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Indinavir and Rifabutin Drug Interactions in Healthy Volunteers

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Pages: 36

Tables: 4

Figures: 6

Short Title: Indinavir and rifabutin drug interactions

Journal Category: Pharmacokinetics and Pharmacodynamics

Abstract

Objectives: Two studies examined the pharmacokinetics of indinavir and rifabutin when coadministered in healthy subjects. Rifabutin, which induces expression of cytochrome P450 (CYP) 3A, and indinavir, which inhibits that enzyme system, are frequently coadministered in patients infected with HIV. The second study was undertaken to determine if altering the dose of rifabutin coadministered with indinavir would minimize the drug interaction observed in the first study. **Methods**: Two studies, each with a three period crossover design,, were performed. In study 1, standard doses of rifabutin and indinavir (300 mg of rifabutin qd and 800 mg indinavir q8h) were administered as monotherapy (with placebo to the other drug) or in combination to 10 volunteers for ten days. In study 2, 150 mg qd of rifabutin together with 800 mg q8h of indinavir, 300 mg qd of rifabutin alone, or 800 mg q8h of indinavir alone was administered to 14 volunteers for ten days.

Results: In study 1, the geometric mean ratio (GMR) (90% CI) of the $AUC_{(0-8\ hr)}$ of indinavir, coadministered with rifabutin 300 mg qd compared to indinavir alone (with rifabutin placebo), was 0.66 (0.56, 0.77) while that of the $AUC_{(0-24\ hr)}$ of rifabutin, coadministered with indinavir compared to rifabutin alone (with indinavir placebo), was 2.73 (1.99, 3.77). In study 2, the GMR (90% CI) of the $AUC_{(0-8\ hr)}$ of indinavir, coadministered with rifabutin 150 mg qd compared to indinavir alone, was 0.68 (0.60, 0.76) while that of the $AUC_{(0-24\ hr)}$ of rifabutin, when rifabutin 150 mg qd was coadministered with indinavir compared to rifabutin 300 mg qd alone , was 1.54 (1.33, 1.79). For both Studies 1 and 2, indinavir and rifabutin administered alone or in combination were generally well-tolerated. No clinical or laboratory adverse experience was serious.

Conclusions: These data demonstrate the important pharmacokinetic interactions between indinavir and rifabutin when they are coadministered. Indeed, these observations formed the basis for the subsequent ACTG 365 study that explored dose adjustments for these agents in combination regimens in order to preserve the sustained antiviral activity of indinavir in the absence of adverse events as a result of elevated circulating levels of rifabutin.

INTRODUCTION

Optimal therapy for HIV infection incorporates the use of a combination of antiviral medications. Indinavir is a potent antiretroviral of the protease inhibitor class. Specifically, it inhibits HIV-1 aspartyl protease[1] and thereby prevents the cleavage of HIV *pol-gag* polypeptides. As a result of inhibition of this enzyme, the HIV viral particles released from infected human cells are noninfectious.[2] Indinavir has been employed as one component of Highly Active Antiretroviral Therapy (HAART), the strategy of using combinations of potent antiretroviral agents to produce durable reductions in HIV viral load.[3,4]

The use of HAART has significantly reduced the incidence of infections due to opportunistic organisms in patients infected with HIV. However, chemoprophylaxis remains an important part of the care of HIV infected individuals and has survival benefit, even in patients receiving HAART.[5] Since disseminated infection with *Mycobacterium avium* complex (MAC) may occur with advanced immunosuppression, the 2001 USPHS/IDSA guideline recommends primary prophylaxis against MAC when the CD_4 count falls below 50 cells/μL.[6] The macrocyclic antibiotic rifabutin is an alternate agent for use in MAC prophylaxis, and has a role in the treatment of disseminated disease.[7] Additionally, the CDC guideline for treatment of tuberculosis in patients infected with HIV endorses the substitution of rifabutin for rifampin in those patients who receive protease inhibitors, as rifabutin causes less induction of drug metabolizing cytochromes than rifampin.[8]

Indinavir is primarily metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4); it also inhibits CYP3A4.[9] Rifabutin is also metabolized by hepatic CYP3A4, but induces its activity.[10] Since coadministration of rifabutin and indinavir is common in treating patients infected with HIV, and each drug has an effect on, and is metabolized by, CYP3A4, it is reasonable to predict some degree of interaction between these two drugs. Evaluation of their pharmacokinetics individually and when coadministered would help define an optimal combination therapy for treatment of patients infected with HIV. Therefore, the first study examined the pharmacokinetics of indinavir and rifabutin when coadministered and the second study was undertaken to determine if altering the dose of rifabutin coadministered with indinavir would minimized the drug interaction observed in the first study.

METHODS

Both of the two studies described herein were performed in the Clinical Research Unit at the Thomas Jefferson University Hospital in Philadelphia, Pennsylvania.

Subjects

Ten healthy male subjects (5 Caucasian, 4 Black, 1 Hispanic) completed Study 1 and fourteen healthy subjects (12 male; 8 Caucasian and 4 Black, 2 female; both Caucasian) completed Study 2.. All subjects were non-smokers between 21 and 41 years of age. All were within 20% of their ideal body weight, and were judged to be in good health based on history, physical examination, and laboratory examination (complete blood count, serum electrolytes, creatinine, liver function tests, HIV test and urinalysis). Subjects with a history of nephrolithiasis, positive

hepatitis B surface antigen, or liver disease, or elevations in total or direct bilirubin were excluded. Subjects who have consumed excessive alcoholic (more than two drinks) and/or caffeine (more than 6-12 oz drinks) containing beverages per day or subjects who have used any prescription medication within 14 days of the study especially rifampin, triazolam, midazolam, astemizole, or cisapride or any non prescription medications within 7 days of study start of the study or subjects who donated blood or participated in another clinical trial within the last 4 weeks, or subjects who were regular users of illicit drug or a history of drug or alcohol abuse were excluded. All subjects provided written informed consent prior to participation in these clinical studies. All protocols were reviewed and approved by the Institutional Review Board of Thomas Jefferson University.

Study Design

Both studies were multiple-dose, randomized, three period crossover studies. Subjects received, in randomized order, three different treatments, each for 10 days, as described below. Given that rifabutin and indinavir were generally well tolerated as seen in study 1, and a smaller dose of rifabutin was used, placebo was not administered in study 2. All study drugs were administered by witnessed dosing. All study drugs were supplied by Merck Research Laboratories, Inc. For Study 1 the placebo for rifabutin grossly matched active rifabutin.

Study 1: Treatment A consisted of indinavir 800 mg q8h (4 x 200 mg capsules) and rifabutin placebo, treatment B consisted of rifabutin 300 mg qd (2 x 150 mg capsules) and indinavir placebo, and treatment C consisted of indinavir 800 mg q8h and rifabutin 300 mg qd. Rifabutin was administered at the same time of day for

each subject. On Day 10 of each period indinavir/placebo was administered for 3 doses (q8h). Each period of treatment was separated by at least a 10 days. Venous blood samples for the determination of plasma indinavir were collected at time 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours after the morning dose of indinavir on the morning of Day 10 for both treatments A and C. Venous blood samples for the determination of plasma rifabutin and 25-O-desacetyl rifabutin, the active metabolite of rifabutin,[11] were collected at time 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours after the administration of the last dose of rifabutin on the morning of Day 10 for treatments B and C. Liver function tests were performed 4 hours after the last dose of drug, and safety labs (complete blood count, serum electrolytes and creatinine and urinalysis) and physical examination were performed 24 hours after the last dose of drug.

Study 2: The dose of rifabutin was decreased to 150 mg when coadministered with indinavir. Subjects in treatment D received indinavir 800 mg q8h, those in treatment E received rifabutin 300 mg qd, and those in treatment F received indinavir 800 mg q8h and rifabutin 150 mg qd. Rifabutin was administered at the same time of day for each subject. On Day 10 (Treatment D and F), indinavir was administered for three doses (q8h). Concentrations of indinavir, rifabutin, and 25-O-desacetyl rifabutin were determined in samples of venous blood obtained at various intervals, as described for Study 1.

Analytical Methods

For both studies, plasma concentrations of indinavir[12], rifabutin, and 25-desacetyl-rifabutin were each determined using high-performance liquid chromatographic methods with ultraviolet detection.

For study 1 indinavir was assayed by Merck Research Laboratories (MRL) as previously described[12] except that the standard curve range was 25-5000 ng/mL. The assay limit of quantitation was 25 ng/ml (40.7 nM). Mean intra-day accuracy and precision (n=5) ranged from 97.6-105.0% and 1.1-3.4%, respectively, Inter-day precision of QC samples was 2.25% at 75 ng/mL and 0.93% at 3500 ng/mL Rifabutin and 25-O-desacetyl rifabutin were assayed by MDS-Pharma (Lincoln, Nebraska) using a proprietary method. Briefly, the assay method consisted of liquid-liquid extraction of drug, metabolite and internal standard into an organic solution (hexane:ethyl acetate) followed by separation and evaporation of the organic layer. The residue was reconstituted in a small volume and injected onto and HPLC system with UV detection at 275 nm. The assay limit of quantitation was 5 ng/ml for rifabutin and 2.5 ng/ml for 25-O-desacetyl rifabutin. Replicated standards (n=5) were all accurate to within 7.4% of nominal values and the coefficients of variation were all less than 8.6% for both analytes. For inter-day precision of QC samples was 5.9% at 10 ng/mL and 2.9% at 400 ng/mL for rifabutin and 4.1% at 5 ng/mL and 2.4% at 200 ng/mL for -O-desacetyl rifabutin,

For study 2 indinavir, rifabutin and its 25-desacetyl metabolite were assayed by BAS Analytics (West Lafayette, Indiana). Indinavir was assayed as previously described[12] except that the last liquid-liquid extraction step was omitted and the

calibration curve range was 12-15,000 ng/mL. The indinavir assay limit of quantitation was 12 ng/mL (19.5 nM). Accuracy and precision ranged from 98.3-107.2% and 4.3-5.6%, respectively. Inter-day precision of QC samples was 10.4% at 50 ng/mL, 4.1% at 1,000 ng/mL and 8.5% at 10,000 ng/mL. For rifabutin and 25-O-desacetyl rifabutin, the assay was comprised of liquid-liquid extraction into n-butylchloride followed by separation and evaporation of the organic layer. The residue was reconstituted in an aqueous solution containing 32% acetonitrile and 0.2% trifluoroacetic acid followed by liquid-liquid extraction with hexane. The aqueous phase was then injected onto an HPLC system with UV detection at 275 nm. The assay limit of quantitation was 5 ng/mL for rifabutin and 3.7 ng/mL for 25-O-desacetyl rifabutin. For rifabutin, mean accuracy and precision ranged from 94.9-103.7% and 2.1-11.7%, respectively. Inter-day precision of QC samples was 10.4% at 10 ng/mL, 3.5% at 80 ng/mL and 2.9% at 400 ng/mL. For 25-O-desacetyl rifabutin, mean accuracy and precision ranged from 98.8-101.4% and 1.3-8.8%, respectively. Inter-day precision of QC samples was 7.0% at 5 ng/mL, 3.4% at 40 ng/mL and 2.3% at 200 ng/mL.

Assays in both studies were checked for cross-interference by assaying plasma samples from treatments where only the non-assayed drug was administered. For both studies, indinavir concentrations were converted to a molar basis by using a molecular weight of 613.81.

Pharmacokinetic Analysis

For both studies, peak plasma concentration, C_{max}, time to peak concentration, T_{max}, and area under the concentration-time curve over the final dosing interval,

$AUC_{(0-8\ hr)}$ for indinavir and $AUC_{(0-24\ hr)}$ for rifabutin and its metabolite, were determined for each treatment in which the respective drugs were administered. C_{max} and T_{max}, were obtained directly from the concentration-time data. AUC was calculated by a modified trapezoidal rule using piecewise cubic polynomials.[13] Actual sample times recorded by the investigator were used to calculate AUC. Trough plasma concentration, C_{8hr}, also was assessed for indinavir. All concentrations below the limit of quantitation were treated as zeroes for pharmacokinetic calculations. Excel (Microsoft, Redmond, WA) was the software used for this analysis.

Statistical Analysis

Power:

For Study 1, as the primary objective was to evaluate the effect of rifabutin on the pharmacokinetics of indinavir, this study was powered for indinavir only. (The large effect seen of indinavir on rifabutin was unexpected in this early study). To address the primary objective of the effect of rifabutin on the AUC of indinavir the MSE=0.13 (on the log scale) was estimated from a previous early clinical trial using 600 mg q8h (data on file). Given a three-period crossover study with n=12 subjects and a type I error = 0.05 and assuming similar variation of indinavir and rifabutin, there was a 99% probability that the observed 90% confidence interval for the ratio of geometric mean AUC (indinavir and rifabutin/indinavir alone) will fall within the equivalence interval (0.5, 2.0), if the true ratio 1.0. There was 80% probability that the 90% confidence interval would fall within the equivalence interval (0.64, 1.56), if the true ratio was 1.

For Study 2, the objectives were to evaluate both the effect of rifabutin on indinavir and indinavir on rifabutin with an adjusted rifabutin dose. For this study, data (MSE) from study 1 were used in the power calculations as follows. In study 1, the observed AUC ratio of rifabutin when rifabutin was administered with indinavir relative to rifabutin 300 mg alone was 2.73. It seemed reasonable to assume based on these results that the AUC ratio of rifabutin with half the dose, relative to rifabutin alone could be as high as 1.37. Therefore if the true ratio was 1.37 given the same three-period design with 15 subjects there was 83% probability that the observed 90% confidence interval the ratio of geometric mean AUCs (combination/ rifabutin alone) could fall within the equivalence interval (0.50, 2.0). For the effect of rifabutin on indinavir, the MSE = 0.034 (on the log scale) was used. Given the same three-period crossover design with 15 subjects, a type I error = 0.05 and a similar variation as seen in study 1, there was 99% probability that the observed 90% CI for the ratio of the geometric mean AUCs (combination/indinavir alone) would fall within the equivalence interval (0.5, 2.0) assuming the true ratio was 1.0.

Methods:

Although the clinical design of both studies were a standard three period crossover, the usual linear model (and the consequent ANOVA analysis) with subject, period, treatment and carryover effects entered as independent variables was modified to accommodate the following particular feature of these drug interaction trials. Unlike a conventional three period crossover study, in these studies subjects receiving indinavir alone provide no data for assessing the effect of coadministration of

rifabutin with indinavir on the pharmacokinetics of rifabutin. This assessment involves only a comparison of two of the three treatment groups, i.e., rifabutin 150 mg and indinavir combined versus rifabutin 300 mg alone. Similarly, subjects receiving rifabutin 300 mg alone provide no data for assessing the effect of coadministration of rifabutin 150 mg with indinavir on the pharmacokinetics of indinavir. To account for this, a classification variable called 'pair' was defined to capture the variability due to the different pairs of periods in which two treatments were compared. This variable 'pair' is based on a model proposed by Ciminera et al.[14] It was of interest to test whether the treatment comparisons varied across the three different pairs, i.e., the treatment by pair interaction. The interaction was tested using the contrast proposed by Ciminera et al., through the use of a modified three period ANOVA model on log-transformed data. The modified ANOVA model initially contained terms for subject, period, treatment, carryover, and period by carryover interaction. A contrast containing both carryover and period by carryover effects[15] was run to test the treatment by pair interaction. In the case of a non significant interaction (p>0.05), a second ANOVA model was run in which the carryover and period by carryover terms were dropped from the model. A 90% confidence interval was constructed about the treatment differences using the results of the ANOVA. In both studies, the treatment by pair interaction was found to be non significant, therefore no interaction terms were included in the final models. . The antilogs of the upper and lower limits were then calculated to obtain the confidence interval for the ratio of geometric means. SAS version 6.12 (SAS Institute, Cary, NC) was used to analyze the data.

Results

Study 1: Coadministration of Indinavir 800 mg q8h and Rifabutin 300 mg daily

Thirteen healthy male subjects with a mean age of 29.5 yr (range 22-41) and weight of 79.5 kg (range 60.8-101.8) enrolled in the study. Three subjects were discontinued; one due to a laboratory adverse experience considered drug related (see Safety), one due to a clinical adverse experience considered not drug related, while another subject withdrew consent to further participate during the third period. Data from all 13 subjects who enrolled were included in the safety analysis and data from the 10 subjects who completed the study were included in the pharmacokinetic analysis.

Plasma profiles of indinavir were consistently lower when indinavir was administered with rifabutin (Fig. 1). The $AUC_{(0-8h)}$, C_{max} and C_{8h} of indinavir were lower when coadministered with rifabutin 300 mg daily (Table I). For $AUC_{(0-8h)}$, the geometric mean ratio (90% C.I.) for combination/monotherapy was 0.66 (0.56, 0.77). For C_{8h}, the geometric mean ratio (90% C.I.) was 0.61 (0.50, 0.75). The arithmetic means of indinavir T_{max} with and without rifabutin were identical at 0.8 ± 0.2 hours. Conversely, plasma concentrations of rifabutin (Fig. 2) and its 25-desacetyl metabolite (Fig. 3) were increased upon coadministration of rifabutin and indinavir. The point estimates for the geometric mean $AUC_{(0-24h)}$ and C_{max} for rifabutin increased more than 2-fold when coadministered with indinavir (Table II). The $AUC_{(0-24h)}$ and C_{max} of 25-desacetyl rifabutin were similarly increased when coadministered with indinavir (Table II).

These observations were indicative of a clinically important pharmacokinetic interaction upon coadministration of indinavir and rifabutin. The decreased plasma concentrations of indinavir were considered clinically significant due to the propensity of HIV to develop resistance in the face of decreased concentrations of protease inhibitors. Conversely, the increases in circulating rifabutin concentrations were considered clinically significant due to a potential increase in concentration dependent toxicity. Consequently, Study 2 was undertaken to determine if altering the dose of rifabutin coadministered with indinavir could minimize the drug interaction observed in Study 1.

Study 2: Comparison of Rifabutin 150 mg Daily Coadministered with Indinavir 800 mg q8h and Rifabutin 300 mg Daily Alone

Sixteen healthy male and four healthy female subjects with a mean age of 28.3 yrs (20-40) and mean weight of 70.5 kg (50.5-96.8) began the study. Six subjects were discontinued from the study; 4 subjects were discontinued for personal reasons not related to study drug and 2 subjects discontinued due to adverse experiences considered drug-related by the investigator (see Safety). Data from all 20 subjects who were enrolled in the study were included in the safety analysis. Data from the 14 subjects who completed the study were included in the pharmacokinetic analysis.

Plasma profiles of indinavir were decreased when indinavir was coadministered with 150 mg rifabutin (Fig. 4) to an extent that was similar to that observed with the coadministration with 300 mg rifabutin (Study 1, Figure 1). Coadministration with rifabutin 150 mg daily resulted in a decrease in the $AUC_{(0-8h)}$, C_{max} and C_{8h} of

indinavir (Table III). For $AUC_{(0-8h)}$, the geometric mean ratio (90% C.I.) for combination/monotherapy was 0.68 (0.60, 0.76). For C_{8h}, the geometric mean ratio (90% C.I.) was 0.60 (0.51, 0.72). The arithmetic means of indinavir T_{max} with and without rifabutin were 0.9 ± 0.4 hours and 1.3 ± 0.9 hours, respectively.

Plasma concentrations of rifabutin (Fig. 5) and 25-desacetyl-rifabutin (Fig. 6) were higher when 150 mg rifabutin was coadministered with indinavir compared to plasma concentrations of these analytes when 300 mg rifabutin was administered alone. The geometric mean ratio (90% C.I.) for $AUC_{(0-24h)}$ in the combination vs. monotherapy arms was 1.54 (1.33, 1.79), and for C_{max} was 1.29 (1.05, 1.59) (Table IV). Similarly, the $AUC_{(0-24h)}$ and C_{max} of 25-desacetyl rifabutin were higher when rifabutin 150 mg was coadministered with indinavir compared to rifabutin 300 mg alone (Table IV). The geometric mean ratio was 4.1 for $AUC_{(0-24h)}$, and 2.4 for C_{max}. The arithmetic mean of rifabutin T_{max} with and without indinavir was identical at 3.5 ± 1.0 hours. The arithmetic mean of 25-desacetyl rifabutin T_{max} with and without indinavir was 3.5 ± 1.4 hours and 3.9 ± 0.9 hours, respectively.

Safety and Tolerability

The combinations of Indinavir 800 mg q8h and rifabutin at either 300 mg daily or 150 mg daily were generally well-tolerated. There were no serious adverse events in either study.

In Study 1, 4 of 11 subjects had clinical adverse experiences which were mild and possibly related to study drug. Taste perversion was the most common drug-related clinical adverse experience and occurred on indinavir alone, on indinavir and rifabutin, and on rifabutin alone.

Two of 3 subjects had laboratory adverse experiences which were judged possibly related to the study drug. One subject had liver function and hematologic abnormalities and was discontinued from the study. He had an increase in ALT while on indinavir alone, an increase in AST while on indinavir and rifabutin, and increases in ALT and AST while off drug. All increases in transaminase values were less than twofold. Although he had increases in bilirubin while on indinavir, his highest total bilirubin was 1.6 mg/dL. Also, this subject developed leukopenia (1.7 x 10^9/L from baseline of 5.3 x 10^9/L), decreased circulating neutrophils (prestudy, 51%; post-dose, 8%) and decreased circulating platelets (prestudy, 235 x 10^9/L; post-dose, 137 x 10^9/L) while on indinavir and rifabutin. Following 8 days off drug his circulating leukocytes, neutrophils, and platelets returned to within normal limits. The second subject had increases in transaminases; AST and ALT while on indinavir alone and increases in AST while on rifabutin alone. All increases were less than twofold.

In Study 2, 5 of 10 subjects had clinical adverse experiences judged by the investigator to be drug-related. Of these drug-related clinical adverse experience, one subject experienced upper respiratory infection symptoms while on indinavir and rifabutin, one subject had mild abdominal pain while on combination therapy, one subject developed vaginitis while on rifabutin alone, and one subject had a change in bowel patterns on rifabutin and dyspepsia while on indinavir and a fifth subject was discontinued for a rash judged as probably related to treatment while on indinavir and rifabutin 150 mg.

Four of 5 subjects had drug-related laboratory adverse experiences. Two subjects had increases in transaminases; one subject had an increase in AST (< 3 fold) while on indinavir and rifabutin 150 mg and one subject had increases in AST and ALT while on rifabutin 300 mg alone (a transient 5 -fold increase which decreased to ~ 2 fold within 2 days). Two subjects had decreases in circulating neutrophils which were possibly related to study drug. One had a decrease in circulating neutrophils of 34% (with a total WBC of 3.3) during washout (4 days following completion of Period 2, rifabutin 300 mg alone) and was discontinued. Within 8 days, his circulating neutrophils returned to within normal limits at 61% (with a total WBC of 5.0). The other subject experienced decreases in circulating neutrophils of 34% (with a total WBC of 3.4) on Day 11, Period 2 while on rifabutin 300 mg alone. Within 7 days, his neutrophils returned to within normal limits at 48%, and he completed the study.

Discussion

All HIV protease inhibitors currently approved for clinical use, including indinavir, are metabolized by the CYP3A4 isoenzymes. Indinavir inhibits CYP3A4, whereas rifabutin induces CYP3A4. Given the simultaneous inhibition and induction of CYP3A4 following coadministration of these two drugs, prediction of proper dosing schedules for combined therapy is challenging. The standard dose schedule of indinavir is 800 mg q8h, while the standard dose of rifabutin for MAC prophylaxis is 300 mg daily.[16,17] When administered to healthy subjects, this combination led to a 44% decrease in the geometric mean $AUC_{(0-8h)}$ of indinavir compared to indinavir administered alone, presumably reflecting induction of indinavir metabolism by

rifabutin and/or its active metabolite. Conversely, this combination resulted in a rifabutin $AUC_{(0-24h)}$ that was 2.7-fold higher compared to rifabutin administered alone, presumably reflecting inhibition of CYP3A4 by indinavir. Similarly, this interaction likely contributed to the 4.8-fold increase observed in 25-desacetyl rifabutin $AUC_{(0-24h)}$, the most abundant urinary metabolite of rifabutin[18], when rifabutin and indinavir were coadministered. This metabolite has equivalent antibacterial activity to rifabutin, but normally achieves a 10-fold lower concentration in the serum compared to the parent drug.[11] Since this compound is found at a concentration one log lower than the parent compound, the clinical implication of the differential increase is likely minor.

The greater than 30% decrease in geometric mean plasma indinavir AUC and trough concentration when coadministered with rifabutin, compared to indinavir alone, is likely clinically important. Concentrations of protease inhibitor which are sub-therapeutic select for drug-resistant virus and eventually lead to failure of the treatment.[19] This occurs despite the fact that such drug-resistant viruses tend to be less virulent.[20] The goal of a rational schedule for dosing with indinavir is to maintain antiviral efficacy. In a similar fashion, supra-therapeutic concentrations of rifabutin found in Study 1 might be expected to increase the incidence of concentration-dependent side effects.

Because pharmacokinetic interactions between indinavir and rifabutin were observed in Study 1, Study 2 was conducted in which rifabutin was administered at one half the standard daily dose (150 mg) in combination with indinavir and rifabutin 300 mg alone was used as the reference arm. Note that the predication was that

150 mg rifabutin with indinavir would have a similar exposure to 300 mg rifabutin when used alone. In this study, the dose of indinavir was not increased because it was presumed that induction of CYP3A4 by lower doses of rifabutin would have a smaller impact on circulating indinavir concentrations. Surprisingly, the AUC and the geometric mean ratio of the AUC of indinavir when administered with rifabutin 300 mg and 150 mg were nearly identical. That plasma concentrations of indinavir were decreased by the same magnitude with full doses (300 mg) and reduced doses (150 mg) of rifabutin suggests that both doses of rifabutin induced the metabolism of indinavir by CYP3A4 to a similar extent. In contrast, administration of rifabutin 150 mg daily with indinavir resulted in circulating rifabutin concentrations that were 1.54-fold higher of those achieved by administering rifabutin 300 mg alone. This is substantially less than the 2.73-fold increase in geometric mean rifabutin AUC when 300 mg daily of rifabutin was administered with indinavir.

Treatments administered in these studies were generally well-tolerated without a clear difference in the pattern of adverse experiences observed during combination therapy and monotherapy. The laboratory experiences, for study 1 and 2, appeared to indicate the leukopenia/neutropenia was occurring with rifabutin 300 mg alone and rifabutin 300 mg and indinavir. Neutropenia may be associated with the use of rifabutin and therefore, possible increases in rifabutin concentrations when coadministered with indinavir may have contributed to the laboratory adverse experience in the healthy subject in study 1

The limitations imposed by available rifabutin dosage strength, coupled with the lack of efficacy data for alternate day dosing, suggest that the modest increase in

rifabutin concentrations noted in study 2 are in a range that would maintain efficacy with reasonable safety. In contrast, the need to avoid a subtherapeutic indinavir concentration suggests the requirement of a higher indinavir dose when coadministered with rifabutin. Therefore, the results described herein resulted in a subsequent study sponsored by the AIDS Clinical Trials Group (ACTG 365) in which the regimen of indinavir 1000 mg q8h and rifabutin 150 mg daily was evaluated in healthy volunteers and HIV seropositive patients.[21]   In this study, systemic exposure of indinavir was similar between 800 mg administered alone and 1000 mg administered with 150 mg rifabutin.   Rifabutin concentrations were increased by 70%.   These pharmacokinetic observations are the basis of the present recommendation of indinavir 1000mg q8 hr when coadministered with rifabutin at 150 mg q24 hr.[22]   However, the clinical importance of the increase in rifabutin remains unknown.

Tables

Table I. Geometric means, geometric mean ratios and 90% confidence intervals of indinavir administered with and without rifabutin 300 mg daily.

Indinavir Measurement	Geometric mean without rifabutin 300 mg	Geometric mean with rifabutin 300 mg	Geometric mean ratio combination/ monotherapy	90% CI
$AUC_{(0\text{-}8h)}$ (nM•h)	27231.4	17984.9	0.66	(0.56, 0.77)
C_{max} (nM)	14438.9	10764.6	0.75	(0.61, 0.91)
C_{8h} (nM)	162.4	99.1	0.61	(0.50, 0.75)

Table II. Geometric means, geometric mean ratios and 90% confidence intervals of rifabutin and 25-desacetyl rifabutin when rifabutin is administered at 300 mg qd with and without indinavir.

Pharmacokinetic Parameter	Geometric mean without indinavir	Geometric mean with indinavir	Geometric mean ratio combination/ monotherapy	90% CI
Rifabutin measurement				
$AUC_{(0-24h)}$ (ng•h/mL)	2562.8	7006.7	2.73	(1.99, 3.77)
C_{max} (ng/mL)	292.8	686.2	2.34	(1.64, 3.35)
25-desacetyl rifabutin measurement				
$AUC_{(0-24h)}$ (ng•h/mL)	166.7	793.0	4.76	(3.07, 7.36)
C_{max} (ng/mL)	22.7	80.9	3.56	(2.46, 5.16)

Table III. Geometric means, geometric mean ratios and 90% confidence intervals of indinavir concentration administered alone and in combination with rifabutin 150 mg daily.

Indinavir Measurement	Geometric mean without rifabutin	Geometric mean with rifabutin 150 mg	Geometric mean ratio combination/ monotherapy	90% CI
$AUC_{(0-8h)}$ (nM•hr)	27340.1	18483.6	0.68	(0.60, 0.76)
C_{max} (nM)	12169.7	9729.6	0.80	(0.72, 0.89)
C_{8h} (nM)	147.9	89.2	0.60	(0.51, 0.72)

Table IV. Geometric means geometric mean ratios and 90% confidence intervals for rifabutin and 25-desacetyl rifabutin following rifabutin 300 mg alone and rifabutin and 25-desacetyl rifabutin following rifabutin 150 mg in combination with indinavir.

Pharmacokinetic Parameter	Geometric mean 300 mg rifabutin alone	Geometric mean rifabutin 150 mg with indinavir	Geometric mean ratio combination/ monotherapy	90% CI
Rifabutin measurement				
$AUC_{(0-24h)}$ (ng•h/mL)	2866.0	4422.2	1.54	(1.33, 1.79)
C_{max} (ng/mL)	289.4	374.0	1.29	(1.05, 1.59)
25--desacetyl rifabutin measurement				
$AUC_{(0-24h)}$ (ng•h/mL)	130.7	529.9	4.05	(2.92, 5.64)
C_{max} (ng/mL)	18.7	45.6	2.43	(2.00, 2,95)

Legends for Figures

Figure 1: Mean (SE) plasma concentrations of Indinavir after oral administration of indinavir 800 mg q8h alone and in combination with 300 mg rifabutin for 10 days (n=10).

Figure 2: Mean (SE) plasma concentrations of rifabutin after oral administration of 300 mg rifabutin daily alone and in combination with indinavir 800 mg q8h for 10 days (n=10).

Figure 3: Mean (SE) plasma concentrations of 25-desacetyl-rifabutin after oral administration of 300 mg rifabutin daily alone and in combination with indinavir 800 mg q8h for 10 days (n=10).

Figure 4: Mean (SE) plasma concentrations of Indinavir after oral administration of indinavir 800 mg q8h alone and in combination with 150 mg rifabutin (n=14).

Figure 5: Mean (SE) plasma concentrations of rifabutin after oral administration of 300 mg rifabutin daily alone or 150 mg rifabutin daily in combination with indinavir 800 mg q8h for 10 days (n=14).
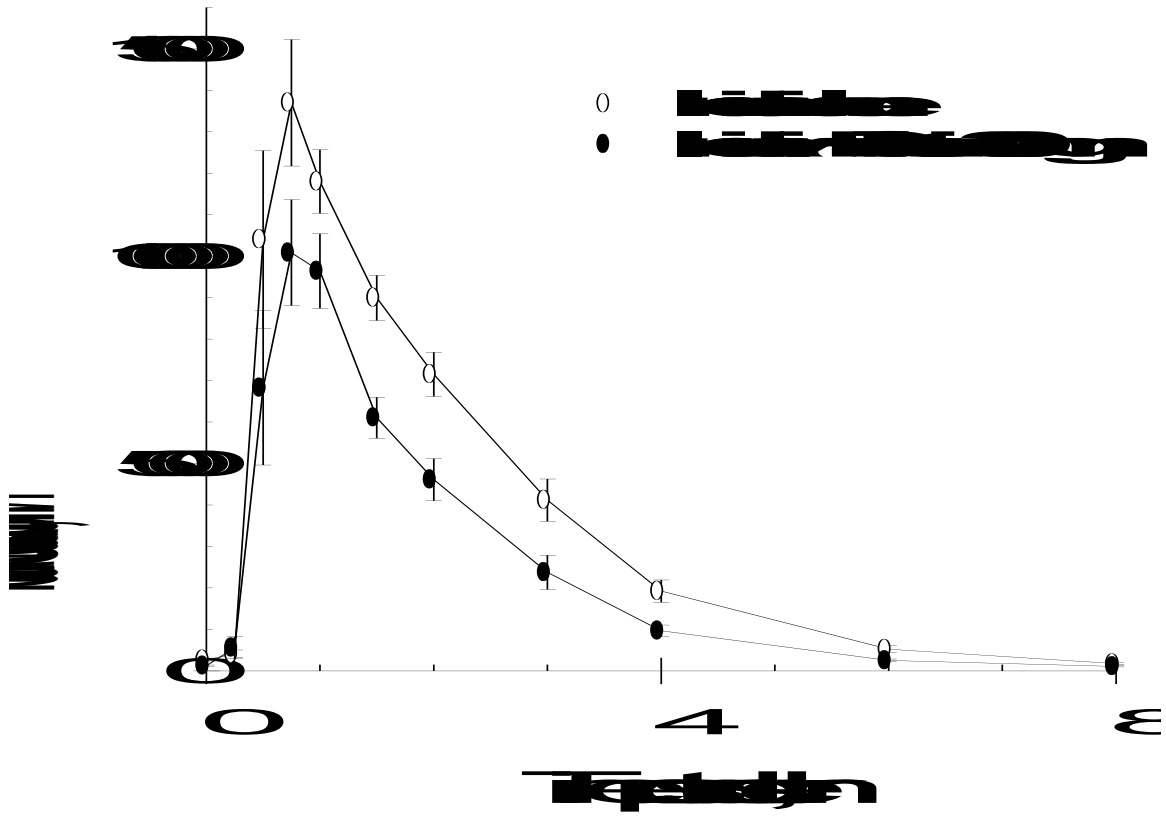
Figure 6: Mean (SE) plasma concentrations of 25-desacetyl-rifabutin after oral administration of 300 mg rifabutin daily alone or 150 mg rifabutin daily in combination with indinavir 800 mg q8h for 10 days (n=14).
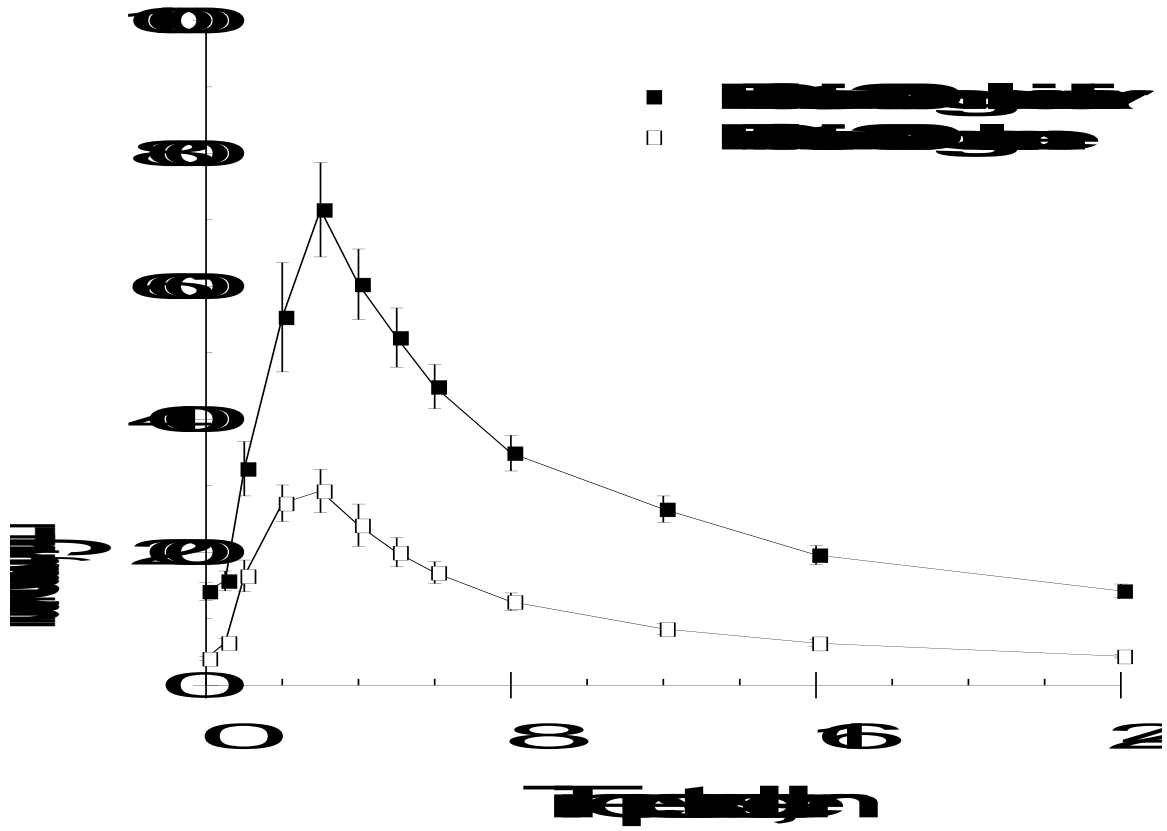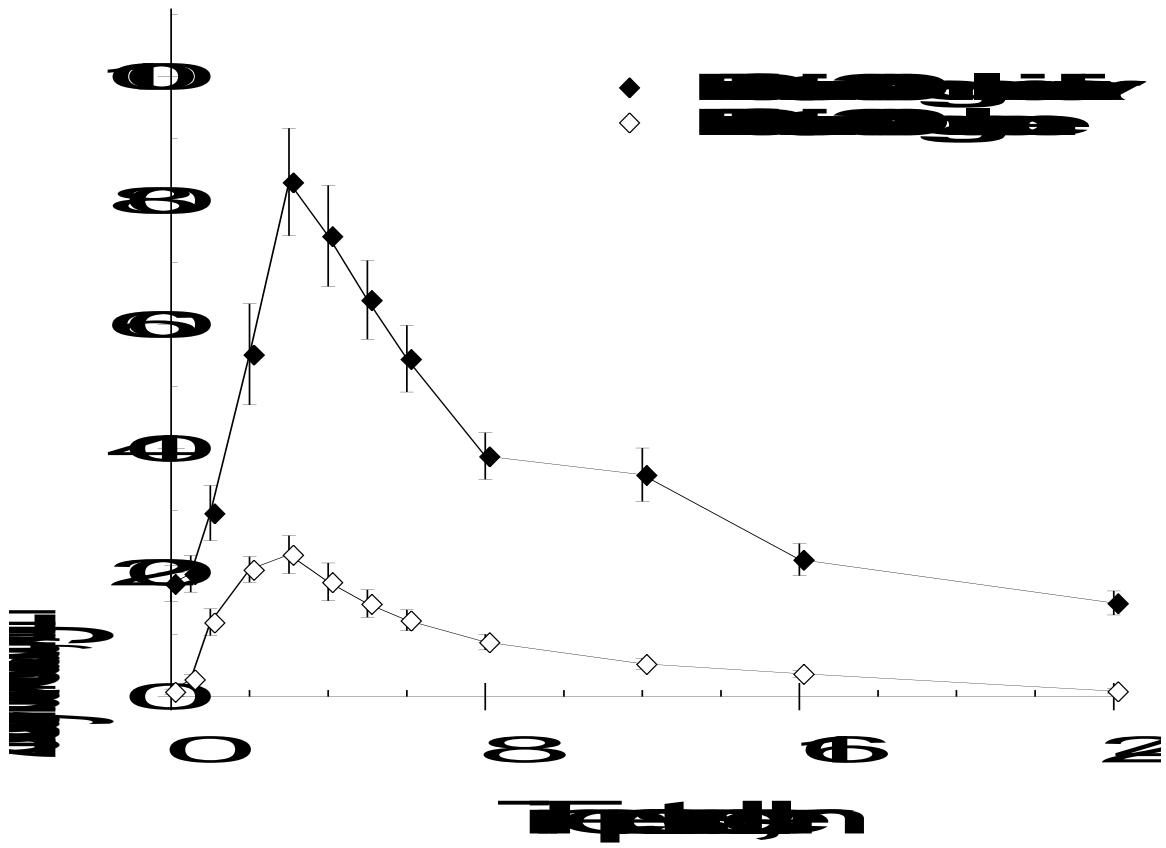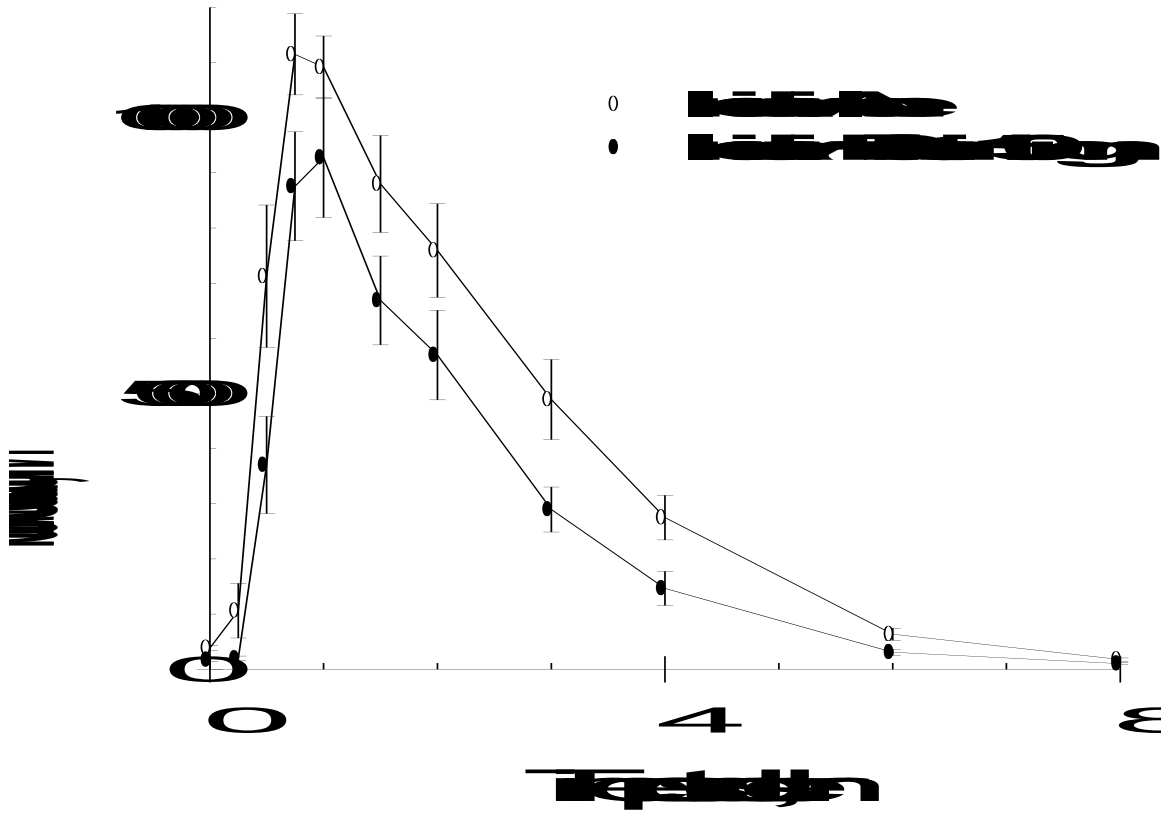
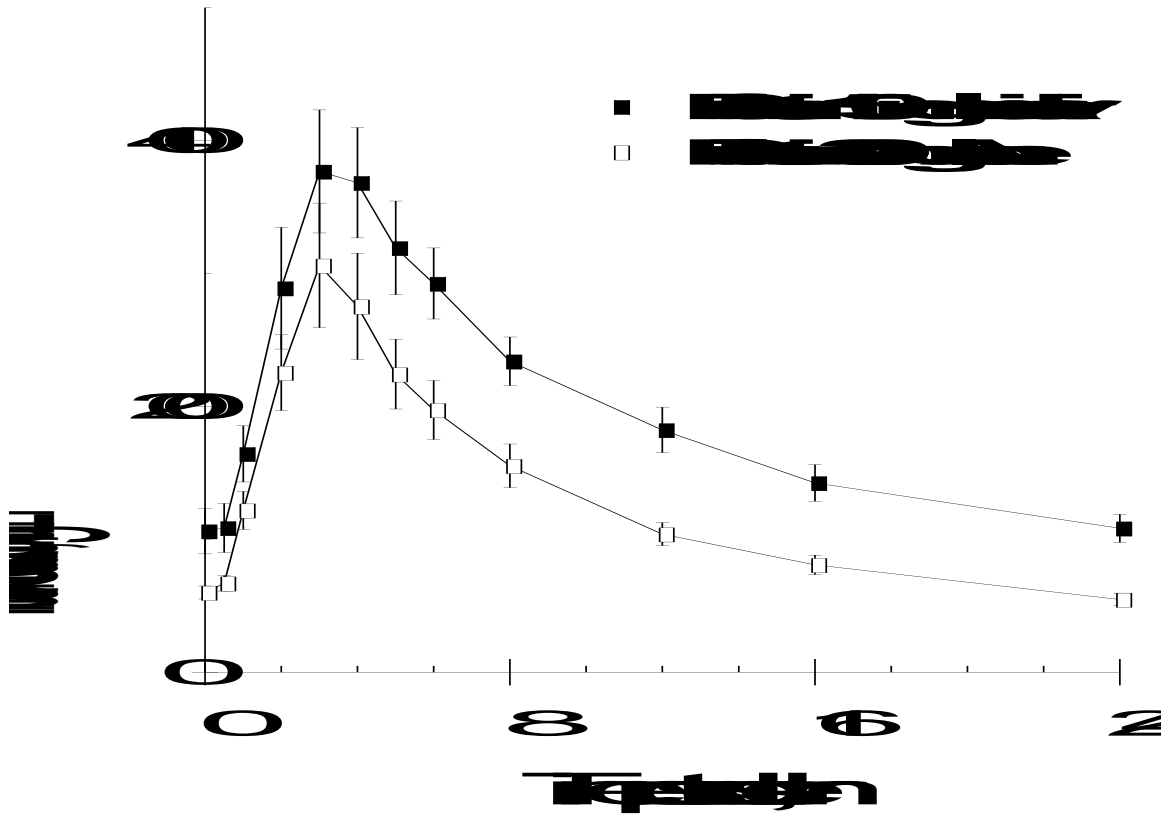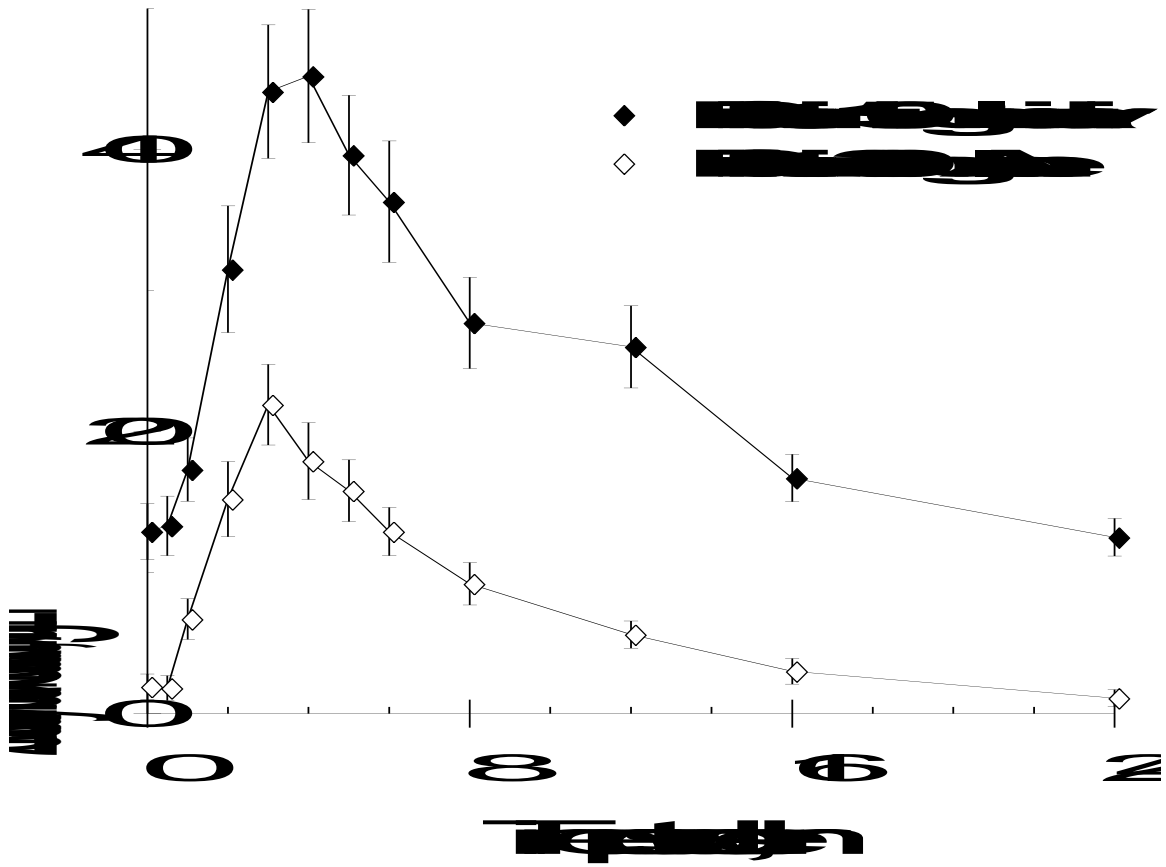**Figure 1**

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

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