# IVB. NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

## i. Delavirdine Mesylate / Rescriptor® (Pharmacia & Upjohn)

*by Spencer Cox*

### BACKGROUND

Delavirdine mesylate is an inhibitor of the HIV reverse transcriptase enzyme. Unlike the nucleoside analogue reverse transcriptase inhibitors (RTIs), non-nucleoside RTIs (NNRTIs) such as delavirdine do not act as DNA chain terminators. Instead, delavirdine binds directly to reverse transcriptase and blocks RNA- and DNA-dependent DNA polymerase activities. Delavirdine was the second NNRTI to receive marketing approval from the US Food & Drug Administration (FDA), after Boehringer Ingelheim's Viramune® brand nevirapine.

NNRTIs have a spotty history as anti-HIV therapies. The earliest products to enter the clinic were abandoned when monotherapy trials showed that, while the drugs were initially very potent, resistance developed rapidly and virologic effects were short-lived following initation of therapy. Even today, with two NNRTIs approved and several others in development, the role of these drugs in the treatment of HIV remains unclear: most have major interactions with protease inhibitors that have not yet been well-characterized, and controversies remain about their potency and capacity to produce cross-resistance within the class.

***Indication.*** The Rescriptor® labeling indication is confusing, due to the failure of several studies to suggest clinical efficacy or even significant antiviral activity. According to the label, "Rescriptor tablets are indicated for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents when therapy is warranted. This indication is based on surrogate marker changes in clinical studies. Clinical benefit was not demonstrated for Rescriptor based on survival or incidence of AIDS-defining clinical events in a completed trial comparing Rescriptor plus didanosine with didanosine monotherapy. Resistant virus emerges rapidly when Rescriptor is administered as a monotherapy. Therefore, Rescriptor should always be administered in combination with appropriate antiretroviral therapy." (Pharmacia & Upjohn, 1997). The recommended dosage for Rescriptor tablets is 400 mg (four 100 mg tablets) three times daily. Rescriptor has not been evaluated in children under 16 years of age, and no pediatric dosing recommendations are offered.

***About the sponsor.*** Pharmacia & Upjohn, Inc., is a research-based, pharmaceutically focused company formed by the 1995 merger of Pharmacia AB (Sweden) and The Upjohn Company (US). Pharmacia & Upjohn has more than 30,000 employees and, in 1995, had annual sales of approximately $7 billion. Pharmacia & Upjohn is the ninth largest pharmaceutical company in the world. Its key areas of research focus include infectious diseases, oncology, inflammatory diseases, metabolic diseases, and nervous-system diseases. Key products manufactured by Pharmacia & Upjohn include the antibiotics clindamycin (Cliacin/Dalacin) and cefpodoxime (Vantin), the anti-TB and MAC drug rifabutin (Mycobutin),

Genotropin (rHGH) for treatment of dwarfism, Halcion for insomnia, Xanax for anxiety, and adriamycin for various cancers. After an accelerated NDA was submitted to the FDA for Pharmacia & Upjohn's Rescriptor® brand delavirdine in the second quarter of 1996, the agency's Antiviral Drugs Advisory Committee split evenly on a recommendation to approve the drug. Approval was finally granted in March of 1997. Pharmacia & Upjohn is also working on a new line of antibiotics that may be effective against drug-resistant gram-positive bacteria, and is currently in phase II testing.

***Mechanism of activity.*** HIV is a retrovirus, which means that it stores its genetic material as RNA, rather than as DNA. In order to infect a human cell, HIV's RNA must be converted to DNA. This conversion is accomplished by a viral enzyme called reverse transcriptase. NNRTIs, including delavirdine, bind to reverse transcriptase, blocking its activity. HIV-2 is not inhibited by delavirdine, and HIV-1 group O, a group of highly divergent strains that are not common in North America, may not be inhibited by delavirdine.

## ANTIRETROVIRAL POTENCY

***Test-tube studies.*** *In vitro*, delavirdine is effective against HIV-infected monocytes, lymphoblasts, and plasma lymphocytes from both laboratory and clinical (wild-type) HIV-1 strains. Its 50% inhibitory concentration ($IC_{50}$) for clinical isolates ranged from 0.001 to 0.69 micromolars (FM). The mean 90% inhibitor concentration ($IC_{90}$) in clinical isolates ranged from 0.04 to 0.10 FM respectively. *In vitro*, delavirdine is additive or synergistic with AZT, ddI, ddC, 3TC, interferon-$\alpha$, and protease inhibitors. However, these results may not be relevant *in vivo*, since test-tube cultures lack the hepatic cytochrome p450 system through which all protease inhibitors, as well as the NNRTIs, are metabolized, leading in some cases to *in vivo* pharmacokinetic synergy or antagonism which would not be predicted *in vitro*.

***Clinical trials.*** Four major clinical trials have been conducted to assess the *in vivo* effects of delavirdine on CD4 cell counts, plasma HIV RNA levels, and rates of clinical disease and death.

***Study 0021*** compared delavirdine plus AZT to AZT monotherapy in 718 HIV-infected patients who were treatment-naïve or who had received less than six months of prior AZT treatment. Mean baseline CD4 cell count was 334 and baseline plasma HIV RNA was 5.25 $\log_{10}$ copies/ml. Participants were treated with 200 milligrams (mg) of AZT thrice daily (TID), or with delavirdine at doses of 200, 30, or 400 mg TID in combination with AZT. At 24 weeks, there was no significant difference in CD4 counts between the delavirdine-containing arms and the AZT arm. Patients treated with delavirdine in combination with AZT experienced a reduction of approximately one log in plasma HIV RNA levels at week four, as compared to a reduction of only about 0.5log in patients treated with AZT monotherapy. By week 24, the combination therapy arm had about an 0.7 log drop in HIV RNA levels, while the AZT monotherapy arm had an 0.4 log reduction (Pharmacia & Upjohn 1997).

***Study 0021 - Part B*** randomized 352 patients to one of three treatment arms: AZT/3TC, delavirdine/AZT or AZT/3TC/delavirdine. The small percentage of treatment-experienced patients (less than 20%) in this study, all had less than six months of prior AZT exposure. Baseline CD4 cell count was about 360, and baseline HIV RNA was between 4.35-5.0 logs. Enrollment in the study was discontinued when it was recognized that the AZT/3TC control arm fell short of the standard of care. An interim analysis was undertaken of data collected through 52 weeks of treatment. Using the standard Roche Amplicor HIV

RNA PCR assay with a 400 copy lower limit of detection, 68% of patients treated with AZT/3TC/delavirdine had undetectable viral load measurements, versus 22% percent treated with AZT/3TC, and no patients treated with AZT/delavirdine. The company also conducted an analysis using 40 copies/ml as the lower limit of detection: at week 52, 59% of participants treated with AZT/3TC/delavirdine had undetectable viral load measurements, versus 11% of patients treated with AZT/3TC and no patients treated with AZT/delavirdine (Sargent 1998).

***Study 0017*** compared ddI monotherapy to combination treatment with delavirdine and ddI in 1,190 HIV-infected patients who had received up to four months of prior ddI therapy. Mean baseline CD4 cell count was 142 and mean baseline plasma HIV RNA was 5.77 logs. Patients were treated with ddI (dosing adjusted for body weight), with or without 400 mg delavirdine TID. At week eight, patients treated with the combination therapy arm experienced a CD4 increase of about 30 cells, while patients treated with ddI monotherapy had a CD4 cell increase of about 15. By week 24, there was essentially no difference in CD4 cell counts. Patients treated with the ddI/delavirdine combination experienced an average reduction of 0.9 log HIV RNA copies week four, as compared to a reduction of about 0.5 log in patients treated with ddI alone. By week ten there was essentially no difference between the treatment arms. At 24 weeks, no difference could be seen between rates of clinical illness and death between the two treatment arms (Pharmacia & Upjohn 1997).

***ACTG 261*** was a study comparing four treatment regimens (delavirdine/ddI vs. delavirdine/AZT vs. delavirdine/ddI/AZT, vs. AZT/ddI) in 544 HIV-infected patients who were either treatment naïve, or who had fewer than six months prior treatment with either AZT or ddI. Thirty-seven percent of patients reported prior therapy. Mean baseline CD4 count was 296 and median baseline plasma HIV RNA was 4.45 log. Treatment doses were 400 mg delavirdine TID, 200 mg AZT TID, and ddI dosing adjusted by body weight. Through week 32, no significant difference was seen in CD4 cell counts or in plasma HIV RNA between the three-drug combination of delavirdine, AZT and ddI as compared to the two-drug combination of AZT and ddI (Pharmacia & Upjohn 1987).

***Pediatrics.*** The pharmacokinetics of delavirdine have not been studied in patients younger than 16.

***Gender.*** In study 021, which enrolled 139 (19%) women among its 718 participants, the mean delavirdine area under the curve (AUC) was 31% higher in women than in men, and the mean trough concentration is 80% higher in women than in men. However, no dose adjustment is recommended (Pharmacia & Upjohn 1997b).

***Pregnancy.*** No studies of delavirdine have been conducted in pregnant women. Delavirdine has been categorized as pregnancy category C, which means that the drug has been shown to cause birth defects in animals. In particular, the drug caused heart defects in rats when administered early in pregnancy at doses that produced systematic exposure comparable to expected human exposure to the drug at normal doses. Additionally, reduced pup survival was seen in rats at exposure levels approximately equal those expected in humans. High doses of delavirdine (approximately six-fold higher than expected human concentrations) also induced miscarriages in rabbits. Of seven unplanned pregnancies in women taking delavirdine, three were ectopic pregnancies, three were normal births, and one infant was born prematurely with a heart defect similar to those seen in rats treated with delavirdine.

***Race & ethnicity.*** No significant differences were seen in delavirdine pharmacokinetics across different racial or ethnic groups.

***Hepatic or renal impairment.*** The pharmacokinetics of delavirdine have not been studied in patients with hepatic or renal impairment.

## RESISTANCE & CROSS RESISTANCE

Following treatment with delavirdine, rapid emergence of HIV strains that are cross-resistant to other non-nucleoside reverse transcriptase inhibitors (NNRTIs) has been observed *in vitro*, including mutations at positions 103 and 181. Delavirdine may confer cross-resistance to other NNRTIs, although the various manufacturers offer conflicting claims in this regard.

## ADVERSE EVENTS & TOXICITY MANAGEMENT

**Studies 0017 and 0021 : Pooled Data on Moderate or Severe Adverse Events Occurring in ≥2% of Study Participants (%)**

| | *Study 0017* | | *Study 0021* | |
|---|---|---|---|---|
| | ***ddI*** | ***ddI+DLV*** | ***AZT*** | ***AZT+DLV*** |
| **Headache** | 4.7 | 5.6 | 4.8 | 5.6 |
| **Fatigue** | 2.7 | 2.9 | 4.8 | 5.2 |
| **Nausea** | 3.4 | 4.9 | 6.6 | 10.8 |
| **Diarrhea** | 4.4 | 4.5 | 2.2 | 3.5 |
| **Vomiting** | 1.2 | 2.4 | 1.1 | 2.8 |
| **Increased SGPT** | 3.6 | 5.2 | 0.7 | 2.4 |
| **Increased SGOT** | 3.0 | 4.5 | 0.7 | 1.7 |
| **Rash** | 3.0 | 9.8 | 1.5 | 12.5 |
| **Maculopapular rash** | 2.0 | 6.6 | 1.1 | 4.5 |
| **Pruritis** | 1.7 | 2.2 | 1.5 | 3.1 |

*(Pharmacia & Upjohn 1997)*

Clearly rash, a side effect shared by the entire class of NNRTIs, is the most common serious toxicity, occurring in 18% of all patients in combination regimens in phase II or III studies who received the recommended dose of delavirdine. Forty-two to fifty percent of patients treated with 400 mg delavirdine TID in studies 0021 and 0017 experienced a rash. 4.3% of these patients discontinued treatment due to rash. Serious rashes occurred in 10-12% of patients receiving the approved dose. The manufacturer notes that "the majority of rashes ... occur within 1 to 3 weeks after initiating treatment... The rash normally resolves in 3 to 14 days and may be treated symptomatically while therapy ... is continued. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches should discontinue medication and consult a physician." Unofficially, the company notes that, in most patients, the rash can be treated through using an antihistamine such as Benadryl to treat symptoms. The mechanism of the rash remains unknown.

In general, no laboratory abnormalities occurred more frequently in patients taking nucleosides in combination with delavirdine than occurred in patients taking nucleosides alone. The one exception

was study 0021, in which patients treated with AZT were about twice as likely to develop neutropenia as patients taking AZT in combination with delavirdine.

**Frequency (%) * of Clinically Important Laboratory Abnormalities**

| | *Study 0017* | | *Study 0021* | |
|---|---|---|---|---|
| | ***ddI*** | ***ddI+DLV*** | ***AZT*** | ***AZT+DLV*** |
| N | 591 | 594 | 271 | 287 |
| **Neutropenia (ANC <750/ mm$^3$)** | 6.7 | 5.7 | 7.7** | 3.5 |
| **Anemia (Hgb <7.0g/dL)** | 0.2 | 0.7 | 1.1 | 1.0 |
| **Thrombocytopenia (platelets <50,000/mm$^3$)** | 1.4 | 1.5 | 0.0 | 0.0 |
| **ALT (>5.0 x ULN)** | 4.6 | 6.7 | 3.7 | 3.8 |
| **AST (>5.0 x ULN)** | 4.9 | 5.6 | 3.0 | 2.1 |
| **Billibrubin (>2.5 ULN)** | 0.7 | 0.5 | 0.4 | 1.0 |
| **Amylase (>2.0 ULN)** | 6.5 | 5.2 | 1.1 | 0.0 |

*(Pharmacia & Upjohn 1997)*

[ANC = absolute neutrophil count; ULN = upper limit of normal]

* Percentage was based on the number of patients for which data on that laboratory test was available.

** Significant ($p<.05$) delavirdine + AZT vs. AZT.

## PHARMACOKINETICS, FOOD & DRUG INTERACTIONS

Delavirdine is easily absorbed when given in oral form, with peak steady-state plasma concentrations of $35\pm20\ \mu M$ at one hour after dosing. Trough concentrations was $15\pm10\ \mu M$ , and area under the curve was approximately $180\pm100\ \mu M$/hr. Bioavailability of the drug can be increased by about 20% by dissolving tablets in water. The plasma half-life of delavirdine increases with dose; mean half-life following 400 mg TID is 5.8 hours.

Delavirdine may be taken with or without food. Although a high-fat meal may lower the peak plasma concentration and area under the curve of a single delavirdine dose significantly, during multiple-dose studies, trough concentrations and area under the curve were not significantly affected by normal diet.

In the bloodstream, approximately 98% of delavirdine binds to plasma proteins (primarily albumin). Delavirdine levels in the CNS fluid, saliva and semen are generally about 20%, 6% and 2% respectively of plasma delavirdine concentrations. Approximately 44% of a dose is excreted in the stool, and approximately 51% in the urine.

The main physicological interaction of delavirdine is with a family of liver enzymes known as the cytochrome p450 isoforms. Delavridine is primarily metabolized by the CYP3A isoform, but *in vitro* data also suggest metabolism by CYP2D6. Delavirdine inhibits CYP3A activity, slowing its own metabolism. *In vitro* studies have also shown that delavirdine reduces CYP2C9 and CYP2C19 activity. Because this liver enzyme system is also responsible for metabolizing a number of other commonly-used drugs, delavirdine can have a significant effect on their plasma half-life and plasma concentration.

**Interactions between Delavirdine & Other Commonly Used HIV/AIDS Drugs**

| *Drug* | *DLV Dose* | *N* | *Interaction* |
|---|---|---|---|
| **Antacids (alumina and magnesia oral suspension)** | 300 mg single dose | 12 | 41% reduction in DLV AUC |
| **Clarithromycin (500 mg BID)** | 300 mg TID | 6 | 44+50% increase in DLV AUC; 100% increase in Clari AUC, 75% decrease in 14-HO AUC |
| **ddI (125 or 250 mg BID)** | 400 mg TID | 9 | 20% decrease in ddI, DLV AUC |
| **Fluconazole (400 mg/qd)** | 300 mg TID | 8 | No change |
| **Fluoxetine** | Not given | 36 | 50% decrease in DLV trough levels |
| **Indinavir (400 mg single-dose)** | 400 mg TID | 14 | Increases IDV AUC to levels like 800mg IDV alone. Dose reduction to 600mg IDV TID recommended. |
| **Indianvir (600 mg single-dose)** | 400 mg TID | 14 | Increases IDV to 40% of 800mg dose level.; IDV dose reduction to 600mg TID recommended. |
| **Ketoconazole** | Not given | 26 | Increases DLV trough levels 50% |
| **Nelfinavir** | Not given | NA | 100% increase in NFV AUC, 146% increase in NFV $C_{min}$, 40% increase in DLV AUC |
| **Pheytoin, phenobarbital** | Not given | 8 | Coadministration not recommended |
| **Rifabutin (300 mg qd)** | 400 mg TID | 7 | 80 decrease in DLV AUC, $\geq$100% increase in rifabutin AUC. Coadministration not recommended. |
| **Rifampin (600 mg qd)** | 400 mg TID | 7 | 96% decrease in DLV AUC. Coadministration not recommended. |
| **Ritonavir (300 mg BID)** | 400 or 600 mg BID | 13 | No change in RTV or DLV PK. |
| **Ritonavir (600mg BID)** | NA | 10 | 60% increase in RTV AUC, 66% increase in RTV $C_{max}$, 84% increase in RTV $C_{min}$. |
| **Saquinavir (600mg TID)** | 400 mg TID | 7 | 500% increase in SQV AUC, 15% decrease in DLV AUC |
| **TMP/SMX (Bactrim, Septra)** | 400 mg TID | 311 | No effect |
| **Zidovudine (AZT)** | NA | NA | No effect |

[NA = not available]

*(Pharmacia & Upjohn 1997)*

**Safety Considerations:**

- **A number of drugs should *NOT* be taken with delavirdine:**

  * The anticonvulsants phenytoin, phenobarbital, and carbamazepine
  * The antimycobacterial drugs rifabutin and rifampin
  * The anti-ulcer drugs cimetidine, famotidine, nizatidine and ranitidine.

- **Several drugs have not been tested with delavirdine, but are expected to have major interactions that could result in "potentially serious and/or life-threatening adverse events":**

  * The antihistamines terfenadine and astemizole
  * The sedatives alprazolam, midazolam and triazolam
  * The digestive aid cisapride

- Fnally, ddI and antacids should be taken at least an hour before or after taking delavirdine.

**PRICING**

At $2,250 per year, delavirdine's cost is comparable to the nucleoside analogues, and to that of nevirapine.

**CURRENT & PLANNED POST-MARKETING STUDIES**

| | |
|---|---|
| **0063** | A 24-week study of AZT/3TC/indinavir vs. AZT/delavirdine/indinavir in 90 HIV-infected patients with CD4<500, HIV RNA >20,000 copies, and <6mos of prior AZT |
| **0073** | A 24-week study of two nucleoside analogues (2NAs) + nelfinavir, vs. NA/delavirdine/nelfinavir vs. 2NAs/nelfinavir/delavirdine in 160 PI & NNRTI-naïve patients with >60,000 HIV RNA copies and ≥50 CD4 cells. |
| **0074** | A 24-week study of AZT/3TC/indianvir, vs. AZT/delavirdine/indiinavir, vs. 3TC/delavirdine/indinavir vs. AZT/3TC/indinavir/delavirdine in 160 treatment-naïve patients with ≥50 CD4 cells and >60,000 HIV RNA copies. |
| **Interaction studies** | Studies are planned or underway to evaluate delavirdine in combination with ritonavir and saquinavir. Another study will attempt to evaluate whether or not delayed indinavir clearance during co-administration with delavirdine permits BID dosing of indinavir. |
| **Dosing** | Several studies may evaluate BID dosing of delavirdine in combination with protease inhibitors. |
| **Pediatrics** | Studies are planned to evaluate delavirdine in pediatric patient populations. |

**DISCUSSION**

In general, the optimal use of NNRTIs has not been determined. However, of this class, the potential utility of delavirdine is particularly difficult to classify. The drug is weakly potent, with no demonstrated clinical benefit, and virologic activity is seen generally for only four to eight weeks when the product is used in combination with one nucleoside analogue. When used in combination with two nucleoside analogues in antiviral naive patients, the drug seems somewhat more efficacious, but insufficient to replace protease inhibitors in an initial regimen. Interactions with protease inhibitors have only been described at the grossest pharmacokinetic level, with little data regarding safety or activity. Anecdotes have abounded, ranging from tales of miraculous responses effected by the combination of delavirdine with Crixivan, to horror stories about serious liver toxicity caused by the same combination.

Because of concerns about cross-resistance to efavirenz (Sustiva™, formerly known as DMP-266), an

NNRTI in development by DuPont Pharma (formerly DuPont Merck) which seems much more potent than either delavirdine or nevirapine, the current marketed NNRTIs seem to be relegated to at best a role in salvage therapy in patients who have failed at least one protease inhibitor, and who , due to extensive pre-treatment, have limited options for combinations with multiple nucleoside analogues.

To some extent, Pharmacia & Upjohn are clearly victims of the rapid changes in clinical care for HIV-infected patients: their studies were designed before the protease revolution, and even before the clinical validation of combination therapy. As a consequence, most of their registration trials involved use of delavirdine in combination with a single nucleoside analogue. However, in the absence of more useful empirical data, doctors are left to prescribe the drug based on a combination of theory and intuition – a poor rationale for prescribing anti-HIV medication, and one that can be harmful by compromising the utility of drugs used in combination and producing cross-resistance to other, more potent drugs.

Perhaps the most problematic aspect of delavirdine is its interaction profile: the drug has serious pharmacokinetic interactions with several important therapies used in the treatment of HIV-infected patients, of which only a few have been well-characterized. While there is great interest in combining NNRTIs with protease inhibitors, Pharmacia & Upjohn presented spotty interaction data on these combinations, mostly from studies of HIV-negative patients (who may differ in absorption from HIV-infected patients), in single-dose studies, or at doses that differ from current recommended doses. Anecdotally, these combinations may be associated with serious side effects, and longer-term studies are needed to define the potency of delavirdine in combination with protease inhibitors. Some of these studies, such as better interaction information regarding delavirdine and ritonavir or nelfinavir have become available since the approval, and Pharmacia & Upjohn have planned several such studies.

However, the FDA's decision to approve the drug based on very limited data on clinical activity (let alone efficacy) raises troubling questions about the standard of approval: the agency should move more expeditiously to define how changes in HIV RNA levels are to be measured, and promulgate guidelines for the design and conduct of clinical trials to evaluate the contribution of a particular drug used in combination to a change in the measurement.

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# IVB. NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

## ii. Nevirapine / Viramune® (Roxane Laboratories)

*by Spencer Cox*

### BACKGROUND

Like Rescriptor®, Viramune® brand nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). On June 24th, 1996, Nevirapine became the first NNRTI to receive marketing approval from the US Food & Drug Administration (FDA). In combination with nucleoside analogues, nevirapine has been shown to produce significant, sustained reductions in plasma HIV RNA levels. However, the currently marketed NNRTIs are generally thought to be somewhat less potent than protease inhibitors over the long term. This may be a function of the relative ease with which replicating HIV can generate mutations associated with reduced sensitivity to NNRTIs. Furthermore, due to the relative lack of data on using nevirapine with protease inhibitors, class-wide cross-resistence, and the probable approval late this year of efavirenz, the role of nevirapine in the treatment of HIV-infected patients remains extremely unclear.

***Indication.*** The Viramune® labeling indication is similar to that of many other anti-HIV therapies, covering a broad class of patients, not all of whom have been adequately studied. According to the label, "Viramune (nevirapine) in combination with nucleoside analogues is indicated for the treatment of HIV-1 infected adults who have experienced clinical and/or immunologic deterioration." Like other drugs approved under the accelerated approval regulations, the label for Viramune® warns that "This indication is based on analysis of changes in surrogate endpoints in studies of up to 48 weeks duration. At present, there are no results from controlled clinical trials evaluating the effect of Viramune® with nucleoside analogues on the clinical progression of HIV-1 infection, such as the incidence of opportunistic infections of survival." Nevirapine is administered in a 200 mg tablet. To reduce the risk of initial side effects, patients are told to begin with one tablet daily for the first 14 days, followed by two tablets daily.

***About the sponsor.*** Roxane Laboratories, Inc., is a subsidiary of the Boehringer Ingelheim Corporation. Roxane is headquartered in Columbus, Ohio. Roxane was founded in 1885 as Columbus Pharmacal, and was acquired in 1978 by Boehringer Ingelheim Corporation. Roxane focuses on palliative care and pain management products, including oral opoid analgesics.

### ANTIRETROVIRAL POTENCY

***Test-tube studies.*** *In vitro*, activity of nevirapine against HIV was measured in peripheral blood mononuclear cells, monocyte-derived macrophages, and lymphoblast cell lines, using both laboratory and clinical (wild-type) HIV-1 strains. The 50% inhibitory concentration ($IC_{50}$) for clinical isolates ranged from 10 to 1000 nanomolars (nM). *In vitro*, nevirapine is additive or synergistic with AZT, ddI, d4T, 3TC, and saquinavir However, these results may not be relevant *in vivo*, since test-tube cultures lack the

hepatic cytochrome p450 system through which all protease inhibitors (as well as the NNRTIs) are metabolized, leading in some cases to *in vivo* pharmacokinetic synergy or antagonism which would not be predicted *in vitro*.

***Clinical trials.*** A number of clinical trials have now been reported assessing the *in vivo* effects of nevirapine.

***Study BI 1046 (the INCAS study)*** compared standard doses of nevirapine in combination with AZT and ddI to AZT in combination with ddI, or AZT in combination with nevirapine. The study enrolled 151 treatment-naive patients, with a mean baseline CD4 count of 376 cells and a mean plasma HIV RNA count of 4.41 log10 copies/ml. After 28 weeks, the triple-combination arm had a significantly better virologic response to therapy than did either double-drug combination arm:

**Virologic Response to Therapy in BI 1046 at Week 28 as Compared to Baseline**

| | *AZT/ddI/NVP* | *AZT/ddI* | *AZT/NVP* |
|---|---|---|---|
| **Viral Load ($log_{10}$ change)** | -1.65 | -0.3 | 0.4 |
| **% w/ RNA <200/ml (PCR)** | 72% | 45% | 0% |

*(Roxane 1996)*

The difference between the triple-combination group and the AZT/ddI group was not significant, however, the triple-combination was significantly better than the AZT/nevirapine group. Follow-up data from patients in this study treated with AZT/ddI/nevirapine have recently been presented:

**Immunologic and Virologic Response to Combination Therapy in BI 1046 / INCAS**

| | *28wks* | *52wks* | *76wks** |
|---|---|---|---|
| ***AZT/ddI/nevirapine*** | | | |
| N | 35-40 | 25-35 | 10-12 |
| CD4 | +120 | +140 | +100 |
| HIV RNA (in log10) | -1.65 | -1.3 | -1.4 |
| % w/ RNA <200 | 70 | 60 | 80 |
| % w/ RNA <20 | 60 | 51 | 70 |
| ***AZT/ddI*** | | | |
| CD4 | +70 | +30 | +30 |
| HIV RNA (in log10) | -1.3 | -0.9 | -0.7 |
| % w/ RNA <200 | 30 | 15-20 | 10% |
| ***AZT/nevirapine*** | | | |
| CD4 | +10 | 0 | -10 |
| HIV RNA (in log10) | -0.4 | -0.3 | -0.2 |
| % w/ RNA <200 | 0 | ND | ND |

*(Levin 1998 and Montaner 1998)*

* Week 76 data are based on a small number of study participants; data from week 52 may be more representative of the effects of therapy. ND = not done.

***In ACTG 241***, 398 patients with a prior history of at least six months of nucleoside analogue therapy were randomized to receive standard doses of nevirapine in combination with AZT/ddI. Mean CD4 cell count at baseline was 153 cells/mm3, and mean baseline plasma HIV RNA count wsa 4.59log10 copies/ml. Median prior anti-HIV therapy was 115 weeks. After 48 weeks of therapy, patients assigned to the triple-combination regimen had an 18% higher mean CD4 cell count (p=0.001), and a 0.25log10 lower plasma HIV RNA count (p=0.028) than did patients assigned to the AZT/ddI combination regimen. No difference was seen in the risk of clinical disease or death (p=0.2), but investigators note that "the study had only moderate power to detect a major difference."

***In ACTG 193a***, 1,314 patients were randomly assigned to be treated with AZT/ddC, AZT alternating with ddI, AZT/ddI and AZT/ddI/nevirapine. Average CD4 count was 20, and most patients had been previously treated with nucleoside analogs. The triple drug arm was superior to the AZT/ddC arm and to the AZT alternating with ddI arm in its impact on survival, but was not superior to the AZT/ddI combination arm. The AZT/ddI combination arm was not superior to either AZT/ddC, or to AZT alternating with ddI (Henry 1996):

**Deaths in ACTG 193a**

| | *AZT/ddC* | *AZT alt ddI* | *AZT/ddI* | *AZT/ddI/NVP* |
|---|---|---|---|---|
| **Deaths** | 142 | 148 | 128 | 118 |

*(Henry 1998)*

***Recent pilot studies.*** Data were recently presented on the combination of nevirapine, indinavir and 3TC in 22 patients with advanced-stage HIV disease and heavy prior nucleoside analogue therapy. Median CD4 cell count was 30, and median plasma HIV RNA count was 5.16 log10. At the end of one year, 11 patients remained on therapy. Seven of those patients had viral load of <20 copies/ml, three patients had viral load of 20-400 copies/ml, and one patient had 1,635 copies/ml (Harris 1998). Researchers at the Fifth Retrovirus Conference reported on a small study (n=7) of a four-drug regimen using AZT, 3TC, indinavir and nevirapine in treatment-naive patients. Four participants had more than 500 CD4 cells, and 3 had fewer than 300 CD4 cells. Patients have been treated for up to eight months, and all had decreases in plasma HIV RNA levels to below 500 copies. Five patients substituted d4T for AZT due to toxicity. CD4 cell counts have increased by a mean 135 cells, and biopsies have found "dramatic declines" in productively infected cells and FDC associated virus. Even one patient who entered the study with 7 CD4 cells has experienced a dramatic increase in his CD4 cell count and evidence of re-establishment of germinal centers within the lymph nodes (Polis 1998). In a small, experimental study, 25 patients were treated with a twice-daily regimen of d4T, 3TC and nevirapine. After twenty weeks, 23 out of 25 patients have viral load of less than 400 copies/ml (Kaspar 1998).

***Pediatrics.*** Nevirapine is not approved for use in children, however some data have been developed. In pooled data from ACTG 165 and ACTG 180, two studies which tested the pharmacokinetics of nevirapine in chidren, clearance of the drug was more rapid than expected, and occurred more quickly in younger children than in adolescents. In ACTG 245, 432 HIV-infected, treated-experienced children aged six months to 20 years were randomly assigned to receive ddI/AZT/NVP, or ddI/AZT or DDI/NVP and were followed for 48 weeks. Seven percent of participants discontinued treatment because of

toxicity (3.7% patients discontinued due to grade 3/4 rash). The study researchers conclude that "Combination therapies were well-tolerated with mortality less than predicted."

**Virologic Response to Therapy in ACTG 245**

| | | | *Change in HIV RNA by Week of Study* | | | |
|---|---|---|---|---|---|---|
| ***Treatment*** | ***N*** | ***Baseline*** | ***4*** | ***12*** | ***24*** | ***48*** |
| **ddI/AZT/NVP** | 47 | 4.9 | -0.7 | -0.4 | -0.3 | -0.3 |
| **ddI/AZT** | 48 | 4.9 | -0.3 | -0.3 | -0.2 | -0.1 |
| **ddI/NVP** | 41 | 4.8 | -0.0 | -0.0 | +0.1 | -0.0 |

*(Burchett 1998)*

***Gender.*** In one phase I study, a slight increase in volume of distribution of nevirapine was seen in women as compared to men, however this was offset by slightly faster clearance, resulting in no clinically significant gender difference in plasma concentrations or oral clearance.

***Pregnancy.*** Studies of nevirapine in pregnant women are ongoing, but at present the drug is recommended for pregnant women "only if the potential benefit justifies the potential risk to the fetus." Nevirapine has been categorized as pregnancy category C because appropriate studies of animal teratogenicity have not been performed. In rats a significant decrease in fetal body weight occurred at doses comparable to about 150% of normal exposure in humans using standard doses.

***Race & ethnicity.*** No significant differences were seen in nevirapine pharmacokinetics across different racial or ethnic groups.

***Hepatic or renal impairment.*** The pharmacokinetics of nevirapine have not been studied in patients with hepatic or renal impairment.

## RESISTANCE & CROSS RESISTANCE

Following treatment with nevirapine, emergence of HIV strains resistant has been observed *in vitro* after as little as one week, including most frequently mutations or positions 106 and 181. By week eight of treatment with nevirapine monotherapy, 24/24 patients had HIV isolates with a >100-fold decrease in susceptability to nevirapine as compared to baseline. Nineteen out of 24 patients had isolates with a position 181 mutation regardless of dose. Combining nevirapine with AZT produced did not alter the speed of resistance development, however the combination did produce a somewhat different distribution of mutations, with the most frequent mutations occurring at positions 103, 106, 188 and 190. The clinical significance of these mutations has not yet been established: in one study, markers of immunologic and virologic did not closely correlate with the appearance of resistance mutations (Roxane 1996).

Nevirapine resistance can produce reduced sensitivity to other non-nucleoside reverse transcriptase inhibitors.

## ADVERSE EVENTS & TOXICITY MANAGEMENT

The most frequently reported adverse event in people taking nevirapine were rash, fever, nausea, headache, and elevated liver enzymes. The rash, which is common to all NNRTIs, occurred in about 17% of patients in combination regimens in phase II/III controlled studies, and severe or life-threatening, Stevens-Johnson syndrome-like rash in approximately 5.5% of patients. Overall, seven percent of patients in these studies discontinued treatment due to rash. The rash usually occurs within the first four weeks of treatment. Although most patients are able to treat through the rash using an antihistamine such as Benadryl to treat symptoms, 25% of patients with severe rashes required hospitalization, and one patient required surgical intervention. The mechanism of the rash remains unknown.

| **Incidence of Rash in Controlled Studies of Nevirapine** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ***ACTG 241*** | | ***BI 1037*** | | ***BI 1011*** | | ***Combined Data*** | |
| | ***NVP +AZT +ddI*** | ***AZT +ddI*** | ***NVP +AZT*** | ***AZT*** | ***NVP +AZT*** | ***AZT*** | ***NVP*** | ***Control*** |
| **N** | 197 | 201 | 30 | 30 | 25 | 24 | 252 | 255 |
| **Any rash** | 39.6% | 23.9% | 26.7% | 6.7% | 32.0% | 4.2% | 37.3% | 20.0% |
| **Grade 3 or 4 rash** | 8.1% | 1.5% | 3.3% | 0% | 8.0% | 0% | 7.6% | 1.2% |

*(Roxane 1996)*

Patients taking nevirapine were about twice as likely to develop elevated GGT levels as patients taking control therapies. Roxane recommends monitoring of liver function in patients taking nevirapine.

## PHARMACOKINETICS, FOOD & DRUG INTERACTIONS

Nevirapine is about 90% absorbed when given in oral form, with peak steady-state plasma concentrations of $45 \pm 1.9 \mu M$. Trough concentration was $4.5 \pm 1.9 \mu M$ /ml. Neither a high-fat meal, antacids, or ddI buffer significantly affected nevirapine pharmacokinetics. In the bloodstream, approximately 60% of nevirapine binds to plasma proteins. Nevirapine is also found in the breast milk, and cerebrospinal fluid (CSF). Approximately 81% of a dose is excreted in the urine, and approximately 10% in the feces. The main physicological interaction of nevirapine is with a family of liver enzymes known as the cytochrome p450 isozymes. Nevirapine is primarily metabolized by the CYP3A isozymre, but *in vitro* data also suggest metabolism by isozymes. Nevirapine induces CYP3A activity, increases its own metabolism. Because this liver enzyme system is also responsible for metabolizing a number of other commonly-used drugs, nevirapine can have a significant effect on their plasma half-life and plasma concentration. Although many interaction studies have not been performed, researchers recommend that some drugs be used in combination only if clearly necessary and with careful monitoring. Those drugs include the antimycobacterial therapies rifabutin and rifampin, oral contraceptives, and the anti-depressents triazolam and midazolam. Caution is also recommended when combining nevirapine with protease inhibitors: nevirapine may lower indinavir levels by 10-30% (many doctors raise indinavir dosage to 1,000 TID when administering in combination with nelfinavir), ritonavir levels by 11%, and

levels of the old Invirase formulation of saquinavir by 25%. Levels of nelfinavir were unchanged when the drug was co-administered with nevirapine. No data were available on the combination of nevirapine with Fortovase, the new soft-gel capsule formulation of saquinavir.

## PRICING

At $3,015 per year, nevirapine's cost is comparable to that of the nucleosides and of delavirdine.

## DISCUSSION

The role of nevirapine in the treatment of HIV infection has been ambiguous ever since the drug's initial approval, and is likely to become more so if efavirenz is approved as expected at the end of 1998. Although not as potent as a protease inhibitor, available data on virologic potency were more complete for nevirapine than for its competitor delavirdine, leading the original draft of the US Public Health Service Guidelines to note that "the only combination of 2 NRTIs +1 NNRTI that has been shown to suppress viremia to undetectable levels in the majority of patients is AZT+ddI+Nevirapine. This combination was studied in antiretroviral naive individuals." Although new data on delavirdine have caused authors of the Guidelines to delete this sentence, the option of substituting nevirapine for a protease inhibitor is still described as "alternative," due to the fact that such a substitution is "less likely to provide sustained virus suppression." Furthermore, the NNRTIs seem to produce cross-resistance throughout the class. As efavirenz seems in ongoing studies to be substantially more potent than nevirapine or delavirdine, it seems unclear what niche these drugs might occupy following approval of efavirenz. When asked directly what the company thought about the future market for nevirapine, one Roxane researcher is said to have responded "Oh, S***!" Perhaps there might be a role for nevirapine in the treatment of patients who cannot tolerate efavirenz, however it remains to be seen if the manufacturer will invest the needed capital to desscribe limited use of the drug. Also, ongoing studies are investigating the effect of very short courses of nevirapine -- even as little as one dose -- on transmission of HIV from mother to child. Such treatment strategies could be useful in the developing world, however again, the manufacturer has made no commitments about the provision of nevirapine at reduced prices at this time.

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# IVB. NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

## iii. Efavirenz / Sustiva™ (DuPont Pharmaceuticals)

*by Spencer Cox*

### BACKGROUND

Efavirinz (Sustiva™, DMP-266) a third, experimental non-nucleoside reverse transcriptase inhibitor (NNRTI). The chemical was first synthesized in 1995 by Merck, which licensed the drug to DuPont Pharmaceuticals when it decided to focus on development of indinavir. Unlike nevirapine and delavirdine, efavirenz seems to be relatively potent drug, easy to administer and with a more promising resistance profile.

***About the sponsor.*** The DuPont Merck Pharmaceutical Company was formed in 1991 as a research-based, independent joint venture between the DuPont Company and Merck & Company, Inc. In spring 1998, DuPont bought out Merck's share of the company and it became known as DuPont Pharmaceuticals. The company has approximately 4,000 employees worldwide, and 1996 sales and revenue totaled $1.4 billion. Overall, DuPont invests more than 20% of revenue into research and development. Key research foci include HIV, cardiovascular disease, radiopharmaceuticals, central nervous system diseases, and cancer. Its leading products include a series of radio-imaging agents, as well as treatments for Parkinson's disease and alcoholism.

***Mechanism of activity.*** Efavirenz , like other NNRTIs, inhibits reverse transcriptase by binding to the enzyme and blocking polymerase activity.

### ANTIRETROVIRAL POTENCY

***Test-tube studies.*** *In vitro*, efavirenz is effective against a wide range of laboratory and clinical HIV isolates. Its $IC_{95}$ for the inhibition of HIV-1 is 1.5nM. In addition, the drug could *in vitro* inhibit viruses with single mutations that confer resistance to other NNRTIs.

***Clinical trials.*** In preliminary results from a Phase II study (DMP 266 -003), a cohort of 16 patients with CD4 counts of 100-500 and plasma HIV RNA levels of >20,000 copies/ml were treated with two weeks of efavirenz monotherapy, resulting in a mean reduction in HIV RNA of 1.68 logs, and a 96-cell increase in CD4 cell counts. Indinavir was then added, resulting in a mean reduction of -3.2 logs in HIV RNA, with 55% having RNA levels below 400 copies/ml. A mean CD4 cell count increase of more than 100 cells was also observed. (Mayers 1997a)

In another arm from this complicated study, 30 patients with 100-500 CD4 cells and HIV RNA levels of >20,000 copies were treated with two weeeks of indinavir monotherapy, and then randomized in a 2:1 fashion to receive efavirenz or a placebo in combination with indinavir. Investigators rapidly found that efavirenz caused a 35% decrease in the indinavir AUC, and so increased the dose of indinavir from

800 mg every eight hours (q8h) to 1,000 mg q8h early in the course of the trial. After 24 weeks, patients on combination therapy had a 2.2 log reduction in HIV RNA levels, compared to a 1.5 log reduction in patients treated with indinavir monotherapy. CD4 cell counts increased by approximately 100 cells in both groups. Viral load was less than 400 copies/ml in 82% of patients treated with the combination therapy, versus 38% of patients treated with indinavir monotherapy.

To follow up on this data, 59 patients were treated with 200 mg of efavirenz (EFV) once daily, and 1,000 mg of indinavir (IDV) three times per day. A control arm consisting of 42 patients was treated with IDV monotherapy for twelve weeks, and then had d4T and EFV added to their treatment. At thirty-six weeks, all patients had their EFV dose raised to 600 mg/day. After sixty weeks of treatment, 91% of patients treated with EFV/IDV had plasma HIV RNA levels of less than 400 copies/mL, and 79% of of patients treated with EFV/IDV/d4T were below the limit of detection. Among patients on EFV/IDV who were undetectable by the standard assay, 84% had no detectable signal by week 12, 96% by week 16, and 100% by week 24. Residual viral detectable viral load (1-400 HIV RNA copies/mL) was associated with the relative risk of treatment failure (Kahn 1998). The CD4 increase in this study was 267 cells for the EFV/IDV arm, and 210 cells for the EFV/IDV/d4T arm.

In a study presented at the Sixth European Conference on Clinical Aspects and Treatment of HIV Infection in Hamburg, Germany, researchers from DuPont presented data from a phase III study of three doses of efavirenz (200, 400 or 600 mg qd) in combination with standard doses of AZT and 3TC. Participants were treatment naive, and had CD4 cell counts of more than 50 cells/$mm^3$, as well as plasma HIV RNA levels of >10,000 copies/ml. After 16 weeks of treatment, the 27 patients treated with the highest dose of efavirenz experienced a 1.9 $log_{10}$ average reduction in plasma HIV RNA levels, 68% achieved undetectable plasma HIV RNA levels (40 copy/ml limit of detection). In addition, these patients experienced an average CD4 cell increase of 120 cells/$mm^3$. (Hicks 1998)

**RESISTANCE & CROSS RESISTANCE**

*In vitro* studies have suggested that, unlike other NNRTIs, virus requires multiple mutations in the reverse transcriptase to develop resistance to efavirenz, and the emergence of highly resistant virus only develops after multiple passages in tissue culture. The primary *in vitro* mutations conferring loss of sensitivity were L100I alone or in combination with either V108I or V179D/Y181C. The K103N mutation is the single observed mutation most resistant to efavirenz, conferring a 10-fold reduction in sensitivity. Normal dosing should produce concentrations sufficient to suppress replication of virus with K103N.

*In vivo* genotyping results were obtained from thirteen patients in study DMP 266-003 who were treated for sixteen weeks with efavirenz 200 mg/day + indinavir 800/1000 mg tid. All of these patients had initially responded to treatment, but failed between weeks eight and twelve. No Y181C, K101E, or L100I single mutants were seen. Seven patients had K103N, one had K103N/G190S, one had K103N/L100I, one had Y188L, and data are pending in 3/13. No indinavir-related mutations associated with high-level resistance were seen in the protease (Batcheler 1997).

**ADVERSE EVENTS & TOXICITY MANAGEMENT**

In general, the main side effects associated with efavirenz seem to involve central nervous system (CNS)

symptoms. According to the manufacturer, these CNS symptoms – possibly resembling those associated with ritonavir, such as dizziness and parasthesias – have been reported after doses of 200, 400 and 600 mg. Episodes recur on daily dosing. Intensity decreases with continued dosing, and seem to pass after about two weeks. Intensity of these symptoms is dose dependent, and may be minimized with dosing in the evening just before sleep. A mild rash has also been associated with use of efavirenz, however investigators note that both the frequency and severity of the rash is less than those seen with use of other NNRTIs.

Because large-scale trials of efavirenz have not yet been completed, toxicity data are somewhat scattered, and differ somewhat between studies.

**Drug-Related Adverse Events in Two Phase I Studies of Efavirenz**

| *Adverse events* | *Number of cases (N=117)* |
|---|---|
| **Headache** | 5 |
| **Dizziness** | 4 |
| **Nausea** | 5 |
| **Diarrhea** | 2 |
| **Vomiting** | 4 |
| **Increased GGT** | 1 |
| **Increased ALT** | 1 |
| **Somnolence** | 1 |

*(Mayers 1997)*

In phase II studies combining efavirenz and indinavir, including now more than 200 patients, the most frequent adverse events reported included diarrhea, headache, rash, dizziness, lightheadedness, nausea, dry skin, insomnia, cough, abdominal pain and fatigue. It is not possible at present to determine which of these side effects are related to Efavirenz.

| **Incidence of Drug-Related Rash in DMP 266-003** | | |
|---|---|---|
| **Toxicity Grade** | **IDV/d4T/EFV** | **EFV/IDV** |
| **1** | 11/42 (26.2%) | 19/84 (22.6%) |
| **2** | 1/42 (2.4%) | 9/84 (10.7%) |
| **3** | 1/42 (2.4%) | 0/84 (0%) |
| **Total** | 13/42 (31%) | 28/84 (33%) |

*(Kahn 1998)*

## DRUG INTERACTIONS

Like other NNRTIs and the protease inhibitors, the main physiological interaction of efavirenz is with a family of liver enzymes known as the cytochrome p450 isoforms. Clinical data show that efavirenz is an inducer of the CYP3A isoform, which may result in interactions between the drug and many other common AIDS treatments. In addition to the previously discussed interaction between efavirenz and

indinavir, DuPont has already determined that efavirenz has no effect on levels of AZT, 3TC, or fluconazole. Clarithromycin levels are lowered by 20% during coadministration with efavirenz. A pharmacokinetic drug interaction study of efavirenz and nelfinavir was conducted in 20 healthy volunteers, divided into two treatment groups. Group one received 750 mg nelfinavir every eight hours for fourteen days, and 400 mg efavirenz every day for seven days starting on study day eight. Group 2 received 400 mg efavirenz a day for 14 days and 750 mg nelfinavir every eight hours for seven days starting on day eight. The preliminary results for efavirenz suggest no difference in peak concentration or AUC values between days seven and fourteen in group 2, or between the two groups on day 14. For nelfinavir, the group 1 day 14 peak concentration was 26% higher and AUC value was 15% higher than the day 7 values. There were no differences between groups in nelfinavir peak concentration or AUC values on day 14 (Fiske 1998).

However, levels of saquinavir (Fortovase™ soft gel capsule formulation) have been shown to decline significantly (60%) when the drug is used in combination with efavirenz. According to DuPont, "until further information is available, patients should not use Fortovase as the only protease inhibitor in combination with Sustiva" (James 1998). The company has promised to provide more information on this interaction as soon as possible.

In combination with amprenavir, levels of amprenavir are decreased by about 40%. Only a slight increase in levels of efavirenz were seen (Piscitelli 1998).

Studies have also shown that efavirenz has no significant effect on azithromycin, and causes only a small (39%) decrease in levels of clarithromycin. These drugs also cause mild increases in levels of efavirenz that are probably clinically insignificant (Benedek 1998).

No interaction was seen with the birth control pill ethinyl estradiol (Joshi 1998). Studies have been completed and are currently being analyzed looking at interactions between efavirenz and famitidine and Mylanta. Other interaction studies are planned, including interactions with ritonavir, rifampin, midazolam, lorazepam, paroxetine, methadone, and abacavir.

**EXPANDED ACCESS**

DuPont Merck has initiated an expanded access program for efavirenz that includes patients who have had less than 400 CD4 cells at any point in their illness, and who cannot assemble a viable treatment regimen based on currently marketed therapies. A viable treatment regimen is defined as one which is reasonably likely to produce sustained undetectable viral loads in the majority of patients who use it. Participants are required to begin at least one new therapy with efavirenz, and may take experimental treatment.

**PREGNANT WOMEN**

Although there are no *in vivo* studies of the effect of efavirenz on pregnant women, the recent completion of animal teratogenicity studies raised troubling questions. Of thirteen pregnant monkeys treated with efavirenz in doses comparable to those used in humans, three had progeny with serious birth defects, including a cleft palate and small eyes. One was born without a brain and missing one eye.

## PEDIATRICS

Dupont Pharma is finalizing a pediatric formulation of efavirenz, and plans to file for approval in conjunction with its adult new drug application (NDA).

## CSF CONCENTRATIONS

Efavirenz has been shown good penetration into the CSF in both monkeys and humans.

## CURRENT & PLANNED STUDIES OF EFAVIRENZ:

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| **ACTG 364** | Efavirenz + nucleoside analogues reverse transcriptase inhibitors (NRTIs) vs. nelfinavir + NRTIs vs. efavirenz + nelfinavir + NRTIs, N=300 |
| **ACTG 368** | Efavirenz + indinavir + abacavir vs. efavirenz + indinavir in 300 NRTI-experienced, protease inhibitor-naïve patients |
| **Combination Studies:** | Studies are planned of efavirenz in combination with all marketed protease inhibitors and NAs, as well as experimental drugs such as abacavir, adefovir and 141W94 |
| **Interaction studies** | Multiple interaction studies are planned for drugs process through the P450 isoform system |
| **Pediatrics** | Studies are planned to evaluate efavirenz in pediatric patient populations. |

## DISCUSSION

So far, efavirenz looks like an extremely promising drug. The company believes that once-a-day dosing may be possible, although this has not yet been confirmed. In addition, exploitation of pharmacokinetic interactions with protease inhibitors may improve administration of those drugs by reducing dosing schedules. In general, the drug appears to be potent and associated with few adverse events, aside from the serious fetal abnormalities observed when the drug was given to pregnant monkeys. The company has planned a wide variety of interaction studies that should illuminate the optimal use of this drug. Development of a pediatric formulation in tandem with the adult formulation is a good sign of the company's commitment to all people with HIV. However, it is important to remember that efavirenz is still in an early stage of development, and that new information may become available as testing continues that limits the rosy picture currently suggested by the very limited available data.

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