A PILOT STUDY OF THERAPEUTIC DRUG MONITORING OF NELFINAVIR IN HIV INFECTED PATIENTS

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By

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Abstract

***Introduction*:** Information regarding plasma concentrations of protease inhibitors and their corresponding antiviral activity or toxicities have recently emerged in the literature. However, the information gathered thus far is conflicting. While some studies suggest therapeutic drug monitoring (TDM) is important in providing optimal suppression of viral load,others fail to report such a relationship. Therapeutic drug monitoring of protease inhibitors may potentially be important for several reasons including: bi-directional drug interactions with in anti-retroviral regimens, variability in drug absorption, adherence issues, and lack of dose adjustment guidelines in patients with hepatic dysfunction, patients of female gender and patients far from their ideal body weight. Nelfinavir is a protease inhibitor that has recently been introduced to clinical practice. There is limited data regarding TDM of nelfinavir. As such, a need exists to determine the utility and practicality of TDM of nelfinavir, and to determine the effect of TDM and dose adjustment on virologic efficacy in a controlled study.

Objectives: There were two parts to the study. The primary objective of the pilot study, was to determine the utility and practicality of nelfinavir TDM. The second part was a controlled study where the primary objective was to determine whether TDM and dose modification of nelfinavir when used as part of salvage antiretroviral combination therapy could improve viral load reduction. The secondary objectives of the controlled study were to determine whether TDM and dose modification of nelfinavir could improve CD_4 cell count rise, to determine whether predose and 2 hour post dose nelfinavir and M8 concentrations were higher in patients showing a positive response to therapy compared to those unresponsive, and to determine whether nelfinavir induced diarrhea was more frequent in patients with higher than average predose and 2 hour post nelfinavir and M8 concentrations.

***Method*:**

Pilot Study
Ten patients on a nelfinavir 1250 mg bid containing antiretroviral regimen had trough and/or peak nelfinavir and M8 plasma concentrations determined for the pilot study. A retrospective review of each patients chart was also completed.

Controlled Study
Five of the required 84 subjects were randomized to either a fixed nelfinavir dose regimen or a concentration controlled nelfinavir regimen. Subjects in the fixed dose regimen received nelfinavir 1250 mg bid in addition to other anti-retroviral agents. Predose and 2 hour post dose plasma nelfinavir and M8 concentrations were determined at regular intervals. In contrast, subjects randomized to the concentration controlled regimen were initiated on a nelfinavir 1250 mg bid regimen with subsequent dose adjustment based on a predose plasma nelfinavir concentration. These subjects also had 2 hour post dose plasma nelfinavir and M8 concentratations measured.

Results:

Pilot Study
Five of the 10 subjects were identified as having nelfinavir plasma concentrations outside the reference population range. Factors that may have contributed to high concentrations included hepatic dysfunction and inhibitor type drug interactions. In contrast, malabsorption secondary to diarrhea, inductive type drug interactions and underdosing in obesity were factors potentially involved in low nelfinavir

concentrations. The practicality of nelfinavir TDM is an issue that needs to be resolved since the results of drug measurements often took more than 4 weeks to obtain.

Controlled Study

Three of the 5 subjects have been randomized to the concentration controlled group. None have required nelfinavir dose adjustment. The longest follow-up has been 128 days. Additional analysis is not available at this time since the criteria for the interim analysis has not been met.

Conclusion:

Therapeutic drug monitoring of protease inhibitors is an emerging technology which has the potential of becoming a very important tool in clinical practice. The pilot study has identified patients who may benefit from nelfinavir TDM however, it may not be practical to all clinical settings at this time. Controlled studies are required to determine the true merits of nelfinavir TDM in improving virologic efficacy.

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1. BACKGROUND

1.1 INTRODUCTION

Protease inhibitors (PI) when used as part of combination drug regimens have had a dramatic impact on therapy for human immunodeficiency virus (HIV) infection.[1, 2] Data from the HIV Outpatient Study clearly shows a positive relationship between the recent reduction in morbidity and mortality amongst HIV-1 infected patients and the use of protease inhibitors as part of combination antiretroviral (ARV) therapy.[3] The benefits are attributed in part to our improved understanding of the pathophysiology of this illness resulting in better use of drug therapy. However, not all patients who start on triple combination therapy achieve maximum viral load suppression. Two reasons for not achieving this goal may include nonadherence and antiretroviral resistance. Inter-individual differences in pharmacokinetics relating to drug absorption, distribution and metabolism are also important reasons for failure. Given the high rates of response in patients on their first ARV regimen, clinical trials to test this hypothesis would need to be large. In patients on salvage therapy where response rates are lower therapeutic drug monitoring and dose adjustment may be more important.

There is a variety of data regarding the pharmacokinetic properties of the four PIs currently being used in clinical practice, namely indinavir (IDV), saquinavir (SQV), ritonavir (RTV) and nelfinavir (NFV). This information reviewed and summarized elsewhere has been used primarily in selecting doses and dose schedules.[4] Data regarding plasma concentrations of PIs and their corresponding antiviral activity, however, has only recently begun to emerge in the literature. Knowledge of the concentration-response relationship of PIs may be potentially helpful in improving efficacy and reducing toxicity as has been demonstrated with other anti-infective medications including aminoglycosides,[5] fluoroquinolones,[6] β-lactams,[7,8] and glycopeptides. [9]

Indinavir has been the PI most studied in terms of its plasma concentration-effect relationship. However, the information gathered from these studies is conflicting. While some studies suggest that therapeutic drug monitoring of IDV [esp. trough concentrations] is important in providing optimum suppression of plasma HIV RNA,[10-13] others fail to report such a relationship.[14-16] There is evidence supporting a relationship between urologic toxicity and high IDV concentrations.[17] Information for other PIs is limited. Recent studies of SQV suggest that trough concentrations may be correlated with reductions in

viral load.[18-20] A similar relationship may also exists for RTV.[20] Peak concentrations of NFV have been found to correlate with declining viral load in two trials.[21,22]

Although the data suggests that therapeutic drug monitoring (TDM) may have an important role in the optimal management of HIV-1 infected patients, firm recommendations are not available at this time. The relatively small sample size of studies reported to date is the greatest limitation for most of the trials. Small sample sizes with wide confidence interval around the results make it difficult to determine the optimal therapeutic range for a given drug.[23] Most of the trials conducted were retrospective or open label and as such, are subject to investigator bias. The studies differed in their definition of response to therapy depending on the sensitivity of their assay to measure viral load, consequently, comparing the results of the various trials is difficult.

Patient factors may have affected the study results. PI naïve patients were evaluated in some studies while others used PI experienced patients. In the former population the virus may be quite susceptible to a given PI and drug levels might be less important, while in the latter, the virus may have had the opportunity to develop resistance and consequently, any concentration of drug would be ineffective. Differences in baseline viral load in the various studies must also be considered. Patients with higher viral loads may require a greater amount of time to achieve undetectable viremia. Consequently, baseline viral load and the length of follow-up are important sources of variability. Other patient factors that may have not been controlled for in the trials include adherence to drug therapy, drug interactions, and differences in weight, absorption [e.g. malabsorption, diarrhea] and metabolic capacity.

Drug factors may also influence outcome. There is inconsistency in which concentration parameter [i.e. Cmax, Cmin, AUC etc.] best predicted response. With both IDV and SQV trough concentrations appear to be important whereas with NFV, peak concentrations were a better predictor. Peak concentrations however may not be practical in an outpatient setting. Secondly, as the drug concentration approaches the upper end of the concentration-response curve, the change in response decreases. Thus, depending at what point of the curve the concentrations were being measured, the investigators either saw a positive or no relationship. Thirdly, other agents being used concomitantly with the protease inhibitor being evaluated could have pharmacokinetic interactions influencing drug levels. This could affect the final outcome if drug concentrations are important and therefore is another variable that must be controlled for.

This report describes a clinical study in HIV infected patients to determine whether a concentration response exists for nelfinavir when used as part of a salvage ARV regimen. It attempts to evaluate the usefulness of TDM and dose adjustment in increasing efficacy. The results from this study will have great significance as it may potentially improve care of HIV infected patients.

1.2 NELFINAVIR PHARMACOLOGY, PHARMACOKINETICS, EFFICACY AND TOXICITY

Nelfinavir mesylate is a HIV-1 protease inhibitor used in combination regimens for the treatment of HIV infection. It has been shown to be effective in adults when dosed at 750 mg tid or 1250 mg bid.[24, 25] Peak plasma drug concentrations are reached approximately 2 to 4 hours after oral administration.[26] Both AUC and peak plasma concentrations are 2 to 3 fold higher when the drug is taken under fed conditions compared to a fasting state.[26] The median peak and trough steady state plasma concentrations (i.e. Cmax,ss and Cmin,ss) in adults (n=11) at the 750 mg tid dosing regimen are 2.6 μg/ml [quartile: 2.0-3.5] and 0.9 μg/ml [quartile: 0.6-1.3] respectively.[24] Similarly, the median peak and trough steady state plasma concentrations at the 1250 mg bid dosing regimen (n=10) are 4.1 μg/ml [quartile: 3.3-4.4] and 0.7 μg/ml [quartile: 0.3-1.0] respectively. The volume of distribution of NFV ranges from 2 to 7 L/kg and is greater than 98% protein bound.[26] The drug is extensively metabolized in the liver with less than 2% excreted in the urine.[26] Multiple cytochrome P-450 isoforms including CYP3A and CYP2C19 are responsible for its metabolism *in vitro*. The major oxidative metabolite, nelfinavir hydroxy-t-butylamide (M8), has *in vitro* activity comparable to the parent drug.[26] However, the *in vivo* activity of M8 is unclear. The absence of M8 had no obvious effect on antiviral response or tolerability to NFV in one clinical study.[27] Steady state plasma concentrations of M8 are typically 33% of NFV concentrations at standard clinical doses.[27] A NFV elimination half-life of 3.5 to 5 hours has been reported.[26] Based on *in vitro* data, the concentration of NFV required for 50% and 95% inhibition of wild type HIV-1 is approximately 20 nmol/L and 60 nmol/L respectively.[28] Data from the manufacturer has suggested that the drug has an unique resistance pattern that may not confer cross resistance to other protease inhibitors. The most common mutation has occurred at position 30 on the protease enzyme.[26] However, clinical data suggests that some degree of cross resistance exists for all PIs.

The efficacy of nelfinavir as part of combination therapy has been established in ARV naïve patients. The combination of zidovudine 200 mg tid (ZDV), lamivudine 150 mg bid (3TC) and NFV 750 mg tid was compared to ZDV/3TC without NFV in a randomized, double blind study of 102 ARV naïve patients with CD_4 counts between 150 and 500 cells/μl.[29] Baseline median viral load (log_{10} copies/ml) were 4.8

for the ZDV/3TC group and 5.0 for the ZDV/3TC/NFV group. After 28 weeks of follow-up, 83% of patients in the triple therapy arm compared to 18% in the double therapy group had viral loads suppressed below 500 copies/ml.

Another group of investigators evaluated a similar regimen in ARV naïve patients with viral loads greater than 4.18 $\log_{10}$ copies/ml.[30] Subjects received ZDV/3TC plus NFV at 500 mg tid, 750 mg tid or placebo. Mean baseline viral load was 4.9 $\log_{10}$ copies/ml and the mean CD_4 cell count was 283 cells/mm^3 . At 24 weeks, mean viral load reduction for the 750 mg dose was 1.99 $\log_{10}$ copies/ml with a mean rise of CD_4 cells of 155 cells/mm^3. At 52 weeks mean viral load reduction was sustained and CD_4 continued to increase from baseline. Approximately 80% of patients maintained viral load below 500 copies/ml. Data was not reported for the 500 mg dose nor placebo.

A multicenter, randomized, double-blind trial compared two NFV dosing regimens (1250 mg bid vs 750 mg tid) in combination with standard doses of stavudine (d4T) and lamivudine (3TC).[24] Patients included in this trial were naïve to either d4T or 3TC, had less than 2 weeks treatment with a protease inhibitor, and had HIV RNA greater or equal to 4.18 $\log_{10}$ copies/ml. Mean baseline viral load ($\log_{10}$ copies/ml) and CD_4 cell counts (per mm^3) were 5.1 and 252 respectively in the NFV tid group and 5.0 and 275 respectively in the NFV bid group. An interim analysis at 48 weeks revealed that both NFV regimens provided equally potent suppression of HIV RNA [reduction of 2.2 $\log_{10}$ for bid group and 2.4 $\log_{10}$ for tid group]. Approximately 80% of patients in the bid and tid groups achieved plasma viral load below the limit of detection (<400 copies/ml). The mean CD_4 cell rise was 189 and 166 cells/mm^3 for the bid and tid groups respectively. Pharmacokinetic analyses of both dosing regimens were also comparable [$AUC_{ss,24}$ - 51 mg•h/l for bid group, and 45 mg•h/l for tid group].

The efficacy of NFV has also been evaluated as part of a salvage regimen in ARV experienced patients. The dual PI combination of NFV (750 mg tid) plus SQV (400 mg bid initially increasing to 600 mg tid) was studied in 13 patients (median HIV RNA – 187,000, median CD_4 – 234) who were refractory to standard triple therapy.[31] The regimen was considered efficacious if viral load decreased by at least 0.5 $\log_{10}$ from baseline. After 4, 8, and 16-24 weeks the regimen was efficacious in 5/13 (38.5%), 3/13 (23.1%) and 1/13 (7.7%) patients respectively.

A 4 drug regimen using NFV (1250 mg bid) plus SQV (1000 mg bid) and 2 nucleoside reverse transcriptase inhibitors (NRTI) has also been studied in 25 HIV patients with CD_4 cells <300 /μl who

had failed or were intolerant to 2 NRTI/PI combination.[32] Nineteen patients completed 24 weeks of therapy and have shown a mean decrease in HIV RNA of 1.6 $\log_{10}$ (baseline: 4.6 $\log_{10}$) and a mean increase in CD_4 of 188 cells/μl. The proportion of patients with plasma RNA levels below 500 and 40 copies were 45% and 35% respectively.

In the above trials, the most common reported side effect from nelfinavir was diarrhea. A retrospective review of this complication has recently been completed. [33] In the investigation diarrhea was graded from 1 to 3: grade 1 (mild or transient diarrhea) - ≤ 4 loose stools/day; grade 2 (moderate) – 5-7 loose stools/day; and grade 3 (severe) - > 7 loose stools/day or requiring intravenous hydration due to the diarrhea. Their results showed that 63 of the 181 evaluated patients (35%) reported diarrhea, of which 16 (25%) had diarrhea prior to beginning NFV. Of those with diarrhea 41% were grade 1, 35% were grade 2, 13% were grade 3 and 11% were undetermined. Treatment of diarrhea included no therapy in 28 patients (44%), over the counter therapy in 9 patients (14%), prescription anti-motility drugs in 17 patients (27%), combination of over-the-counter and prescription medication in 2 patients, IV hydration alone or in combination with other therapy in 3 patients and undeterminable in 4 patients. Only 3 patients of the 183 (1.6%) discontinued NFV due to diarrhea.

Other reported but less common side effects of NFV include nausea, fatigue and/or headache, increased bleeding in hemophiliac patients, hyperglycemia and skin rash.[26]

1.3 RATIONALE FOR STUDY

The drug regimens currently being used to treat ARV naïve patients have virologic success rates in 60% to 90% as judged by achievement of a plasma HIV RNA level less than 500 copies/ml at 24 weeks or beyond.[34] The outcome is less impressive in patients on salvage treatment after failing combination therapy that includes a PI. In a pilot study, 64 patients were evaluated who had detectable viral loads (i.e. >500 copies/ml) on a PI containing regimen and were subsequently switched to a new combination containing NFV 750 mg tid.[35,36] The patients had extensive PI experience (mean 13 months), but most were naïve to NNRTIs. The majority had previous exposure to saquinavir and indinavir. In addition to nelfinavir, approximately 95% of patients had at least 2 other ARV agents changed and 66% initiated an NNRTI. The mean CD4 and viral load at the time of switch was 109/mm^3 and 4.63 log copies/ml respectively. After a mean follow up of 19 weeks, only 33% of patients achieved viral load suppression to <500 copies/ml. An additional 20% had partial viral load suppression with greater than 1 log decrease. The remaining 46% were non-responders with less than 1 log decrease in viral load. On

univariate analysis, no relationship could be found between complete viral suppression and baseline viral load, baseline CD4, previous PI, duration of previous PI use, or number of agents changed in addition to nelfinavir. This is likely because of the homogeneity of the population studied. However, mutations of key codons on the protease and reverse transcriptase enzymes did correlate with virologic response. Patients with 0 or 1 mutation at the protease codons 48, 82, 84, or 90 and who had 4 or fewer mutations at the key reverse transcriptase codons were more likely to respond compared to patients with greater numbers of mutations.

In a similar study, 62 patients were switched to nelfinavir 750 mg tid plus other ARV agents following virologic failure of HAART therapy (i.e. HIV-1 RNA > 1000 copies/ml after > 3 months).[37] All patients were previously exposed to a median of 4 NRTIs and 2 PIs for a median duration of 35.6 and 12.2 months respectively. Three patients were NNRTI experienced with a median duration of 3.2 months. Median baseline CD4 and viral load were 113 cells/mm^3 and 5.16 log copies/ml respectively. After a follow-up of 5.3 weeks (range: 4-12 weeks), the median change in viral load was -0.38 log copies/ml. Only 32% of patients had > 1 log decrease and 3% had viral load < 100 copies/ml. Further analysis showed that baseline CD4 cell counts, baseline viral load, medical history, duration of previous ARV treatment and number of drugs used did not correlate with virologic response. The number of reverse transcriptase inhibitor and protease inhibitor resistance mutations were the only independent predictors of response.

Two main reasons for virologic failure of potent ARV combinations include viral resistance to one or more agents, or lack of adequate drug concentrations at the site of action. The latter may be secondary to altered absorption or metabolism of the drug, poor patient adherence to a regimen due to either poor compliance or inadequate patient education, and/or multi-drug pharmacokinetic interactions that adversely affect therapeutic drug levels. Assuming a correlation between plasma and tissue drug concentrations (excluding the CNS), therapeutic drug monitoring of protease inhibitors and appropriate adjustment of the dose may be one solution to the problem of virologic failure.

Therapeutic drug monitoring of protease inhibitors is an area that has only recently gained attention. There are several reasons why this type information may be clinically useful. Optimization of antiviral outcome is one reason of immense importance. There are data which suggest that a given concentration of drug correlates with optimal antiviral activity of a PI.[10-13, 18-21, 38, 39] In addition, adverse effects of PIs may be asssociated with high drug concentrations (e.g. indinavir and renal stones, ritonavir and GI side

effects).[17, 40, 41] Depending on the antiretroviral regimen, there may also be bi-directional drug interactions involving one or more PIs (e.g. RTV + SQV + efavirenz). Often the extent of these drug interactions are not completely predictable; consequently TDM would be very helpful. Knowledge of PI plasma concentration may also aid in distinguishing between viral resistance and inadequate drug exposure in patients failing ARV therapy. Guidelines for dose adjustment of PIs in patients with hepatic dysfunction is limited.[42] Since PIs are mainly metabolized by the liver these patients are at risk of drug toxicity. Adjusting the dose based on plasma concentrations may alleviate this problem and avoid unnecessary drug discontinuation. Finally , individual infected with HIV vary in presentation from the very advanced, wasted patient to the otherwise healthy ARV naive patient at his/her ideal body weight. Dose ranging studies are generally done in ARV naive, relatively healthy male patients. As such the doses that are recommended may not always be appropriate for individuals who are female gender, far from their ideal body weight or have a co-existing condition thay may affect drug disposition. TDM may be a method to ensure adequate PI concentrations in order to maximize efficacy and minimize drug toxicity.

2. STUDY GOALS

The study was approved by the Toronto Hospital ethics review board and patients were recruited from the Immunodeficiency Clinic of the Toronto Hospital. There were two parts to the trial. The first part was a pilot study of 10 subjects to determine the utility and practicality of nelfinavir TDM. The second part was a controlled trial with the following goals:

1. To determine whether therapeutic drug monitoring and dose modification of nelfinavir when used as part of salvage ARV combination therapy can further improve viral load reduction, and increase CD_4 cell counts.

2. To determine whether predose and 2 hour post dose nelfinavir and M8 concentrations are higher in patients who show a positive response to therapy (i.e viral load reduction of $> 1 \log_{10}$ or viral load < 50 copies/ml) to those unresponsive.

3. To determine whether predose and 2 hour post dose M8/NFV concentration ratio are signficantly different in patients who show a positive response to therapy (as defined above) to those unresponsive.

4. To determine whether nelfinavir induced diarrhea is more frequent in patients with higher than average predose and 2 hour post dose nelfinavir and M8 concentrations.

3. METHODOLOGY (Pilot Study)

Both antiretroviral naive and experienced patients on a nelfinavir 1250 mg bid containing ARV regimen were eligible to participate in the pilot study. Trough and/or peak nelfinavir and M8 plasma concentrations were determined. The time between the blood draw and the last nelfinavir dose was recorded. Blood samples were centrifuged at The Toronto Hospital and then packed in dry ice and appropriately sent by courier to the Ottawa General Hospital where the HPLC assay [43] to measure nelfinavir and M8 levels were performed. A thorough review of each subjects chart was completed with the following items being recorded: sex, age, weight, height, medications at the time of TDM, past ARVs, medical history, CD_4 cell counts, viral loads, LFTs (AST, ALT, ALP, T.bili), glucose, serum creatinine, and lipid profile (if available).

4. METHODOLOGY (Controlled Study)

4.1 Study Design (Fixed Dose versus Dose Adjusted Nelfinavir)

Male or non-pregnant female HIV infected patients 18 years of age or older who failed only one PI containing regimen were eligible to participate. Failure was defined as a detectable viral load following a previous undetectable result or greater than 0.5 log increase in viral load from nadir. At the time of enrollment, the viral load must have been ≤ 5 log copies/ml and the patient switched to at least 2 new ARV agents in addition to NFV and be started on a non-nucleoside reverse transcriptase inhibitor (efavirenz, nevirapine or delavirdine) if previously naive to this class. Patients who were ARV naive or stopped previous therapy secondary to intolerance to medication were not eligible. Neither were patients with AST or ALT greater than 5 times the upper limit of normal (ULN), pancreatic amylase > 1.5 times ULN, or triglycerides > 4.5 mmol/L. Patients were also excluded if they were on the following medications which adversely interact with nelfinavir: rifampin, cisapride, astemizole, terfenadine, amiodarone, quinidine, triazolam, midazolam or ergot derivatives. Written informed consent (refer to Appendix A) was obtained prior to enrollment.

The overall design of the study was a prospective, open label, controlled trial where subjects were randomized to either a standard nelfinavir dose regimen (Std or Group A) or concentration controlled

nelfinavir dose regimen (CC or Group B) for 24 weeks. An initial screening period was required to determine the subject's eligibility to participate in the study and to document on the Case Report Form (refer to Appendix B) pertinent baseline data as follows:

a) informed consent if not previously obtained, documented in writing
b) medical history
c) medication use history [esp. ARV]
d) physical history (including height and weight)
e) documentation of HIV infection by ELISA and Western Blot
f) blood samples for HIV RNA titer, CD_4+ cell count, genotyping for protease resistance, hematology, chemistry, coagulation
g) urine sample for urinalysis [including urine pregnancy test for women]

Following randomization and screening procedures, subjects in both groups were initiated on a nelfinavir containing regimen at a dose of 1250 mg po bid with food. Nelfinavir 250 mg tablets were prescribed. During follow-up clinic visits when pharmacokinetic assessments were made, subjects in both groups fasted from midnight of the previous night until the predose [i.e. NFV dose] blood sample was collected. In the morning following the predose blood collection, subjects in both groups eat a standard breakfast [consisting of 50% carbohydrate, 30% fat, 20% protein] at which time the morning NFV dose was be administered. A 2 hour post dose blood sample was then drawn. Similar procedures to that of the pilot study were carried out to determine nelfinavir plasma concentrations.

Group A (Std Regimen)

Subjects randomized to group A, returned for a follow up visit on day 14. At that time, adherence to drug therapy and the occurrence of diarrhea were assessed in addition to physical and laboratory assessments (including viral load and CD_4+ count). Other adverse events were also documented on the follow up visit case form (refer to Apppendix C). A predose and 2 hour post dose blood samples were drawn to measure nelfinavir and M8 plasma concentrations. These values would not be reported until the completion of the study and the dose of nelfinavir was not adjusted. Additional follow up visits were made on days 28, 56, 84, 112, 140 and 168 of the study where the above procedures were repeated.

Group B (Concentration Control)

Subjects randomized to Group B also had a follow up clinic visit on day 14, at which time the same procedure as in Group A was conducted including drawing predose and 2 hour post dose blood samples. The dose of nelfinavir however was subsequently adjusted depending on the measured predose nelfinavir plasma concentration according to the following guidelines:

Nelfinavir predose concentration	Dose Adjustment
< 0.7 μg/ml	Increased daily dose by 20 % [rounded to nearest multiple of 250 mg] Checked predose concentration in 14 days.
> 0.7 μg/ml	No change

Where dosage adjustment was made, a follow-up drug concentration was determined 14 days later and further adjustments made if required. Follow up visits were also made on days 28, 56, 84, 112, 140 and 168 of the study where the above procedures were repeated.

4.2 SAFETY PARAMETERS

Safety parameters were evaluated in both groups on eight occasions: during screening and during each follow up clinic visit. The parameters included laboratory tests, vital signs and adverse events.

a) *Laboratory tests*

Clinically relevant abnormal results were followed until they returned to baseline, or until an adequate explanation of the abnormality was found. The following were laboratory tests monitored:

Hematology: hemoglobin concentration, hematocrit, total WBC count and differentials, RBC count and platelet count

Biochemistry: electrolytes, BUN, creatinine, calcium, uric acid, amylases, total bilirubin, ALT, AST, alkaline phosphatase, glucose, albumin, triglycerides, total cholesterol

Urinalysis: microscopic examination, pH, blood, glucose, protein, urine pregnancy test for females

Immunology: CD_4+ T cell count

Virology: viral load (RNA-PCR) – Chiron 3.0

b) *Vital Signs* - Blood pressure, heart rate, temperature

c) *Adverse Events*

All adverse events encountered during the clinical trial was reported on the Case Report Form and/or the Serious Adverse Event Form (refer to Appendix D). An adverse event was considered to be any adverse change from the patient's baseline (pre-treatment) condition which occurred during the course of a clinical study after treatment was started, whether considered related to the treatment or not. Adverse events were graded on a four point scale [Grade 1, 2, 3 or 4] according to ACTG guidelines set out in Tables 1 and 2 of Appendix E.

Diarrhea was considered secondary to nelfinavir only after other potential causes (e.g. diet, infection, other drugs) were ruled out. Diarrhea was graded on a four point scale as follows:

Grade of Diarrhea	Description
1	Mild or transient; 3-4 loose stools per day or mild diarrhea lasting < 1week
2	Moderate or persistent; 5-7 loose stools per day or diarrhea lasting ≥ 1 week
3	Bloody diarrhea, or orthostatic hypotension or > 7 loose stools/day or IV hydration required
4	Hypotensive shock or hospitalization required

The type of treatment used to the control the diarrhea (e.g. fluid hydration, antimotility agents, no therapy) and the patient's response was documented.

4.3 ADHERENCE TO THERAPY

Adherence to therapy was determined at each clinic visit through patient interview, drug concentration and pill count. Where a problem arised in compliance, the subject was removed from the study based on the following criteria:

a) patient missed at least two clinic visits without notifying the investigators for the reasons of his/her absence.

b) patient found to have missed greater than or equal to 2 days worth of medication on two separate follow up visits.

4.4 PATIENT DISCONTINUATION

Patients who became pregnant were withdrawn from the study. Any other reasons deemed necessary for patient discontinuation [e.g. hypersensitivity to drug, patient death, severe adverse reaction] were noted by the investigators. Patients could have also withdrew from the study on their own accord.

4.5 OUTCOME MEASURES

Primary Objective:

1. To compare the percentage of subjects showing a response to salvage therapy [defined as at least 1.0 $\log_{10}$ decrease in viral load or a decrease in viral load to < 50 copies/ml by 24 weeks of therapy] between subjects given a fixed dose of NFV (Group A) to those in whom NFV dose was adjusted according to predose drug concentrations (Group B).

Secondary Objectives:

2. To compare the mean change and mean maximal change from baseline of plasma HIV RNA level and CD_4 cell count at weeks 12 and 24 between Group A and Group B.

3. To compare the percentage of subjects in Group A with plasma HIV RNA below 50 copies/ml and 500 copies/ml at 12 and 24 weeks to those in Group B.

4. To compare in Group A steady state plasma pre-dose NFV ($C_{PD,NFV}$) and M8 ($C_{PD,M8}$) concentrations in subjects showing a response to salvage therapy [as defined above] to those unresponsive [defined as less than 1.0 $\log_{10}$ reduction in viral load] at 12 and 24 weeks.

5. To compare in Group A steady state plasma 2 hour post dose NFV ($C_{2H,NFV}$) and M8 ($C_{2H,M8}$) concentrations in subjects showing a response to therapy to those unresponsive [as defined above] at 12 and 24 weeks.

6. To compare in Group A, the mean ratio $C_{PD,M8}/C_{PD,NFV}$ in subjects showing a response to salvage therapy [as defined above] to those unresponsive [as defined above] at 12 and 24 weeks.

7. To compare in Group A, the mean ratio $C_{2H,M8}/C_{2H,NFV}$ in subjects showing a response to salvage therapy [as defined above] to those unresponsive [as defined above] at 12 and 24

8. To compare in Group A, the percentage of subjects with grade 2, 3 or 4 diarrhea who have $C_{PD,NFV}$ and $C_{PD,M8}$ above the median value to those with $C_{PD,NFV}$ and $C_{PD,M8}$ below the median.

9. To compare in Group A, the percentage of subjects with grade 2, 3 or 4 diarrhea who have $C_{2H,NFV}$ and $C_{2H,M8}$ above the median value to those with $C_{2H,NFV}$ and $C_{2H,M8}$ below the median.

4.6 SAMPLE SIZE CALCULATION

From previous studies conducted at The Toronto Hospital,[35,36] the percentage of patients on nelfinavir as part of salvage ARV therapy achieving undetectable viral load (< 500 copies/ml) or at least 1.0 $\log_{10}$ decrease in viral load was 53% leaving ~46% who did not have an adequate response. A sample size of 84 patients (42 in each group) would allow a 50% difference in the percentage of patients showing a response to therapy (i.e. change from 53% to 80% response) as defined under the primary objective to be detected with a power of 80% at the 5% level of significance (α=0.05, one-sided). A one sided sample size determination was justified given that the dose of NFV was only adjusted upward. As such, patients in Group B in the worse case would do as well as patients in Group A in terms of viral load reduction (i.e. the observed % difference between groups can only be greater than or equal to zero).

4.7 STATISTICAL ANALYSIS

An intent to treat (ITT) methodology will be used for all statistical analysis. Results will be presented using both ITT formats: "non-completer equals failure" and "last observation carried forward". Using the first format, subjects who did not complete the full study will be labeled "unresponsive" for the purposes of the primary objective. Their change in viral load and CD_4 cell count will be given a value of zero and will be considered to have a viral load > 500 copies/ml at 24 weeks. Using the latter format, the subject's last viral load and CD_4 cell count prior to discontinuation of the study will be used as their twenty-fourth week data. The particular statistical tests that will be performed and the variables that will be assessed is shown in Table 3 (refer to Appendix F). All comparative analyses will be considered significant at $p<0.05$.

Subject demographics, pertinent medical history information and other baseline data will be tabulated. Inferential statistics will be performed to assure that both groups A and B were similar with respect to baseline characteristics. Adverse events occurring during the study including diarrhea will be tabulated and reported using descriptive statistics.

Descriptive statistics will also be used to present changes in vital signs, body weight, and clinical laboratory values. Clinically significant changes in laboratory values will be identified and tabulated.

4.8 INTERIM ANALYSIS

An interim analysis will be conducted after 50% of patients have been enrolled and completed 12 weeks of therapy. The study will be terminated at that time for the following reasons:

- the percentage of patients showing a response to salvage therapy is equivalent for Group A and B;

OR

- less than 50% of patients in Group B requiring dose adjustment

5. RESULTS

5.1 RESULTS OF PILOT STUDY

A total of 10 subjects were recruited for the pilot project. The results of their nelfinavir plasma concentrations, and their medical history is presented in Table 4. A graphical representation of the results is shown in Figure 1. The reference population used for Figure 1 was data obtained from a study evaluating the pharmacokinetics of nelfinavir given at 1250 mg bid.[24] Individual results with a clinical assessment were given to the subject's physician. An example is shown in Appendix G. A plot of peak and trough nelfinavir plasma concentration against viral load is shown in Figures 2 and 3.

5.2 RESULTS OF CONTROLLED STUDY (FIXED DOSE VERSUS DOSE ADJUSTED NELFINAVIR)

As of June 24, 1999 a total of 10 patients have been screened for the study of which 7 have been entered. Reasons for not entering 3 patients included difficulties with work schedule, past nelfinavir experience and starting nelfinavir prior to screening. Of the 7 subjects entered, 5 have been randomized to one of the two arms (3 concentration controlled, 2 standard regimen). The remaining 2 patients are in the process of being randomized and require further follow-up. Of the 3 patients entered in the concentration control group, none have required nelfinavir dose adjustment. The longest follow-up has been 128 days.

Additional analysis is not available at this time since the criteria for the interim analysis has not been met.

6. DISCUSSION AND FUTURE DIRECTIONS

There have been two studies reported that evaluated drug concentration versus antiviral activity of nelfinavir. In the first of 2 trials, treatment naïve HIV-1 patients received zidovudine and lamivudine (3TC) plus either NFV 500 mg tid (n=97), NFV 750 mg tid (n=99) or placebo (n=101).[16] Both untimed predose and 2 hours post dose plasma NFV concentrations were measured at weeks 2 and 8 after the initiation of therapy. Response to therapy was defined as a viral load less than 50 copies/ml by week 24. The log of the baseline viral load, the log of the sum of NFV and M8 (major NFV metabolite with *in*

vitro activity) 2 hours post dose and the log of NFV 2 hours post dose concentration were the most significant predictors of antiviral response.

A second study was conducted in 30 ARV naïve HIV-1 infected patients.[16] The treatment regimen studied was a combination of stavudine (d4T), 3TC, SQV and NFV. Plasma concentrations of SQV and NFV were determined at baseline and weeks 1, 2, 4, and 8. Viral load was measured from the start of therapy to the first measurement less than 50 copies/ml or until week 8. Both drug concentrations were related to population pharmacokinetic data and expressed as the ratio between observed and population values. This study showed a significant relationship between maximum observed NFV concentration ratio and the slope of decline of HIV-1 RNA in plasma. No significant relationship was observed when SQV concentration ratio was used.

In both of the above studies, the investigator's main goal was to establish a plasma concentration-response relationship for NFV but this information was not used to adjust a patient's therapy. A controlled study comparing twice daily versus three times daily regimens yielded comparable clinical results at 48 weeks.[24] In the pharmacokinetic analysis, similar trough levels were obtained with the 1250 mg BID and 750 mg TID arms. Both trials evaluated patients naïve to ARV therapy. Whether the same results would hold true or be even more important for ARV experienced patients is unknown. Although a relationship was established for peak concentrations and antiviral activity, measuring trough concentrations may be more practical in a clinical setting, given the variability in the time to reach peak concentrations (i.e. tmax ranges between 2 to 4 hours for NFV). As such dose adjustment in our controlled study was based on trough concentrations.

Although results from our controlled trial are not yet available, some observations can be made from the pilot study. Ten subjects were recruited of which 8 were antiretroviral (including protease inhibitor) experienced. All were male subjects ranging from 29 to 51 years of age. Two patients (#6 and #10) were considered to have low trough nelfinavir plasma concentrations and one patient with a low peak nelfinavir concentration (#3). The first patient (#6) may have had a low level secondary to underdosing given a greater than average body weight, or secondary to an drug interaction with efavirenz which is known to induce the metabolism of nelfinavir. Despite the low level, the subject initially maintained an undetectable viral load (< 50 copies/ml) which subsequently increased to 1230 copies/ml approximately two months after the nelfinavir plasma concentration was measured. This may suggest that the low nelfinavir level was clinically significant. In contrast, the second subject (#10) with a low nelfinavir

level continued to maintain an undetectable viral load for several months. The low nelfinavir concentration in his case may have also been due to a drug interaction with efavirenz. Given his maintenance of an undetectable viral load, the efficacy of nelfinavir as part of his antiretroviral regimen was debatable. The third subject (#3) to have low nelfinavir levels may have been secondary to malabsorption. This particular patient was experiencing 5 to 6 loose bowel movements per day while on the nelfinavir containing regimen. Initially, the subject was taking zidovudine, lamivudine and indinavir and had an undetectable viral load (<50 copies/ml). After developing indinavir related renal complications, nelfinavir was substituted. The viral load remained undetectable for a few months while on nelfinavir and then began to rise. Retrospectively this may have been due to nelfinavir resistance secondary to a less than optimal plasma drug concentration.

Two subjects (#1, #8) had greater than the reference population nelfinavir plasma concentrations. For the first subject, the elevated trough concentration may have been due to inhibition of nelfinavir metabolism by ritonavir and delavirdine (both inhibit CYP3A4). Importantly that the patient was already receiving a lower than the usual nelfinavir dose (i.e. 1000 mg bid) in anticipation of this drug interaction. Despite the elevated nelfinavir concentration, the viral load remained elevated possibly suggesting antiretroviral resistance. The second subject had underlying hepatitic C with elevated liver function tests. This may have accounted for the elevated nelfinavir peak concentration since nelfinavir is metabolized by the liver. In contrast to the previous subject, the viral load was undetectable for subject #8.

The remaining five subjects (#2, 4, 5, 7, and 9) had nelfinavir concentrations that were considered with in the range of the reference population. However, only 2 subjects (#7 and #9) had undetectable viral loads. Subject #9 was on his first antiretroviral regimen while #7 was receiving a 5 drug regimen. The remaining 3 subjects had detectable viral loads despite adequate nelfinavir concentrations which may have suggested antiretroviral resistance.

Although the results of the pilot study are purely ancedotal, they do meet the objectives of determining the utility and practicality of nelfinavir TDM. The results of the pilot study suggest that a select population of HIV infected patients may benefit from TDM. The following are situations where TDM may be useful: patients with a hepatic disorder or malabsorption, patients far from their ideal body weight, patients with adherence issues, and patients with suspected clinically important drug interactions or drug induced toxicity.

The practicality of nelfinavir TDM is an important issue. Measuring protease inhibitor plasma concentration is currently a research tool. Therefore, accessibility to this technology is limited. In our study, blood samples were sent to the Ottawa General Hospital for drug concentration determination. This required proper preparation of the samples (i.e. centrifusing, packing in dry ice) prior to shippment. Once the samples were sent, almost 4 weeks were required before the results were available, a situation that would not be very practical in a clinical setting.

One of the limitations to nelfinavir TDM is that a therapeutic range has yet to be established. In our study, published pharmacokinetic data of 11 subjects was used as the reference population to which we compared the results of our subjects and made clinical assessments. However, the validity of this practice is not clear. Due to the limited number of studies of this nature, the reference population we used is the best that is currently available.

A learning curve is always present when new technology emerges. Based on the results of our pilot study, the future of protease inhibitor TDM appears promising. However, controlled trials are required to establish a therapeutric range for a given protease inhibitor, deciding on which concentration (peak, trough, random) should be measured and conducting controlled studies to evaluate the usefulness of TDM in improving virologic efficacy. The completion of our controlled trial should help answer these questions.

7. CONCLUSION

Therapeutic drug monitoring of protease inhibitors is an emerging technology which has the potential of becoming a very important tool in clinical practice. A pilot study of 10 HIV infected patients evaluated the utility and practicality of nelfinavir TDM. Five of the 10 patients were identified as having nelfinavir plasma concentrations outside the reference population range. Factors that may have contributed to high concentrations included underlying hepatic dysfunction and inhibitor type drug interactions. In contrast, malabsorption secondary to diarrhea, inductive type drug interactions and underdosing in obesity were factors potentially involved in low nelfinavir concentrations. Controlled trials are required to establish a therapeutic range and dose adjustment guidelines for nelfinavr, to

identify which concentration parameter best predicts response, and to evaluate the utility of TDM in improving virologic efficacy.

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Table 1: Results of nelfinavir therapeutic drug monitoring (pilot study)

Sub. No.	Sex	Age (yr)	Wt (kg)	Ht (cm)	ARV exp'd or naive (incl. PIs)	CD4 (cells/mm^3)	Viral load [Chiron 3.0] (copies/ml)	LFT's	GI	ARV meds	Other meds	TSLD (hr)	NFV plasma conc. (mcg/ml)	M8 plasma conc. (mcg/ml)	M8/NFV ratio (%)
1	M	47	69	186	exp'd	35	232,984	WNL	nl	NFV 1000 mg bid RTV 300 mg bid DLV 400 mg tid ABC 300 mg bid	TMP/SMX, fluconazole acyclovir, omeprazole, desipramine, morphine, testosterone, methylphenidate	2 13.5	3.605 4.173	1.821 1.424	50.5 34.1
2	M	51	79.5	183	exp'd	485	10,039	WNL	diarrhea	NFV 1250 mg bid d4T 20 mg bid ABC 300 mg bid EFV 600 mg qd	TMP/SMX, acyclovir	2 13	1.497 1.209	0.183 0.152	12.2 12.6
3	M	45	65.3	n/a	exp'd	342	89,422	WNL	diarrhea	NFV 1250 mg bid AZT 300 mg bid 3TC 150 mg bid	TMP/SMX	3	2.814	1.209	43
4	M	36	69	182	exp'd	257	>500,000	WNL	diarhea	NFV 1250 mg bid ABC 300 mg bid EFV 600 mg qd	TMP/SMX, fluconazole, acyclovir	16.6	1.357	0.0348	2.6
5	M	33	79.5	n/a	exp'd	73	13,908	WNL	diarrhea	NFV 1250 mg bid SQV 1000 mg bid d4T 40 mg bid 3TC 150 mg bid ABC 300 mg bid NVP 200 mg bid	TMP/SMX ketoconazole prn nabilone sertaline, amitriptyline, triazolam, Tylenol #3 loperamide, Cotazyme™ Lomotil™	15.5	0.830	0.545	65.7
6	M	47	94.5	n/a	exp'd	264	<50	WNL	diarrhea	NFV 1250 mg bid d4T 40 mg bid ABC 300 mg bid	aerosolized pentamidine, l-thyroxine	12.5	0.323	0.110	34.1

										EFV 600 mg qd					

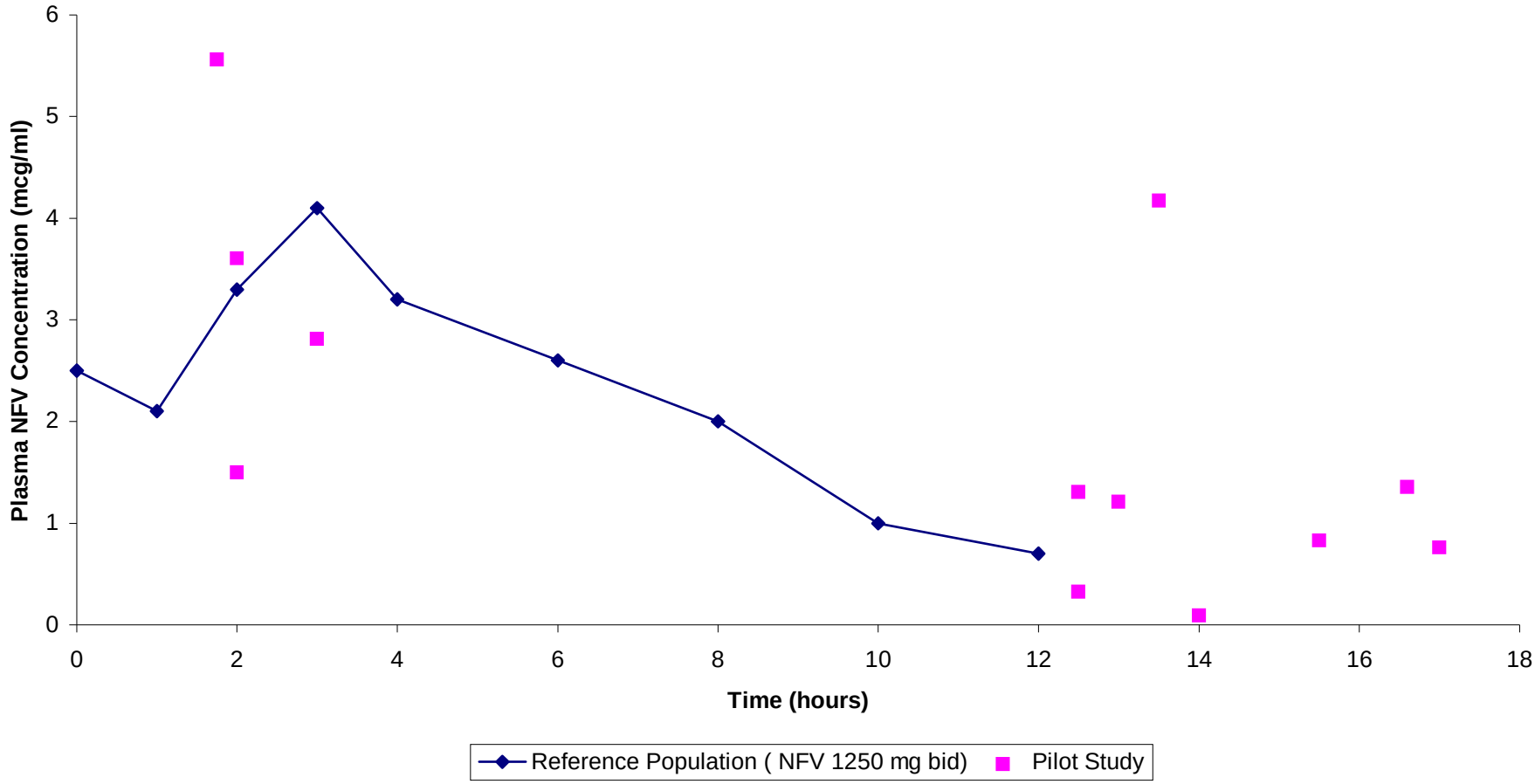
Table 1 (cont'd):

Sub No.	Sex	Age (yr)	Wt (kg)	Ht (cm)	ARV exp'd or naive (including PIs)	CD4 (cells/mm^3)	Viral load [Chiron 3.0] (copies/ml)	LFT's	GI	ARV meds	Other meds	TSLD (hr)	NFV plasma conc. (mcg/ml)	M8 plasma conc. (mcg/ml)	M8/NFV ratio (%)
7	M	29	72	n/a	exp'd	441	<50	WNL	nl	NFV 1250 mg bid SQV 1000 mg bid NVP 200 mg bid AZT 300 mg bid 3TC 150 mg bid	TMP/SMX	17	0.759	0.143	18.8
8	M	51	70	180	exp'd	318	<50	↑ (hepC)	diarrhea	NFV 1250 mg bid SQV 1200 mg bid d4T 40 mg bid	TMP/SMX, fluconazole sertaline, amitriptyline	1.75	5.559	0.821	14.8
9	M	46	73.3	178	naive	61	<50	WNL	nl	NFV 1250 mg bid AZT 300 mg bid 3TC 150 mg bid	TMP/SMX, itraconazole	12.5	1.307	0.566	43.3
10	M	45	61	n/a	naive	219	<50	WNL	nl	NFV 1250 mg bid AZT 300 mg bid 3TC 150 mg bid EFV 600 mg qd	TMP/SMX	14	0.0894	0.0246	27.5

Abbreviations:

ARV - antiretroviral
d4T - stavudine
EFV - efavirenz
n/a - not available
TSLD - time since last nelfinavir dose
SQV - saquinavir
3TC - lamivudine
NVP - nevirapine
exp'd - experienced
LFT's - liver function tests
RTV - ritonavir
AZT - zidovudine
DLV - delavirdine
WNL - with in normal limits
nl - normal
NFV - nelfinavir
ABC - abacavir

Figure 1. Plasma Nelfinavir Concentration vs. Time Curve (Pilot Study)



Appendices