Prognostic value of vitamin D level for all-cause mortality, and association with inflammatory markers, in HIV-infected persons: results from the EuroSIDA cohort study

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BACKGROUND

Low vitamin D is associated with excess morbidity and mortality, and inflammation. It is common in HIV-infected people, and a study within EuroSIDA (1) found that it predicted HIV disease progression. This study aimed at identifying the short and long term role of 25OHD level in the prediction of AIDS, non-AIDS defining events and mortality in HIV-positive persons, and to examine its association with markers of inflammation and innate immune activation, which are also predictive of disease progression.

METHODS

Patients and Study design

A prospective 1-1 matched case–control study nested within the EuroSIDA cohort. Matched cases and controls for AIDS (n=50 pairs), non-AIDS (n=63) and death (n=41) events, with plasma samples available during follow-up, were selected from the 1,981 people included in our previously conducted study (1). Cases and controls were matched on age, sex, region of residence, study entry date, and baseline CD4 count and HIV RNA level.

Measurements

25-hydroxy vitamin D (25OHD), hsCRP, hsIL-6 and sCD14 levels were obtained from stored plasma samples at study entry (baseline), time of event (or latest sample available for controls) and at midpoint of follow-up (if available). Median time between first and last samples, and last sample and event was 44.6 (IQR: 22.7-72.3) and 3.1 (IQR: 1.4-6.4) months respectively.

Statistical methods

Conditional logistic regression investigated associations between nadir, baseline and latest 25OH levels, severe vitamin D deficiency (25OHD<10 ng/mL) and outcomes. Average absolute change per year (ACPY) and average % change per year (ACPY%) were calculated between consecutive measurements of 25OHD, hsCRP, hsIL-6 and sCD14. Conditional logistic regression investigated associations between ACPY and ACPY% of markers with outcomes. Spearman's rank correlation coefficients investigated the relationship between ACPY and ACPY% in 25OHD with ACPY and ACPY% in other markers. Mixed models with random intercepts investigated associations between 25OHD level and hsCRP, hsIL-6 and sCD14 concentrations and CD4 count.

RESULTS

Baseline characteristics of study participants

250 persons were included in the analysis: baseline characteristics for cases and controls are displayed in **table 1**.

Baseline and latest biomarkers levels and events

Baseline biomarker levels are shown in **table 2**, together with latest values. Median latest 25OHD levels were significantly lower in cases than controls for death events. Latest hsIL-6 was higher in cases than controls for all events. Latest hsCRP and sCD14 were higher in cases for AIDS and death events.

Prognostic value of 25OHD levels during follow-up

There was no significant difference in the:

- adjusted odds of any event between persons with 25OH<10 ng/ml at any time during follow-up and persons with 25OHD>10 ng/ml (all *P*>0.11)
- adjusted odds of any event for a 2-fold higher 250HD nadir

In addition (**figure 1**):

- Baseline 25OHD levels were not associated with any outcome (all *P*>0.06)
- Odds of death significantly decreased by 46% (95%CI: 2–70%) for a 2-fold higher latest 25OHD level
- There was no significant association between baseline, latest level or change in 25OHD per year and the occurrence of AIDS or non AIDS-defining events (all *P*>0.33)
- Increasing 25OHD during follow-up was associated with non-significantly lower odds of death (aOR for a 1 ng/ml increase in ACPY/year : 0.94, 95%CI: 0.84,1.05, *P*=0.26).

Correlations between 25OHD level over time, other markers and events (Figure 2)

- In patients with current 25OHD<10 ng/ml, hsIL-6 increased by 4.66% (95% CI: 0.15, 9.36; P= 0.04) per year after adjusting for current log2hsCRP and log2sCD14 (model B).
- hsCRP increased by 8.35% (95%CI: 0.39,16.94; P=0.04) per year (model A) in patients with current 25OHD<10 ng/ml, but was not significant after adjustment (model B).
- Levels of sCD14 increased per year at a similar rate across 25OHD categories (P=0.10)
- CD4 counts significantly increased by 11.14% (95%CI: 3.65,19.18; P<0.01) and 7.02% (95%CI: 4.11,10.01; P<0.01) per year when 25(OH)D was >30 ng/ml or 10–30 ng/ml, respectively (model B) and there was no evidence of change when 25OHD level was <10 ng/ml.
- There was a significant association between increasing ACPY in hsCRP and death (aOR for a 1 unit increase in ACPY: 1.33; 95%CI: 1.03,1.72; P= 0.03).

CONCLUSIONS

Latest 25OHD level was associated with death, but not with AIDS or non-AIDS events. Earlier levels of 25OHD failed to predict death, suggesting the association diminishes with time. Current 25OHD<10 ng/ml was significantly associated with increasing inflammatory markers (particularly hsIL-6) over time. Severe vitamin D deficiency may thus represent a modifiable risk factor for increased inflammation, although reverse causality cannot be excluded.

1. Viard, JP, Souberbielle JC, Kirk O *et al*. Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study. *AIDS* 2011; **25**(10): 1305-15.

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Table 1

Baseline* characteristics of cases and controls for AIDS, non-AIDS and Death events

	AIDS events		non-AIDS events		Deaths	
	Controls	Cases	Controls	Cases	Controls	Cases
Number of patients	*50*	*50*	*63*	*63*	*42*	*42*
	N (%)					
25OHD <10 ng/mL	9 (18)	16 (32)	14 (22)	16 (25)	9 (21)	10 (24)
Male	43 (86)	43 (86)	60 (95)	60(95)	40 (98)	40 (98)
White	44 (88)	42 (84)	44 (70)	56 (89)	36 (88)	37 (90)
Risk group						
Homosexual	23 (46)	23 (46)	39 (62)	39 (62)	22 (54)	23 (56)
Heterosexual	11 (22)	11 (22)	12 (19)	13 (21)	8 (20)	7 (17)
IDU	11 (22)	11 (22)	8 (13)	7 (11)	7 (17)	6 (15)
HBV +	6 (12)	3 (6)	2 (3)	4 (6)	4 (10)	3 (7)
HCV +	14 (28)	11 (22)	8 (13)	11 (17)	6 (15)	8 (20)
	Median (IQR)					
Age (years)	38 (33,44)	39 (34,46)	40 (37,46)	44 (39,48)	41 (36,49)	42 (38,51)
CD4 (cells/mm³)	270 (129,400)	251 (101,390)	279 (185,486)	321 (173,500)	293 (180,402)	234 (141,404)
Log_{10} HIV RNA /ml	2.70 (2.49,4.10)	3.04 (1.96,4.46)	2.48 (1.69,4.21)	2.63 (1.69,4.25)	2.70 (1.69,3.70)	2.74 (1.69,4.06)

*Date of sample at study entry was considered as baseline.
Some percentages do not add to 100% due to missing categories

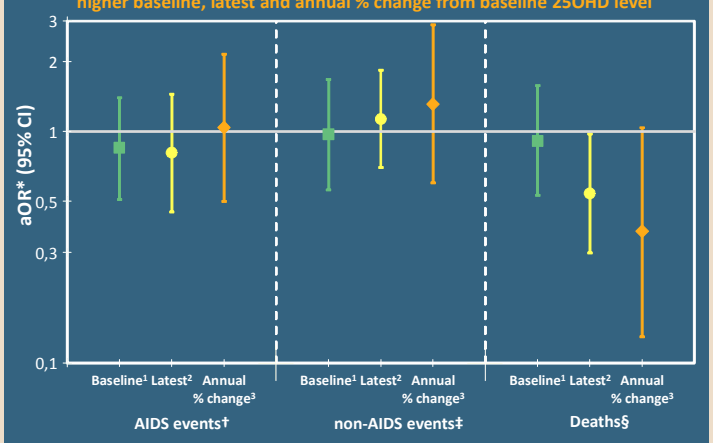
Table 2

Baseline and latest levels of biomarkers in cases and controls

	AIDS events			non-AIDS events			Deaths		
	Controls	Cases	*P*	Controls	Cases	*P*	Controls	Cases	*P*
N. of patients	*50*	*50*		*63*	*63*		*42*	*42*	
	Median (IQR)								
25OHD (ng/ml)									
baseline	17 (12,26)	13 (9,24)	0.07	15 (10,21)	16 (9,26)	0.22	19 (12,27)	17 (10,24)	0.28
latest	17 (11,22)	13 (10,23)	0.65	18 (11,24)	21 (11,28)	0.29	19 (12,28)	12 (8,17)	**0.03**
hsIL-6 (pg/ml)									
baseline	1.7 (1.0, 2.8)	2.0 (1.4,4.2)	0.10	1.9 (1.03.6)	2.2 (1.4,3.4)	0.62	2.0 (1.1,2.8)	3.2 (2.6,4.7)	**0.01**
latest	1.6 (0.9,3,5)	3.0 (1.5,6.4)	**0.01**	1.6 (1.0,3.2)	2.4 (1.5,4.2)	**0.02**	2.1 (1.5,3.9)	6.7 (3.0,14.7)	**<0.01**
hsCRP (mg/ml)									
baseline	1.1 (0.6,3.5)	2.5 (1.1,4.7)	0.09	2.8 (1.0,4.9)	2.0 (1.1,4.6)	0.56	1.6 (0.8,4.8)	3.1 (2.0,8.7)	**0.01**
latest	1.7 (0.4,4.6)	2.9 (0.7,12.9)	**<0.01**	2.0 (0.7,3.9)	2.5 (1.2,5.7)	0.47	2.1 (0.9,4.3)	8.7 (3.3,30.0)	**<0.01**
sCD14 (ng/ml)									
baseline	1226 (922,1586)	1241 (1077,1526)	0.59	1329 (1056,1531)	1296 (971,1507)	0.96	1158 (882,1674)	1301 (1080,1517)	0.80
latest	1695 (1433,2324)	2170 (1860, 2617)	**<0.01**	2128 (1647,2505)	2132 (1634,2471)	0.38	1980 (1477,2373)	2507 (1954,2876)	**<0.01**

Figure 1

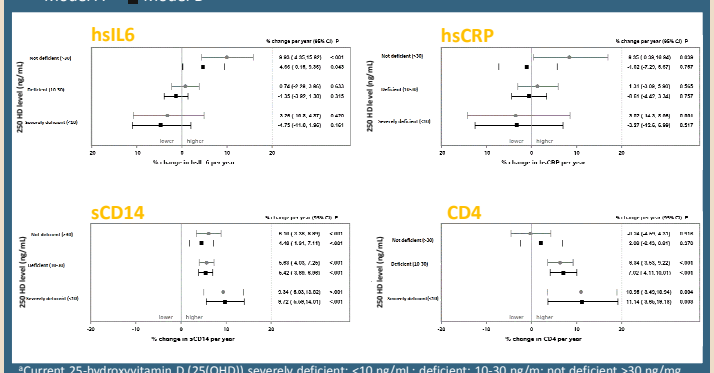
Adjusted odds ratios (95% CI) of AIDS, non- AIDS and death events for a two-fold higher baseline, latest and annual % change from baseline 25OHD level



*Models adjusted for baseline season, prior AIDS and ethnicity
Matched pairs: †N1 =50, N2 = 44, N3=48; ‡N1 =63, N2 = 61, N3=62; § N1 =41, N2 = 38, N3=41

Figure 2

Percentage Change in hsIL-6, hsCRP, sCD14 and CD4 per year according to current 25OHD deficiency category[a]



[a]Current 25-hydroxyvitamin D (25(OHD)) severely deficient: <10 ng/mL; deficient: 10-30 ng/m; not deficient >30 ng/mg
[b]Mixed models adjusted for season, gender, age, region, ethnicity, baseline CD4 count, baseline HIV viral load, hepatitis C status, hepatitis B status, prior aids, baseline treatment.
[c]Mixed models adjusted for current log IL6, hsCRP, CD4 and sCD14 concentration in addition to (b).

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