

# Efavirenz (EFV) is a Significant Inducer of CYP3A4 (SIM) and Atorvastatin (ATR) Metabolism: Results of ACTG A5108 Study.

J G Gerber\*<sup>1</sup>, C J Fichtenbaum<sup>2</sup>, S Rosenkranz<sup>3</sup>, J M Vega<sup>4</sup>, A Yang<sup>4</sup>, B Alston<sup>5</sup>, S W Brobst<sup>6</sup>, Y Segal<sup>3</sup>, and J A Aberg<sup>7</sup> for the ACTG A5108 team.

<sup>1</sup>U of Colorado Hlth Sci Ctr, Denver, CO; <sup>2</sup>Univ of Cincinnati, OH; <sup>3</sup>SDAC, Harvard Sch of Publ Hlth, Boston, MA; <sup>4</sup>Merck & Co., Inc., West Point, PA; <sup>5</sup>NAID, NIH, Bethesda, MD; <sup>6</sup>Social and Sci Sys, Inc., Silver Spring, MD; <sup>7</sup>Washington Univ, St Louis, MO

## ABSTRACT:

**Background:** The use of antiretroviral drugs is associated with increases in serum lipid levels often requiring lipid-lowering therapy to reduce the risk of cardiovascular complications. EFV is one of the most commonly used and effective drugs for the treatment of HIV infection. EFV use is associated with hyperlipidemia either when used in combination with protease inhibitors or nucleoside reverse transcriptase inhibitors. EFV is a mixed inducer/inhibitor of CYP3A4; SIM and ATR, two widely used and potent HMG-CoA reductase inhibitors, are primarily metabolized via CYP3A4. Thus for the safe and effective use of SIM or ATR with EFV, it is important to establish how concomitant EFV affects the metabolism of these two drugs.

**Methods:** ACTG A5108 examined the effect of 600 mg/day EFV on the plasma pharmacokinetics (PK) of 40 mg/day SIM and 10 mg/day ATR, two of the most popular and effective statins used for lipid-lowering therapy. Twenty-eight HIV-seronegative healthy subjects participated in the SIM and ATR arms of this study. The protocol compared the PK of SIM and ATR alone and following administration of 14 days of EFV. The non-steady state effects of SIM and ATR on EFV plasma PK were examined as well.

**Results:** EFV was very well tolerated in these subjects with very few dropouts or significant toxicities reported. EFV reduced SIM acid exposure (AUC 0-24hrs) by 58% from 36.5 to 14.5 ng<sup>2</sup>h/mL (medians, Wilcoxon signed rank,  $p = 0.003$ ; 90% CI of geometric mean ratio [GMR] 0.32-0.61). In addition, the AUC<sub>0-24hrs</sub> of the active HMG-CoA reductase inhibitory activity was reduced by 60% (medians,  $p = 0.0001$ , 90% CI of GMR 0.32-0.48). EFV reduced ATR exposure by 43% from 11.2 to 6.6 ng<sup>2</sup>h/mL (medians,  $p = 0.0002$ ; 90% CI of GMR 0.50-0.66). In addition, the total active ATR exposure (AUC<sub>0-24hrs</sub>) was reduced by 34.5% (medians,  $p = 0.0052$ , 90% CI of GMR 0.59-0.79), because EFV induces the metabolism of ATR active metabolites as well. Neither SIM nor ATR affected the non-steady state EFV concentrations.

**Conclusions:** These data suggest that EFV, when used with SIM or ATR therapeutically, can result in significant induction of their metabolism. The reduced inhibition of HMG-CoA reductase activity during co-administration of EFV may result in diminished antilipid efficacy at the usual doses of SIM and ATR. Some patients taking EFV may require titration to higher SIM and ATR doses to achieve target lipid goals, but this should only be attempted with increased monitoring for toxicity.

## INTRODUCTION:

The use of PIs and NNRTIs is associated with increased serum LDL-cholesterol (LDL-C), sometimes to levels mandating therapy for elevated serum LDL-C (1-3). The increase can sometimes be high enough to mandate therapy for elevated serum cholesterol. HMG-CoA reductase inhibitors (statins) are effective first-line therapy for elevations in LDL-C. Statins are lipophilic drugs that require hepatic metabolism to more water-soluble metabolites for eventual elimination. Simvastatin and atorvastatin utilize CYP3A4 for oxidative metabolism. Consequently there is considerable potential for drug-drug interaction with PIs (including CYP3A4) and NNRTIs (induce CYP3A4). We have previously shown that RTV/SQV greatly inhibits the metabolism of simvastatin and moderately inhibits that of atorvastatin (4). EFV is a mixed inducer/inhibitor of CYP3A4. In the PDR EFV is listed as contraindicated with astemizole, cisapride, midazolam, and ergots because of potential inhibition of metabolism via CYP3A4. In order to use simvastatin and atorvastatin safely with EFV, knowledge of the extent of drug-drug interaction is critical before concomitant use of these drugs can be recommended.

Simvastatin is a lactone prodrug which is converted by enzymatic (esterase) or chemical hydrolysis to the active HMG-CoA reductase inhibitor simvastatin acid. Both simvastatin and simvastatin acid undergo oxidative metabolism predominantly by CYP3A4 resulting in inactive lactone metabolites and their corresponding open acid forms, some of which are also active. These downstream active metabolites are also partially dependent on CYP3A4 for clearance. Simvastatin undergoes extensive first-pass metabolism in the intestine and liver and its oral bioavailability is low. Inhibitors of CYP3A4 can increase simvastatin acid levels and their co-administration with simvastatin has been associated with an increased risk of muscle toxicity (5,6). Atorvastatin is mainly metabolized by CYP3A4 with the generation of 2-OH and 4-OH metabolites which are equally active as the unchanged atorvastatin, as well as to inactive metabolites (7). Therefore, in order to establish the safe use of these statins with EFV, we evaluated the short-term effects of EFV on the metabolism of simvastatin and atorvastatin in HIV-seronegative volunteers.

## MATERIALS AND METHODS:

ACTG A5108 was a follow-up study to ACTG A5047 (4). In A5108 the primary objectives were to examine the effect of EFV on the PK of pravastatin, atorvastatin, and simvastatin and the effect of NFV on the PK of pravastatin. A secondary objective was to examine the effect of the statins on the non-steady state PK of EFV. The data presented here address the effect of EFV on the PK of simvastatin and atorvastatin. We have previously presented the effect of EFV and NFV on the PK of pravastatin (9). We studied healthy HIV-seronegative volunteers to avoid potential confounders from other co-morbidities and drugs used in the management of HIV disease. All subjects took both EFV and statins in the evening (see PK schema).

### Subject inclusion:

1. Absence of HIV-1 infection by ELISA within 21 days of entry
2. Normal blood hematology and chemistry values
3. Fasting serum triglycerides less than 400 mg/dL
4. CPK less than or equal to 4 x ULN
5. Age between 18-60 years
6. Ability and willingness to give written informed consent
7. Subject is within 30% of ideal body weight
8. All subjects of reproductive potential agreed not to participate in a conception process

(Female subjects of reproductive potential were not included in the EFV arms of the study)

### Subject exclusion:

1. History of any active medical illness
2. Pregnancy
3. Use of any prescription or OTC drugs except for ASA, acetaminophen, diphenhydramine, multivitamins, hormonal replacements
4. Active alcohol and illicit drug use

## OTHER ASSESSMENTS

1. Adherence measures using questionnaires and pill counts
2. Throughout the study, history and physical exam were conducted and blood chemistries and hematology were monitored; all grades of toxicities were recorded

## CRITERIA FOR TREATMENT DISCONTINUATION

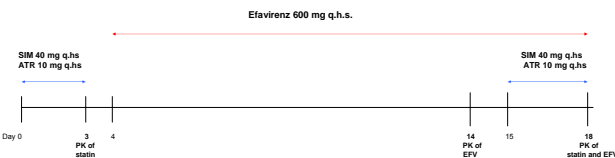
1. Drug-related toxicity (any grade 2 or above)
2. Requirement and use of prohibited concomitant medication
3. Non-adherence to study medications and visits
4. Pregnancy
5. Request of the subject to withdraw
6. Request by primary care provider or study coordinator that the study is not in the best interest of the subject

## STATISTICAL CONSIDERATIONS AND ANALYSIS

A priori sample size calculation was based on a within-subject coefficient of variation of simvastatin and atorvastatin AUC of 37% (based on data obtained from BMS). A sample size of 12 would allow detection of a decrease in statin AUC of 38% or an increase of 60%. The accrual target was 14 in each arm to ensure that at least 12 subjects had evaluable data.

Atorvastatin and metabolites plasma concentrations were determined at Advion BioSciences, Inc. (Ithaca, New York) using a validated LC/MS/MS technique with deuterated internal standards and LLQ of 0.1 ng/mL. Simvastatin and active metabolite plasma concentrations were measured at Merck & Co using LC/MS/MS with LLQ of 0.05 ng/mL. In addition plasma HMG-CoA reductase activity inhibition was measured using EIA since not all active metabolites are captured by the LC/MS/MS assay. LLQ for active and total inhibitors was 2.0 ng-eq/mL. EFV plasma concentration were determined at the U. of Alabama, Birmingham Pharmacology Support Laboratory using a validated HPLC separation with UV detection and LLQ of 50 ng/mL. Individual subject concentration-time profiles were analyzed using standard noncompartmental techniques to calculate AUC and C<sub>max</sub>. AUCs before and after EFV intervention and the differences were compared using a Wilcoxon Signed Rank test.

## PK schema for EFV – simvastatin and EFV – atorvastatin interaction



PK consisted of blood draws at times 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours after drug administration

## RESULTS:

A total of 14 evaluable subjects were included in each arm of this study. The demographics were similar for the arms in that the median age was 38 years for the SIM arm and 32 for the ATR arm. By far the majority of subjects were male (86%, 93%, respectively). Also 57% of the subjects in each group were White, Non-Hispanic. In general the study drugs were well tolerated. The overall adherence to the medications was measured to be excellent with the majority demonstrating 100% adherence. Only one subject in the ATR arm developed grade 2 CPK elevation and no subject in the SIM arm had drug-induced CPK elevation requiring protocol-defined drop-out. One subject in the SIM arm dropped out because of grade 2 sleeplessness and diarrhea. The vast majority of subjects continued with both the statins and EFV without any significant toxicity. There were two drop-outs unrelated to drug therapy.

The effect of EFV on the PK of SIM and ATR is shown in the table and the two figures. EFV was a potent inducer of SIM metabolism in that the overall decrease in plasma exposure of either simvastatin acid or total active HMG-CoA reductase inhibition was ~60%. The effect on ATR was slightly less in that the decrease for total active ATR (ATR + 2 active metabolites) was 34.5%. All these changes were statistically significant. We also evaluated the non-steady state change in EFV exposure by the statins and did not demonstrate any change. However EFV has a long plasma half-life and 3 days of ATR may not have been long enough to demonstrate a significant PK change of EFV by statins if the effect was minor.

Table 1. AUC<sub>0-24hrs</sub> of statins at baseline (day 3) and after EFV (day 16) [AUC for simvastatin acid, atorvastatin, and total atorvastatin is expressed as ng<sup>2</sup>h/mL, while for active HMG-CoA reductase inhibition was as ng<sup>2</sup>h/mL]

	Mean (±SD)	Median (range)	Median % change	90% CI around geometric mean ratio	p
Simvastatin acid – day 3	35.2(22.2)	36.5(14.9, 69.2)	-58	(0.32, 0.61)	
Simvastatin acid – day 16	17.9(19.3)	14.5(2.1, 76.7)			
Active HMG-CoA reductase inhib- day 3	157 (96.3)	136.9 (52.5, 388.9)	-60.2	(0.32, 0.48)	$p = 0.0031^*$
Active HMG-CoA reductase inhib- day 16	65.6 (54.6)	45.7 (24, 228.8)			$p = 0.0001^*$
Atorvastatin – day 3	15.9 (15.1)	11.2 (6.9, 66.3)	-42.7	(0.50, 0.66)	
Atorvastatin – day 16	8.5 (4.9)	6.6 (3.7, 21.3)			$p = 0.0002^*$
Total active atorvastatin – day 3	36.4 (25.3)	28.1 (17.8, 116.8)	-34.5	(0.59, 0.79)	
Total active atorvastatin – day 16	23.6 (10.4)	21.4 (12.9, 47.0)			$p = 0.0052^*$

\* = statistical comparison of the AUC on day 3 to day 16 was performed using Wilcoxon signed rank test.

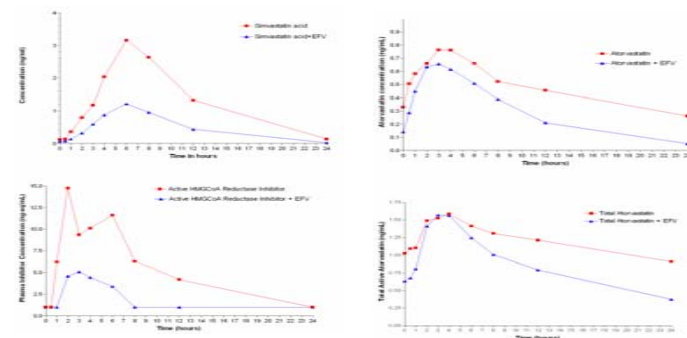


Figure 1: The effect of EFV on the pharmacokinetics of simvastatin acid (top) and active HMG-CoA reductase inhibitor in plasma (bottom). The data are the median values in the two periods. These changes are significant ( $p < 0.005$  for both).

Figure 2: The effect of EFV on the pharmacokinetics of atorvastatin (top) and total atorvastatin (ATR + 2 active metabolites) (bottom). The data are the median values in the two periods. The changes are significant ( $p < 0.05$  for both).

## DISCUSSION:

EFV is one of the most effective drugs in the treatment of HIV infection and is the most commonly used in clinical settings. EFV use has been associated with elevation in LDL-C, which may result in the need for statin therapy. Our study in HIV-seronegative volunteers investigated the PK interaction between EFV and both simvastatin and atorvastatin. Our data demonstrated that EFV is a very potent inducer of simvastatin metabolism and a less potent inducer of atorvastatin metabolism. These data suggest the EFV in vivo is not an inhibitor of CYP3A4 but a potent inducer as the effect on simvastatin would indicate. The induction of metabolism of statins by EFV is similar in magnitude to the effect of EFV on PK of HIV-PIs. Although the effect of EFV on simvastatin PK is not as great as described for rifampin (8), it is of sufficient magnitude to consider whether the antilipid activity may be compromised to the point that higher doses should be considered if the cholesterol-lowering response is not adequate with the usual doses. However further evaluation is necessary to determine the proper dosage to achieve the desired antilipid activity without added toxicity. The same concern can also be for atorvastatin although the overall induction of drug metabolism was approximately half of what was observed with simvastatin. One of the interesting aspects of this study in healthy seronegative volunteers is the excellent tolerability of EFV despite being administered for 10 days. The overall conclusion of this study is that both simvastatin and atorvastatin metabolism is induced by EFV, similar to what we previously described for pravastatin (9), and this induction of metabolism may result in suboptimal response to statin therapy. However, this needs to be scrutinized in other clinical trials.

## CONCLUSIONS:

- EFV induces the metabolism of simvastatin as demonstrated by the ~60% reduction in plasma exposure of simvastatin acid and active HMG-CoA reductase inhibitors (Figure 1)
- EFV induces the metabolism of atorvastatin by 43% as well as the total active atorvastatin (atorvastatin + active metabolites) by 34.5% (Figure 2)
- Neither simvastatin nor atorvastatin appear to affect the plasma PK of EFV, and this was evaluated under non-steady state conditions
- EFV, simvastatin, and atorvastatin were very well tolerated in these healthy seronegative volunteers and there were very few drop-outs for protocol-defined toxicities
- The induction of statin metabolism by EFV may affect the overall antilipid response during therapy but any dose escalation will require increased monitoring for toxicity and efficacy

## REFERENCES:

1. Muller R, Grollman C, Tai VW, Alger H, Peng M, Chernoff D, et al. Hyperlipidemia and insulin resistance are both induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr* 23:343-344, 2000.
2. Behrens G, et al. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* 13:1663-1670, 1999.
3. Van Leth F, Phairhak P, Gazzard B, et al. Lipid changes in a randomized comparative trial of first-line antiretroviral therapy with regimens containing either Nevirapine alone, Efavirenz alone or both drugs combined, together with zidovudine and lamivudine (ZDV Study). *9th CROI*, Feb 10-14, 2003, Boston, MA, USA, abstract 752.
4. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, Segal Y, Aberg JA, Bianchi F, Alston B, Fung F, Knott B, Awofola F. NAID AIDS Clinical Trials Group. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 16(4):569-77, 2002.
5. Vickers S, Duncan CA, Vass KP, et al. In vitro and in vivo biotransformation of simvastatin, an inhibitor of HMG-CoA reductase. *Drug Metab Dispos* 18:476-83, 1990.
6. Schwanninger-Schwarz D, Ballestrin R, Gasser R, et al. Biotransformation due to interaction of simvastatin with mifepristone. *Lancet* 351:1929-30, 1998.
7. Malhotra HS, Gou KL. Atorvastatin: An updated review of its pharmacological properties and use in dyslipidaemia. *Drugs* 61:1835-81, 2001.
8. Rytland C, Backman JT, Kyvijo KT, et al. Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 68:592-7, 2000.
9. Gerber JG, Rosenkranz S, Fichtenbaum CJ, et al. The effect of efavirenz and nevirapine on the pharmacokinetics of pravastatin. The SP-1AAS Conference on HIV Pathogenesis and Treatment, July 13-16, 2003, Paris, France, abstract 870.

ACKNOWLEDGEMENTS AND CONTACT INFORMATION: This research was supported by grants from the National Institute of Allergy and Infectious Diseases - Adult AIDS Clinical Trials Group (U01 AI58358), Merck & Co, Inc. Bristol-Myers Squibb Company, Pfizer Pharmaceuticals, Inc., Dupont Pharmaceuticals Company.

Contact: John G. Gerber, MD e-mail: John.Gerber@UCHSC.edu