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 function.
- 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 CYP3A4.

OBJECTIVE

Investigate the effect of beta-carotene supplementation on 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.

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)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N = 9</th>
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<tbody>
<tr>
<td>Age (years) (mean ± SD, range)</td>
<td>46.8 ± 7.2 (35-55)</td>
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<tr>
<td>% male</td>
<td>88.9</td>
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<tr>
<td>% caucasian</td>
<td>66.7</td>
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<tr>
<td>Weight (kg) (mean ± SD, range)</td>
<td>79.6 ± 15.5 (52.2-102)</td>
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<tr>
<td>BMI (kg/m²) (mean ± SD, range)</td>
<td>27.0 ± 3.9 (18.1-30.8)</td>
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<tr>
<td>% Viral load ≤ 50 copies/mL</td>
<td>88.9</td>
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<tr>
<td>CD4+ (cell/µL) (mean ± SD, range)</td>
<td>646.8 ± 238.6 (361-947)</td>
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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)

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 CYP2C9 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.

Acknowledgements

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