to their existing treatment regimen. From the CAESAR trial.

Table 2. Effects of NNRTIs on the Metabolism of Selected Drugs.

Nevirapine	Induces cytochrome P450 Reduces levels of protease inhibitors, rifampin/rifabutin, oral contraceptives
Delavirdine	Inhibits cytochrome P450 Increases levels of protease inhibitors, rifampin/rifabutin, astemizole, loratidine, terfenadine, cyclosporin, estradiol, ketoconazole, itraconazole, macrolides, warfarin, progesterone, and testosterone
DMP-266	Induces cytochrome P450 Expected to have the same effects as nevirapine
Loviride	Appears to have no effect on metabolism of other drugs

Loviride

Loviride has been studied primarily in Europe. The current dose of 100 mg tid results in good plasma levels, and the drug does not appear to significantly alter hepatic enzyme functions. In the AVANTI-1 trial study, loviride was added to the combination of zidovudine and lamivudine in antiretroviral-naïve patients. The median maximal decrease in plasma HIV RNA from baseline (occurring at 4 weeks) was 2.1 log in the triple-combination group and 1.9 log in the zidovudine/lamivudine group. At week 52, the median decreases in viral load from baseline were 1.4 log and 1.3 log, respectively. The median maximal increases from baseline at 52 weeks in CD4+ cell counts were 127/ μ L and 69/ μ L, respectively.

In the CAESAR study, naïve and experienced patients with 25 to 250 CD4+ cells/ μ L were randomly assigned to add lamivudine (150 mg bid), lamivudine (150 mg bid)/loviride (100 mg bid), or placebo to their current treatment regimen. No further reduction in morbidity or mortality was observed with the addition of lamivudine/loviride compared with the addition of lamivudine alone (Figure 2). The role of loviride in potent antiretroviral regimens is unclear.

DMP-266

The investigational NNRTI, DMP-266, differs from other current NNRTIs in that viral resistance requires multiple mutations, and administration of the drug is not associated with a significant incidence of rash. DMP-266 has entered clinical trials in the United States.

The Use of NNRTIs with Protease Inhibitors

The NNRTIs are metabolized by the hepatic cytochrome P450 system and thus affect the metabolism of a number of other drugs (Table 2). The use of the NNRTIs in combination regimens that contain protease inhibitors requires careful evaluation of the potential interactions.

In small combination studies, use of nevirapine was associated with significant reductions in steady-state area-under-the-curve (AUC), C_{\min} , and C_{\max} of saquinavir and indinavir; there was no significant reduction in these measures when nevirapine was combined with ritonavir. The protease inhibitors had no effect on the concentration of nevirapine, and there was no loss in viral suppression after 120 days when indinavir and nevirapine were administered together.

Coadministration of delavirdine and saquinavir in non-HIV-infected persons was associated with an increase in concentrations of saquinavir compared with those achieved with the administration of saquinavir alone (Figure 3). The effects of delavirdine on ritonavir and indinavir concentrations were less marked than those observed on saquinavir concentration.

Summary

Despite the limitations created by their effects on hepatic metabolism, the NNRTIs offer options for prolonged aggressive antiretroviral therapy. In chronic HIV infection in adults, it is currently understood that the optimal use of the NNRTIs is in regimens that are intended to achieve maximal suppression in antiretroviral naïve patients who have low plasma HIV RNA levels. Nevirapine, in combination with two nRTIs, results in significant improvements in antiretroviral-naïve patients. In addition, the rapid reduction in viral load observed with initial NNRTI therapy may prove useful in specific clinical situations such as managing occupational exposure to HIV or preventing vertical transmission. According to Dr Phair, the ultimate therapeutic niche for the NNRTIs remains to be defined.

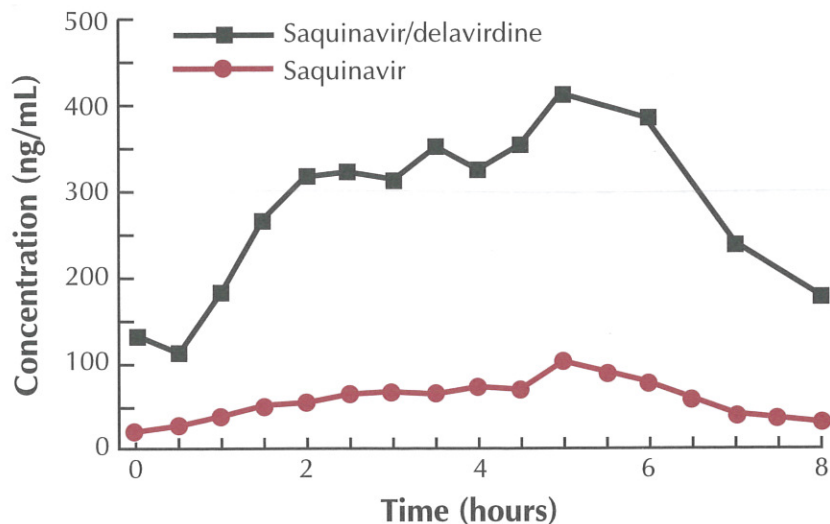


Figure 3. Mean steady-state plasma saquinavir concentrations in non-HIV-infected persons given saquinavir alone or saquinavir/delavirdine. From Protocol 0052.

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Suggested Readings

Freimuth WW, Wong Y, Docci S, et al. Surrogate marker responses from an open-label extended use of delavirdine mesylate (DLV) treatment of triple combination (ZVD+DLV+DDI, or ZVD+DLV+DDC) for HIV-1 patients. Presented at the XIth International Conference on AIDS; July 7-11, 1996; Vancouver, British Columbia, Canada. Abstract MOB 1134.

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Havir D, McLaughlin MM, Richman DD. A pilot study to evaluate the development of resistance to nevirapine in asymptomatic human immunodeficiency virus-infected patients with CD4+ cell counts of $>500/\text{mm}^3$. AIDS clinical trials group protocol 208. *J Infect Dis.* 1995;172:1379-1383.

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Richman DD, Havir D, Corbeil J. Nevirapine resistance mutations of human immunodeficiency virus type-1 selected during therapy. *J Virol.* 1994;63:1660-1668.

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