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Vitamin D and Clinical Disease Progression in HIV Infection: Results from the EuroSIDA Study

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BACKGROUND

Low levels of vitamin D, assessed through measurement of 25(OH)D [insufficiency: <30 ng/ml (75 nmol/l) and deficiency: <10 ng/ml (25 nmol/l)] are common in the general population and associated with morbidity such as osteopenia, cancer, autoimmune diseases, inflammation, infections (TB), CV disease, neurocognitive disorders, frailty, and mortality (e.g. elderly, renal insufficiency, heart transplant, high CV risk, diabetes). However, there are only a few placebo-controlled intervention studies.

Vitamin D deficiency among HIV-positive patients may be more prevalent than in the general population due to HIV disease-related factors, such as poor intake and absorption, impaired liver and kidney function, impaired storage in fat, less sun exposure, and interference of ARVs with vitamin D metabolism.

OBJECTIVES

To assess the prevalence of 25(OH)D deficiency and factors related in the EuroSIDA study and to examine the association between 25(OH)D level and disease progression in HIV-positive patients with prospective follow-up.

METHODS

Patients should be >16 years, have >1 month of follow-up and available CD4 and viral load measurements within 6 months.

In order to obtain a power >80% to detect a 1.5 fold increase of all-cause mortality over 5 years of follow-up, a group of 2,000 samples were randomly selected from 5,435 stored samples after stratification by region.

25(OH)D levels were measured in a single laboratory from the stored plasma samples.

The 1,985 available 25(OH)D results were stratified into tertiles.

Factors associated with 25(OH)D levels and associations of 25(OH)D levels with subsequent risk of all-cause mortality, AIDS and non-AIDS events were analyzed, using Poisson regression.

RESULTS

Characteristics of patients with low, intermediate and high 25(OH)D are shown in **table 1**.

Factors associated with low 25 OHD in univariate and multivariate logistic regression models are shown in **table 2**.

A total of 159 patients progressed to a new AIDS event, 188 patients died and 149 were diagnosed with a non-AIDS event.

At 5 years after baseline, 10.3 (95%CI: 7.8-12.8)% of patients had developed AIDS in the low 25(OH)D group, 6.0 (3.9-8.1)% in the medium 25(OH)D group and 5.1 (3.3-6.9)% in the high 25(OH)D group.

The corresponding figures for death were 11.1 (8.5-13.7), 6.6 (4.7 -8.9) and 5.6 (3.7-7.5)% and, for non-AIDS events were 8.8 (6.3-11.3), 6.7 (4.4 -8.8) and 6.5 (4.4-8.7)%, respectively.

Factors associated with these clinical outcomes were analysed in univariable and mulitivariable Poisson models (**figure 1**).

Results from a supplementary model on AIDS- and non-AIDS-related deaths are listed in **table 3**.

CONCLUSIONS

- Vitamin D deficiency was common in HIV-positive patients in Europe.
- Vitamin D deficiency at baseline was associated with subsequent all-cause mortality and AIDS events in a large European population with standardized, well documented follow-up.
- The association was independent of known prognostic factors, including baseline and time-adjusted CD4 and HIV RNA, anaemia, eGFR and ARVs.
- The main limitation in this study is the observational design and the assessment of vitamin D levels exclusively at baseline – a longitudinal study is ongoing.
- Intervention studies on correction of vitamin D deficiency are warranted to gain a better understanding of the pathophysiological mechanisms behind these findings.

Table 1

Baseline characteristics of patients according to vitamin D status

25 (OH)D tertiles		Low (<12 ng/ml) n=714	Medium (12.1-20 ng/ml) n=622	High (>2 ng/ml) n=649	*P*
Gender	Female	26.6	22.3	24.2	0.19
Ethnic	White	81.9	87.8	90.6	<0.0001
HIV risk	Homosexual	35.3	44.4	45.9	0.0022
	Heterosexual	23.0	20.9	21.7	
	IDU	32.5	26.8	25.4	
Region	South	24.5	27.5	33.7	<0.0001
	Central	27.7	21.9	19.9	
	North	25.2	21.5	27.9	
	East	21.9	27.8	17.3	
	Argentina	0.7	1.3	1.2	
Season (months)*	Spring (3-5)	26.1	26.2	17.3	<0.0001
	Summer (6-8)	19.2	27.0	39.1	
	Autumn (9-11)	12.2	17.0	20.3	
	Winter (12, 1-2)	42.6	29.7	23.3	
Prior treatment	cART	82.2	80.7	86.4	0.043
Age	Years	39.3(33.2-46.1)	38.1(32.4-45.2)	38.0(33.4-44.2)	0.19
CD4	/mm³	356 (216-534)	376(288-546)	360(220-509)	0.13
Viral load	Log¹⁰copies/ml	2.5 (1.7-3.6)	2.6(1.7-3.8)	2.6(1.7-3.5)	0.36
Sample	Month/year	02/02 (12/98-12/05)	11/01 (11/98-7/04)	9/99 (1/98-10/02)	<0.0001
Months	From enrolment	9 (0-23)	7 (0-23)	12 (3-29)	<0.0001

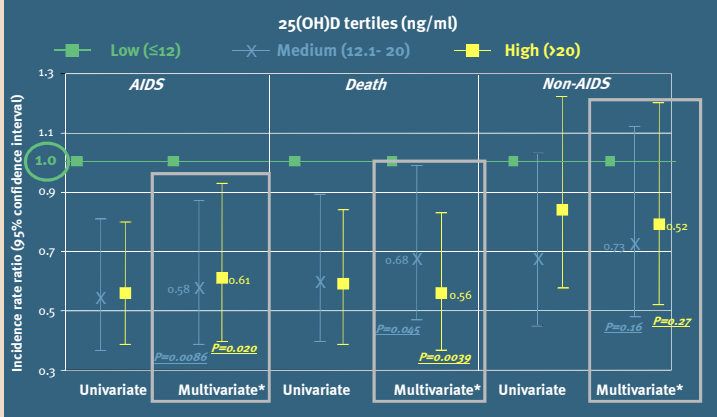
Table 2

Factors associated with low 25(OH)D
Results from logistic regression models

		Univariate			Multivariate		
		OR	95% CI	*P*	OR	95% CI	*P*
Ethnic origin	White	1.00			1.00		
	Other	1.83	1.41-2.37	0.0001	1.60	1.19-2.15	0.0017
HIV risk	Homosexual	1.00	-	-	1.00	-	-
	IDU	1.38	1.08-1.76	0.0099	1.65	1.26-2.15	0.0003
	Heterosexual	1.59	1.27-1.99	<0.0001	1.51	1.18-1.92	0.001
	Other	1.60	1.13-2.27	0.0082	1.28	0.88-1.85	0.20
Region	South	1.00	-	-	1.00	-	-
	Central	1.67	1.29-2.15	<0.0001	1.55	1.16-2.07	0.0032
	North	1.27	0.99-1.64	0.064	1.39	1.05-1.83	0.021
	East	1.22	0.94-1.59	0.14	0.85	0.62-1.16	0.30
	Argentina	0.57	0.21-1.59	0.20	1.06	0.37-3.06	0.91
Sample date (mo/yr)	≤7/98	1.00	-	-	1.00	-	-
	1/99-1/01	0.98	0.75-1.30	0.91	1.03	0.77-1.38	0.84
	2/01-4/04	1.62	1.26-2.10	0.0002	1.94	1.45-2.59	<0.0001
	≥5/04	1.78	1.37-2.31	<0.0001	2.03	1.50-2.75	<0.0001
Season	Spring	1.00	-	-	1.00	-	-
	Summer	0.48	0.27-0.63	<0.0001	0.44	0.33-0.58	<0.0001
	Autumn	0.54	0.40-0.74	<0.0001	0.51	0.37-0.71	<0.0001
	Winter	1.34	1.05-1.70	0.019	1.44	1.12-1.85	0.0051
Age	per 10 yr older	1.09	0.99-1.19	0.076	1.12	1.01-1.24	0.035

Figure 1

Incidence rate ratios of events – univariate and multivariate analyses



*Adjusted for baseline values of gender, ethnic origin, HIV risk group, region of Europe, HBsAg and HCV antibody status, piror AIDS, exposure to antiretrovirals, age, CD4 count, Nadir CD4, HIV-RNA viral load, date of baseline sample date, season of sample and date of recruitment to EuroSIDA

Table 3

Incidence rate ratios of AIDS vs. non-AIDS deaths

160 deaths of known cause :
- 48 (30%) AIDS-related
- 112 (70%) non-AIDS-related

	25OH tertiles (ng/ml)		
	Low (≤12)	Medium (12.1-20)	High (>20)
IRR of AIDS death	1	0.53 (0.24-1.15)	0.61 (0.28-1.32
P		0.11	0.21
IRR of non-AIDS death	1	0.67 (0.41-1.09)	0.60 (0.37-0.98)
P		0.10	0.043

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