

# Low omega-3 index in erythrocytes is a risk factor for progression of atherosclerosis in people living with HIV

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HIV and Co-morbidities

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**CHANGING THE COURSE** OF THE  
**HIV PREVENTION, ENGAGEMENT** AND  
**TREATMENT CASCADE**

# Disclosures

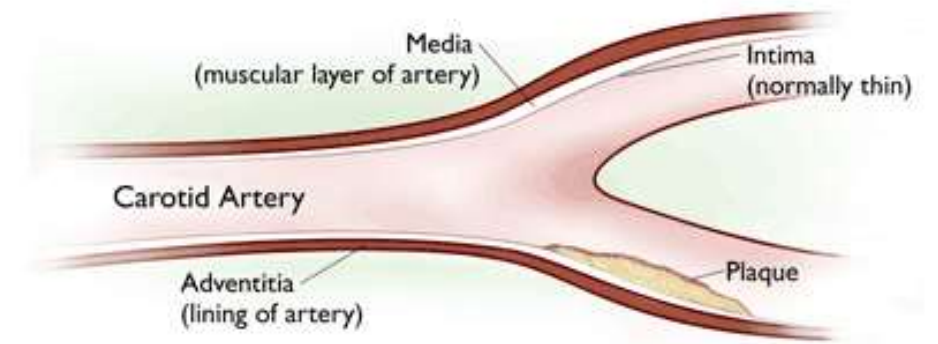
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# Cardiovascular disease risk in HIV

- HIV infection is associated with increased risk of CVD
  - surrogate markers
    - **carotid intima media thickness (CIMT)**
    - arterial stiffness, endothelial dysfunction, platelet function
  - cardiovascular events
- CVD is one of the leading causes of death in PLHIV
  - relevance ↑ in aging population



van Vonderen et al. *JAIDS* 2009;50:153–61; Hulten et al. *Heart* 2009;95:1826–35; Oliviero et al. *Atherosclerosis* 2009;204:586–9; Varriale et al. *Am Heart J* 2004;147:55–9; Obel et al. *Clin Infect Dis* 2007;44:1625–31; Satchell et al. *AIDS* 2010;24(5):649–57; Hsue et al. *J Am Heart Assoc* 2012;1: jah3-e000422, Tsien et al. *J Am Coll Cardiol* 2012;59(21):1891–6;  
Image: [www.preventionhealthscreenings.com/portfolio-item/carotid-intima-media-thickness-test/](http://www.preventionhealthscreenings.com/portfolio-item/carotid-intima-media-thickness-test/)

# Risk factors for CVD in PLHIV

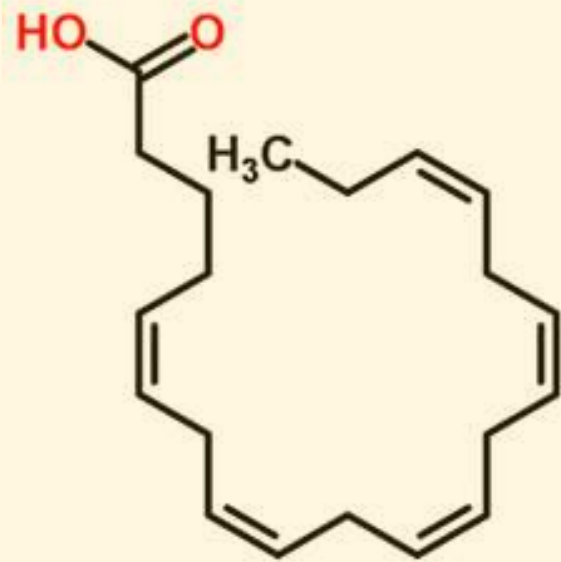
- Classic risk factors

- Age
- Metabolic parameters
  - dyslipidemia, diabetes, hypertension
- Genetic predisposition
  - family history, gender, ethnicity
- Lifestyle
  - diet, exercise, alcohol & drug use

- HIV specific factors

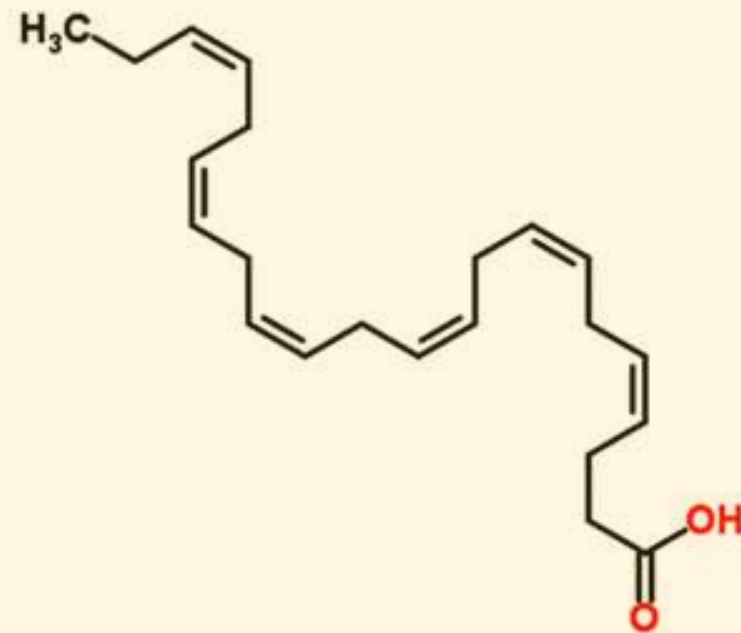
- Viral infection
- Immune activation
- Chronic inflammation
- Side effects of antiretroviral therapy

# Omega-3 polyunsaturated fatty acids (PUFA)



**EPA 20:5n3**

Eicosapentaenoic acid



**DHA 22:6n3**

Docosahexaenoic acid

## Biological role

- important structural components of cell membranes
- production of anti-inflammatory mediators



# Omega-3 PUFA and CVD

## Beneficial effects of omega-3 PUFA

- reduce triglyceride and cholesterol
- reduce insulin resistance
- anti-coagulation
- anti-inflammatory effects

## Effect on CVD surrogate markers

- Carotid intima media thickness (CIMT)
- endothelial function
- platelet activation & aggregation

## Effective protection from cardiac events?

- Controversial findings
- Fish consumption might be more beneficial than supplementation

He et al. *Circulation* 2004, 109:2705-11; Chowdhury et al *BMJ* 2012;345:e6698; Djousse et al. *Clin Nutr* 2012;31:846-53; Rizos et al. *JAMA* 2012;308:1024-33; [no authors listed] *Prescrire Int* 2013;22:218; Gao et al. *Atherosclerosis* 2013;226:328-34; He et al. *Can J Cardiol* 2013;29:196-203; Larsson et al. *Eur J Epidemiol* 2012;27:895-901; Lorente-Cebrian et al. *J Physiol Biochem* 2013;69:633-51; Mariani et al. *J Am Heart Assoc* 2013;2:e005033; McEwen et al. *Semin Thromb Hemost* 2013 Feb;39(1):25-32

# Objectives

- To assess in PLHIV
  - red blood cell (RBC) omega-3 content, which reflects dietary intake of omega-3 PUFA
  - progression of carotid intima media thickness (CIMT), a marker of atherosclerosis

# Hypothesis

- Low RBC omega-3 content is associated with enhanced progression of CIMT over time

# Study design

- Prospective cohort study
- Sub-study of the Canadian HIV Vascular Study following 300 PLHIV for a period of five years
- Patients had yearly follow up to measure CIMT
- Erythrocyte samples were taken at one time point during the follow-up period

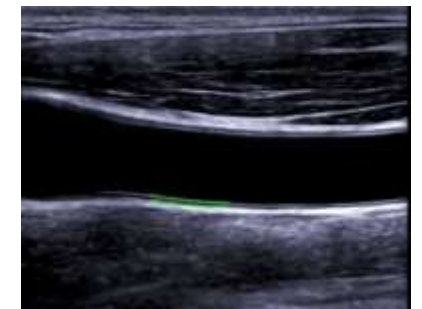


# Participants

- Inclusion criteria
  - HIV infected out-patients
  - male, female, transgender
  - age at study entry >35 years
  - participating in the Canadian HIV vascular study
- Exclusion criteria
  - less than two CIMT measurements during the study period
  - no blood sample available for RBC collection

# Measurements

- Clinical assessments (yearly)
  - clinical risk factors for CVD (age, sex, ethnicity, obesity, smoking,...)
  - fasting lipids and glucose
  - immune and viral status
  - medication exposure, .....
  
- CIMT (yearly)
  - Twelve-segment mean maximal CIMT by high-resolution carotid artery ultrasound
  - Mean yearly change in CIMT (dCIMT) was calculated



# Measurements

- RBC omega-3
  - Total lipids extracted from RBC
  - Gas chromatography (62 fatty acids from C14:0 to C22:6n3)
  - Omega-3 index = EPA + DHA (in % of total fatty acids)



# Statistics

- t-test, Wilcoxon test, Spearman correlations
- Regression models
- SPSS v. 20 (IBM, Armonk, NY) and SAS Enterprise Guide 4.3 (SAS Institute, Cary, NC)
- $p < 0.05$  statistically significant

# Clinical characteristics

Characteristic	Value
n	69
Age, y	49.4 ± 8.8
Male, % (n)	88.4% (61)
Current smokers, % (n)	30.4% (21)
Previous smokers, % (n)	36.2% (25)

Values are mean ± SD, median (range)  
or % of participants

Characteristic	Value
Body mass index, <i>kg/m<sup>2</sup></i>	25.0 ± 4.2
Overweight (BMI 25-29.99)	40.0% (26/65)
Obese (BMI ≥ 30)	9.2% (6/65)
Waist circumference, <i>cm</i>	90.7 ± 12.6
Central obesity (men >102 cm, w >88 cm)	17.8% (8/45)

# Clinical characteristics

Characteristic	Reference Range	Value
Systolic BP, <i>mmHg</i>	< 120	125 ± 17.3
Diastolic, <i>mmHg</i>	< 80	80.1 ± 10.8
Fasting glucose, <i>mmol/L</i>	3.8-6.0	5.30 (2.10-8.10)
Total cholesterol, <i>mmol/L</i>	<5.5	4.86 (2.59-8.43)
LDL cholesterol, <i>mmol/L</i>	<3.3	2.61 ± 1.00
HDL cholesterol, <i>mmol/L</i>	>0.9	1.19 (0.47-3.02)
Triglycerides, <i>mmol/L</i>	<2.0	1.96 (0.57-8.26)

Characteristic	Value
Diabetes, % ( <i>n/n</i> )	2.9% (2/69)
Hypertension, % ( <i>n/n</i> )	31.9% (22/69)
Lipid drugs, % ( <i>n/n</i> )	
Fibrates	10% (7/69)
Statins	20% (14/69)
Framingham CVD Risk	
Low (<10%)	56.5% (39/69)
Intermediate (10-20%)	31.9% (22/69)
High (≥ 20%)	11.6% (8/69)

Values are mean ± SD, median (range) or % of participants

# HIV specific data

Characteristic	Value
n	69
HIV Risk factor	
MSM	64.7% (44/68)
Bi/heterosexual	22.1% (15/68)
IV drug use	5.9% (4/68)
Other	13.2% (9/68)
Peak viral load, <i>log<sub>10</sub> copies/mL</i>	4.99 (1.81-6.15)
CD4 count, <i>cells/mm<sup>3</sup></i>	
Baseline	650 (100-1,520)
Nadir	150 (10-990)

ART exposure	% of patients (n)	
	current	ever
Protease Inhibitors		
Lopinavir (LPV)	20% (14)	26% (17)
Atazanavir (ATV)	10% (7)	10% (7)
NNRTI		
Efavirenz (EFV)	39% (27)	57% (39)
Nevirapine (NVP)	9% (6)	10% (7)
NRTI		
Abacavir (ABC)	39% (27)	49% (34)
Zidovudine (AZT)	25% (17)	58% (40)
Stavudine (d4T)	6% (4)	41% (28)
Tenofovir (TNF)	29% (20)	38% (26)

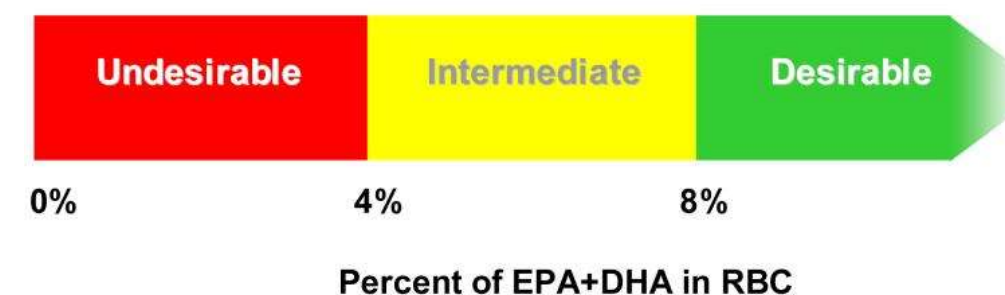
Values are median (range) or % of participants

# Omega-3 index and CIMT

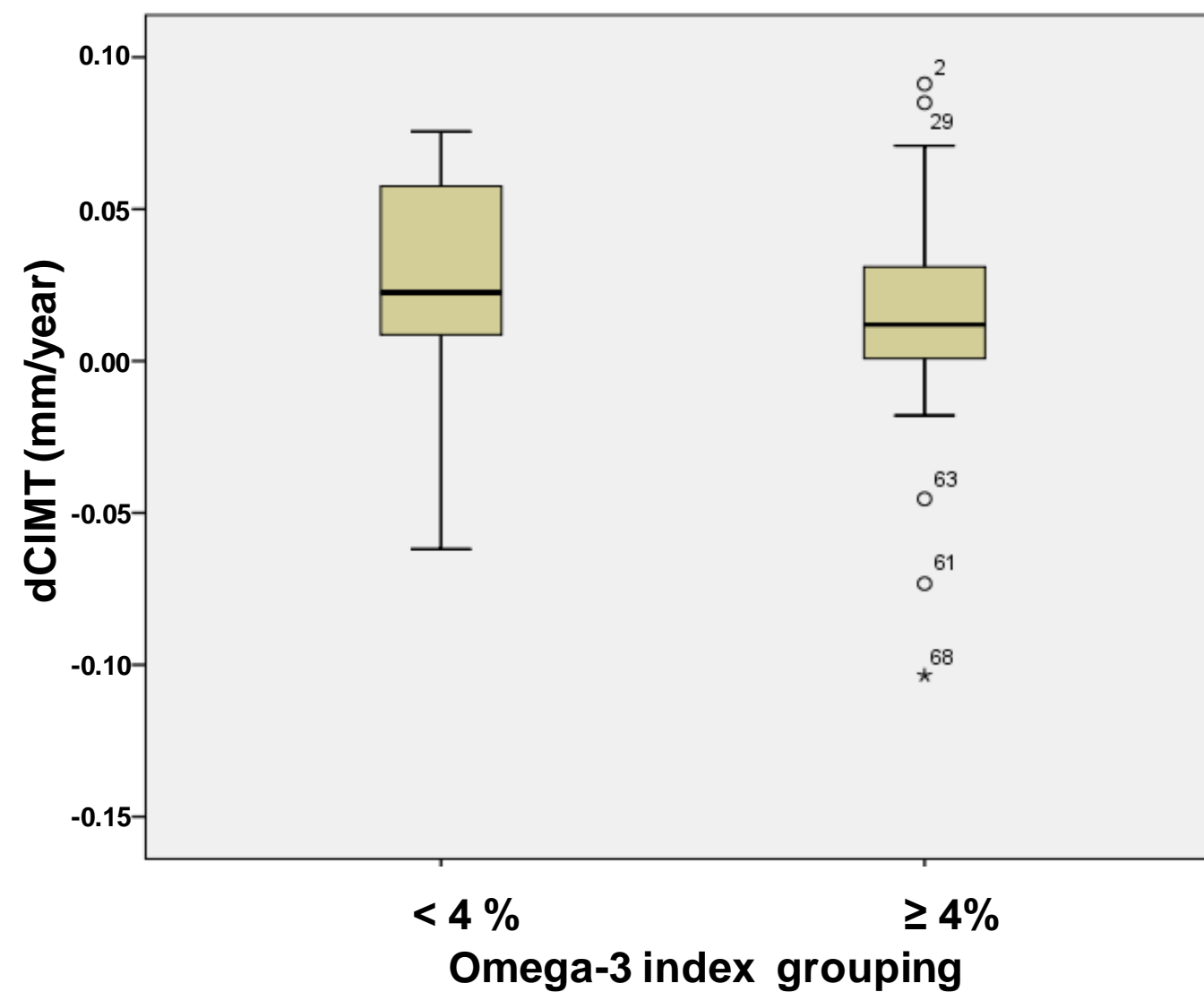
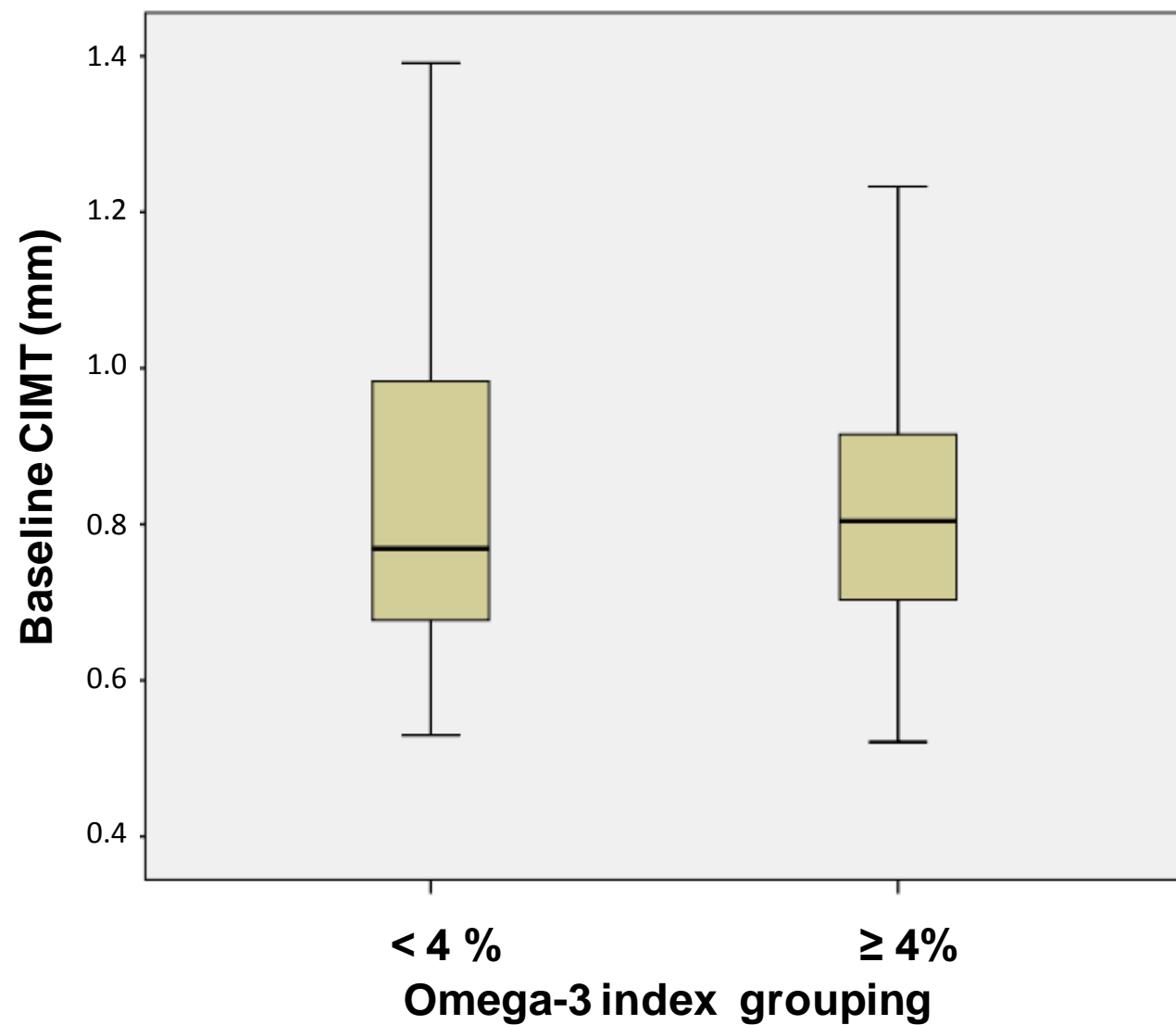
Parameter	Value
n	69
Omega-3 index, % of total lipids	4.4 (2.7-8.1) %
Omega-3 index, % (n)	
Low (<4%)	49.3% (34)
Intermediate (4-8%)	46.4% (32)
Desirable (>8%)	4.3% (3)
CIMT at baseline, mm	0.82 ± 0.19
Change in CIMT, mm/year	0.018 ± 0.036

Values are mean ± SD, median (range) or % of participants

Proposed Risk Zones for the Omega-3 Index



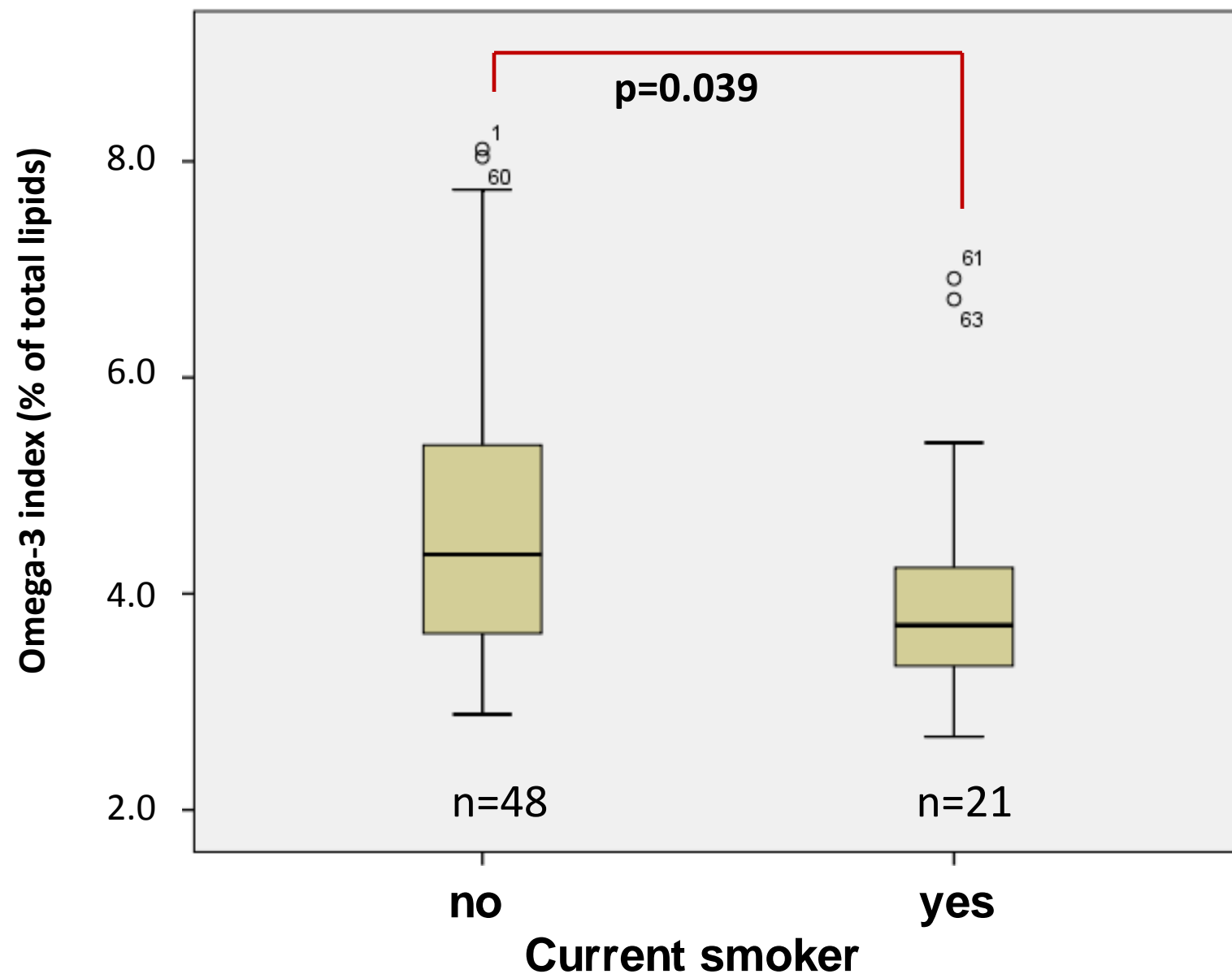
# CIMT by RBC omega-3 index



**No significant difference between the groups**



# Omega-3 index and risk factors for atherosclerosis



Lower erythrocyte omega-3 index in current smokers vs. non-smokers (Wilcoxon test)

Omega-3 index was

- not different between men and women
- not correlated with age, or other risk factors for CVD

# Regression analysis

Model		Unstandardized coefficient B	p-value
1	(Constant)	0.028	0.000
	<b>Omega-3 index &lt;4%</b>	<b>0.007</b>	<b>0.026</b>
2	(Constant)	0.026	0.000
	<b>Omega-3 index &lt;4%</b>	<b>0.008</b>	<b>0.017</b>
	Framingham Risk Score	0.021	0.267

Cases were weighted by years of follow-up

# Summary

- 49% of the study participants had low RBC omega-3 index
- Omega-3 was lower in smokers but not associated with other CVD risk factors
- No significant difference in CIMT or dCIMT between patients with omega-3 index  $<4\%$  and those with  $\geq 4\%$
- Regression model
  - low omega-3 index was associated with faster progression of CIMT over time
  - association persisted after adjusting for the Framingham risk score

## Conclusion

- ❑ Low RBC omega-3 index is a risk factor for faster progression of CIMT and therefore of atherosclerosis in PLHIV even when correcting for Framingham risk score**
- ❑ Similar to the general population, increased intake of omega-3 PUFA might be a way to reduce CVD risk in PLHIV**
- ❑ This requires further investigation**

# Thank you!

- Marek Smieja and all other investigators of the Canadian HIV Vascular Study
- All study participants
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Gilead Sciences Canada