

on the response to vitamin D supplementation in HIV-positive patients

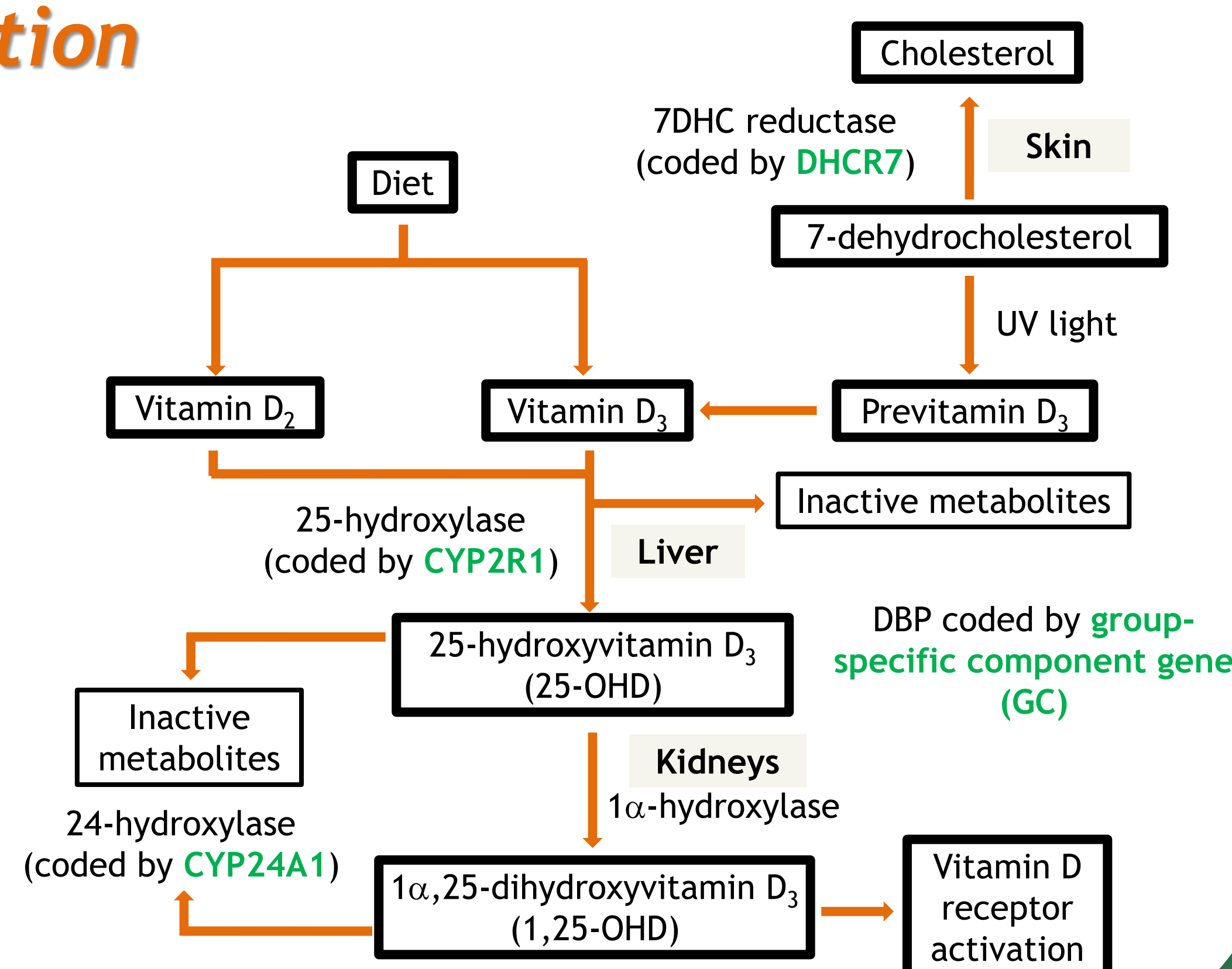
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Introduction

- Bioactivation of vitamin D into 1,25-OHD is regulated by several polymorphic enzymes; vitamin D forms (D₂ and D₃) and metabolites are transported in blood by vitamin D binding protein (DBP).
- Vitamin D insufficiency: [25-OHD] < 30 ng/ml.
- HIV-positive patients have a higher risk of developing vitamin D insufficiency and are supplemented with vitamin D.
- Risk factors for vitamin D insufficiency: season and latitude, skin type, obesity, smoking, genetic factors and antiretroviral therapies (ART).



Objectives

- To characterize the 25-OHD concentration-time profile in HIV patients before and after vitamin D supplementation.
- To test the influence of genetic polymorphism, ART and non-genetic factors on 25-OHD levels.
- To establish the best vitamin D supplementation regimen for HIV-positive patients.

Methods

Data

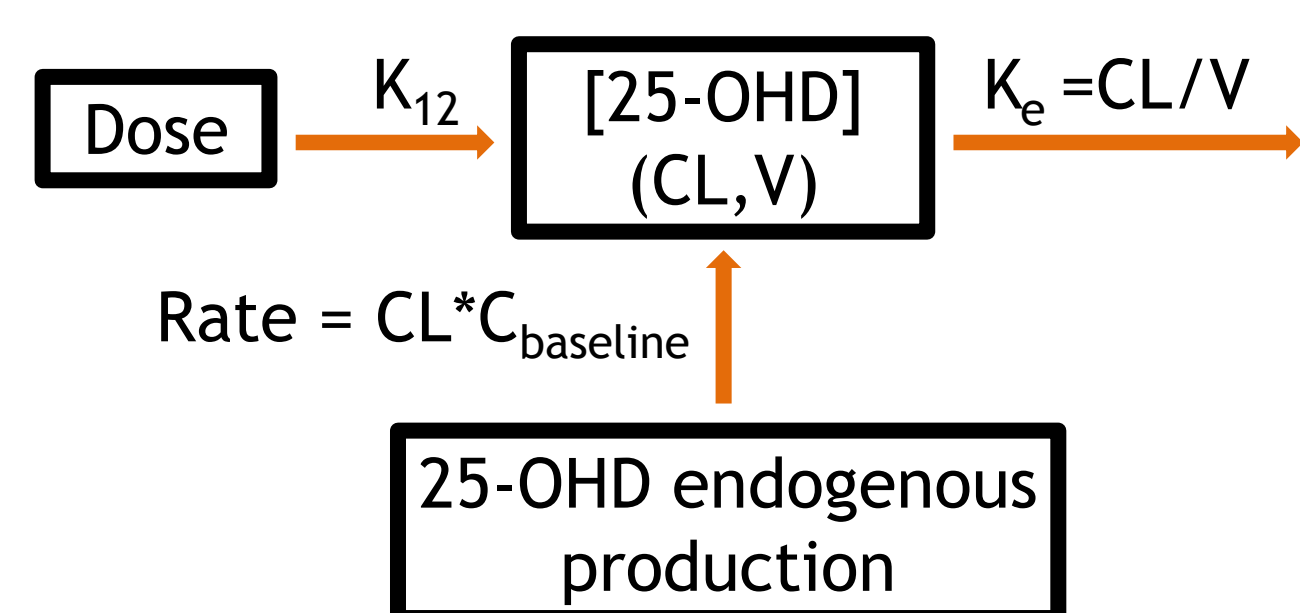
- 1285 25-OHD concentrations before or after a vitamin D single oral dose (300000 IU most often) were obtained from 618 HIV-positive Caucasian patients in three centers in Switzerland (Basel, Bern, Lausanne).

Covariates

- Demographic and environmental characteristics: gender, age, body mass index (BMI), smoking status.
- Comedications: ART drugs.
- Genetic polymorphisms: rs2282679 and rs7041 (located on GC), rs3829251 and rs12785878 (on DHCR7), rs12794714 and rs10741657 (on CYP2R1), rs6013897 (on CYP24A1).

Data analysis

- One-compartment model with first-order absorption and elimination with endogenous production of 25-OHD (NONMEM®).
- Absorption/metabolism (K₁₂) and elimination (K_e) rate constants were set to be equal (equilibrium condition).



$$\frac{d[25\text{-OHD}]}{dt} = K_{12}[\text{vitD}] - K_e[25\text{-OHD}] \quad \text{with } [25\text{-OHD}]_{t=0} = C_{\text{baseline}}$$

- Interpatient variability (IIV) was associated to C_{baseline} only.

Covariates analyses

- Linear models were used for demographic covariates (centered on their median value) and comedications (coded as 0 or 1).
- To assess genetic impact on C_{baseline} a fixed effect was associated to each genotypic group: homozygous reference (Hom-Ref), heterozygous (Het-LOF) and homozygous (Hom-LOF) loss of function alleles.

- Cosine model was employed to depict the season effect:

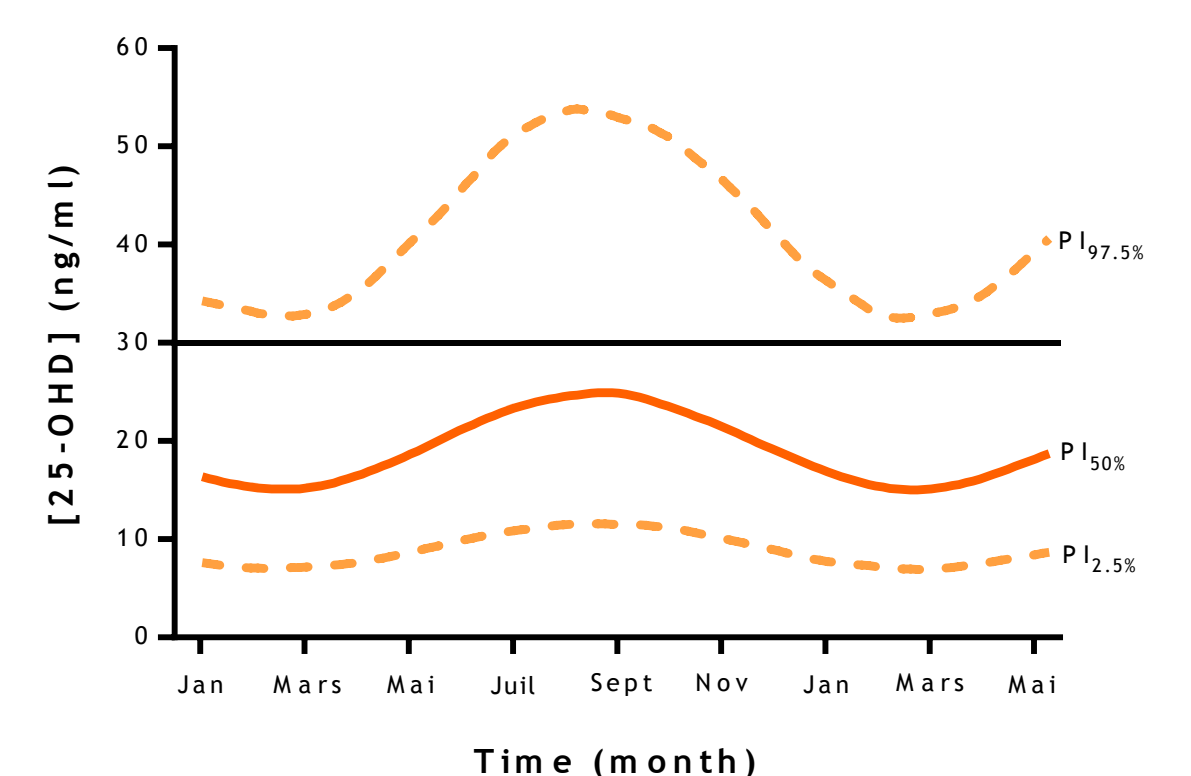
$$C_{\text{baseline}} = \text{TVC}_{\text{baseline}} * \left(1 + \text{AMP} * \cos \left(2\pi \frac{\text{DAY} - \text{T}_{\text{peak}}}{365} \right) \right)$$

Simulations

- Minimal and maximal [25-OHD] for various dosage regimens were derived by Monte Carlo simulations using 1000 individuals.

Results

- Season had the most salient impact on C_{baseline}.
- C_{baseline} was also affected by BMI, smoking status, study center (Basel and Lausanne vs Berne), rs2282679 (Hom-Ref and Het-LOF vs Hom-LOF) and darunavir (DRV) administration.
- Efavirenz (EFV) was not found to be associated to 25-OHD pharmacokinetics.

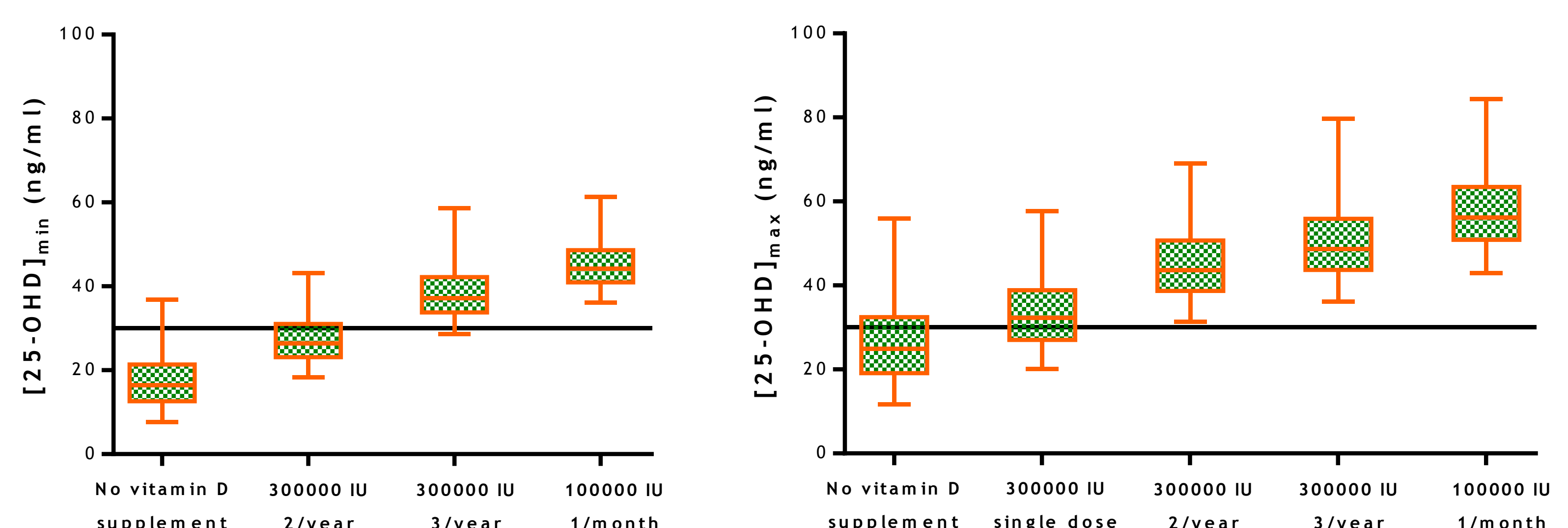


Natural seasonal variation of 25-OHD levels

Parameter	Population mean			
	Estimate	SE(%)	IIV(%)	SE(%)
CL (L/day)	2.66	6		
V _c (L)	259	6		
C _{baseline} (ng/ml)	19.9	3	39	29
AMP	0.25	6		
T _{peak} (day)	228	2		
θ _{BMI}	-41	19		
θ _{SMOKE}	-13	22		
θ _{rs382679,LOF}	-20	33		
θ _{DRV}	16	36		
θ _{BE}	-36	10		

θ_x: effect of the X covariate on C_{baseline} expressed as (1 + θ_x * X)

- [25-OHD] > 30 ng/ml over a year is predicted after administration of a single oral vitamin D dose of 300000 IU 3 times per year or 100000 IU once per month*.



[25-OHD]_{min} (left panel) and [25-OHD]_{max} (right panel) for various dosage regimens over a year. Only seasonal variation was included in the model.

* Proposed by F. Foissac et al., Br J Clin Pharmacol, 2013, 75, 1312.

Conclusions

- Low baseline 25-OHD concentrations were observed in this HIV population.
- In addition to sunlight exposure, 25-OHD levels are affected by BMI, smoking, rs2282679 mutation in DBP and administration of DRV. Analytical methods differences accounted for the observed differences in study centers.
- Administration of 300000 IU of vitamin D every four months or of 100000 IU once per month should avoid vitamin D insufficiency over a year.