THE EFFECT OF BETA-CAROTENE ON THE STEADY-STATE PHARMACOKINETICS OF NELFINAVIR AND ITS M8 METABOLITE

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INTRODUCTION

❖ Natural health products (NHP) are widely used by HIV – infected individuals but little is known on the risk of drug-NHP interactions.

❖ Carotene deficiency is common in all stages of HIV infection and *in vitro* and *in vivo* studies have shown that beta-carotene may modulate immune fonction.

❖ *In vitro* studies have also shown that beta-carotene inhibits CYP2C9, CYP2C19, and CYP3A4. Other *in vitro* studies have shown that beta-carotene activates the pregnane X receptor, inducing CYP2B6, CYP3A4 and p-glycoprotein. *In vivo* studies are lacking.

❖ Thus, we hypothesized that beta-carotene may influence the plasma concentrations of nelfinavir (NLF) and its active metabolite M8 as NLF is metabolized by CYP2C19 to M8 which is subsequently metabolized by CYP3A4.

OBJECTIVE

Investigate the effect of beta-carotene supplementation (25 000 IU twice daily) on the steady-state pharmacokinetics of NLF and its active metabolite M8 in HIV-1 infected patients.

METHODS

A steady-state pharmacokinetic study was conducted at the Ottawa Hospital and the Montréal Chest Institute. Ethics approvals from the Institutional Review Boards were obtained prior to starting the study.

Study population

Inclusion criteria:

❖ HIV-1+, age ≥18 years, signed written informed consent

❖ Vital signs, physical exam, and laboratory measurements showed no sign of acute illness, including AIDS-defining illness

❖ All natural health products discontinued at least 2 weeks prior to pharmacokinetic analysis

❖ Receiving NLF 1250 mg twice daily with food + 2 NRTIs for more than 2 weeks

Exclusion criteria:

❖ Pregnant or breastfeeding

❖ Cigarette smoker

❖ History of acute or chronic renal, liver or pancreatic disease

❖Malignancy

❖ Concomitant drugs known to induce or inhibit NLF or M8 metabolism.

Treatments

Beta-carotene 25 000 IU twice daily + NLF 1250 mg twice daily with food for 28 days + 2 NRTIs

12 hour pharmacokinetic sampling

Day 1 (prior to start of beta-carotene) and Day 28

- On PK days, NLF given with standardized breakfast (625 cal, 42% fat)
- PK samples: pre-NLF and at 1,2,3,4,5,6,8,10 and 12 hours post-dose

Other tests: $CD4^+$, viral load, biochemistry, complete blood count, carotene level, and carotene content of capsules.

NLF and M8 concentrations were measured with a sensitive and selective, validated LC-MS/MS assay. Pharmacokinetic analysis was done with non-compartmental methods using WinNonLin Pro Version 4.0 (Pharsight Corporation, NC).

Geometric mean ratios (95% confidence intervals) are presented. Two-tailed paired sample T-tests were used for comparison of means.

RESULTS

The results for the first 9 participants are presented. 12 participants in all will be recruited for this study.

Table 1: Baseline demographics (n = 9)

Demographics	N = 9
Age (years) (mean ± SD, range)	46.8 ± 7.2 (35-55)
% male	88.9
% caucasian	66.7
% black	33.3
Weight (kg) (mean ± SD, range)	79.6 ± 15.5 (52.2-102)
BMI (kg/m^2) (mean ± SD, range)	27.0 ± 3.9 (18.1-30.8)
% Viral load < 50 copies/mL	88.9
$CD4^+$ ($cell/mm^3$) (mean ± SD, range)	646.8 ± 238.6 (361-947)

Figure 1: Median NLF concentrations (mg/L) prior to and after 28 days of beta-carotene (n=9)

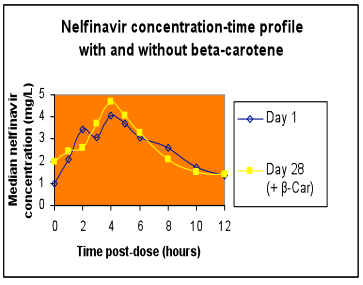

Figure 2: Median M8 concentrations (mg/L) prior to and after 28 days of beta-carotene (n=9)

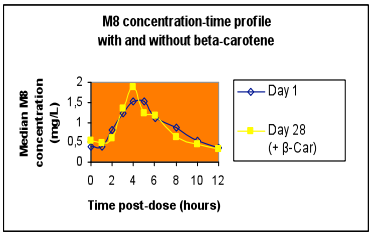

Table 2: Steady-state pharmacokinetics of NLF and M8 before and after 28 days of beta-carotene (n=9)

	Geometric mean Day 1	Geometric mean Day 28 (+ β-Car)	Geometric mean ratio D28:D1 (95% CI)	p*
Nelfinavir				
Cmax (mg/L)	4.31	4.54	1.05 (0.93,1.20)	.43
Tmax (h)	3.34	4.46	1.33 (0.85,2.10)	.22
C_{12} (mg/L)	1.22	1.22	1.00 (0.62,1.60)	1.0
$AUC_{0\text{-}12}$(mg.h/L)	3039	30.06	0.99 (0.85,1.16)	.83
$T_{½}$ (h)	4.10	4.13	1.01 (0.80,1.27)	.88
CL/F (L/h)	41.14	41.58	1.01 (0.87,1.18)	.95
Vd/F (L)	243.01	24764	1.02 (0.79,1.32)	.58
M8				
Cmax (mg/L)	1.71	1.75	1.02 (0.80,1.30)	.62
Tmax (h)	4.04	4.81	1.19 (0.81,1.75)	.31
C_{12} (mg/L)	0.32	0.34	1.09 (0.64,1.86)	.92
$AUC_{0\text{-}12}$(mg.h/L)	10.22	10.15	0.99 (0.79,1.24)	.56
$T_{½}$ (h)	2.77	3.16	1.14 (0.86,1.52)	.32
M8 / NLF ratio $AUC_{0\text{-}12}$	0.34	0.34	1.00 (0.88,1.15)	.65

* significance if $p < 0.05$

A mean increase in $CD4^+$ count of 81 $cells/mm^3$ was seen at day 28, but this difference was not significant (p=0.11). Beta-carotene was well tolerated.

Pharmaceutical analysis of the beta-carotene supplements confirmed the content of the capsules (mean 97.8% beta-carotene) during the study period.

CONCLUSIONS

❖ Beta-carotene does not significantly alter the steady-state pharmacokinetics of NLF and M8. A trend suggests that beta-carotene delays NLF absorption.

❖ Thus, beta-carotene does not appear to influence significantly CYP2C19 and CYP3A4 – mediated metabolism of NLF and M8 *in vivo*.

❖ Concomitant use of beta-carotene with nelfinavir appears safe.

❖ A greater number of participants (n=12) are needed to confirm these results.

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