Vitamin D and Clinical Disease Progression in HIV Infection

Results from the EuroSIDA Study

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for the EuroSIDA Study Group

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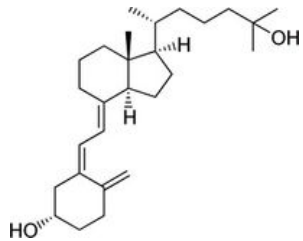
Vitamin D Insufficiency / Deficiency

- **Assessed through measurement of 25OHD**
  - Insufficiency: < 30 ng/ml (75 nmol/l)
  - Deficiency: < 10 ng/ml (25 nmol/l)
- **Frequent and increasing in general population**
- **Associated with morbidity :**
  - Osteopenia, cancer, autoimmune diseases, inflammation, infections (TB), HCV disease, neurocognitive disorders, frailty …
- **Associated with mortality in :**



Vitamin D Deficiency in HIV

- **Frequent : more than in general population ?**
- **HIV disease-related factors ?**
  - Less sun exposure ?
  - Poor intake and absorption ?
  - Impaired liver and kidney function ?
  - Impaired storage in fat ?
  - Interference of ARVs with vitamin D metabolism ?

Spectrum of conditions associated with vitamin D deficiency includes HIV disease complications and comorbidities

Objectives

- **To assess the prevalence of 25OHD deficiency** and factors related therewith
- **To examine the association between 25OHD level and disease progression:**
  - All-cause deaths
  - AIDS-defining events
  - Non-AIDS events
- **In HIV-positive patients from the EuroSIDA study**

Methods: *Patients*

- **Study size of 2000 samples**
  - >80% power to detect a 1.5 fold increase of all-cause mortality over 5 yr FU
- **Sample selection:**
  - closest to enrolment
  - stratification by region
  - ≥ 1 month FU, available CD4 and VL within 6 months, age > 16
  - 5435 samples available
  - random selection of 2000

Methods: *25OHD Measurement*

- **Stored plasma**
- **Single laboratory, single technician**
  - Necker Hospital
- **DiaSorin* radioimmunoassay**
  - Intra-assay variation <6%
  - Inter-assay variation <8%
- **1985 available 25OHD results**

Methods: *Statistical Analyses*

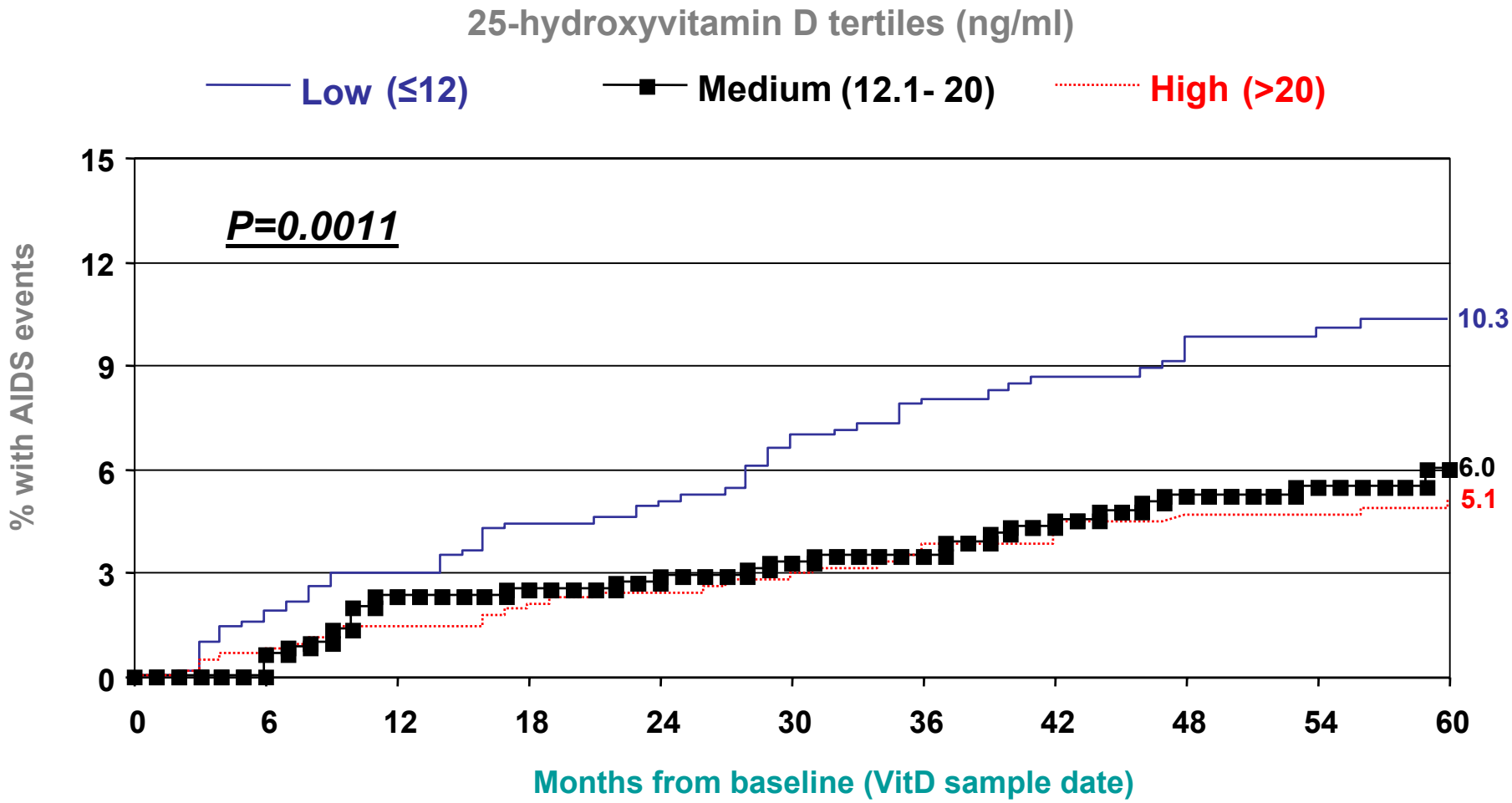
- **Patients divided into 25OHD tertiles**
  - Comparisons : χ–square, Kruskal-Wallis
- **Factors associated with low 25OHD**
  - Cross sectional analysis, logistic regression,
- **Incidence rate of events**
  - Baseline : date of 25OHD sample
  - Kaplan-Meier estimation
  - Poisson regression, adjusting for baseline factors

25OH D tertiles (ng/ml)		Low (≤12) n=714	Medium (12-20) n=622	High (>20) n=649	P
Gender	Female (%)	26.6	22.3	24.2	0.19
Ethnic origin	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	Spring (%)	26.1	26.2	17.3	<0.0001
	Summer (%)	19.2	27.0	39.1	
	Autumn (%)	12.2	17.0	20.3	
	Winter (%)	42.6	29.7	23.3	
Treatment	cART (%)	82.2	80.7	86.4	0.043
Median age (years)		39.3 (33.2-46.1)	38.1 (32.4-45.2)	38.0 (33.4-44.2)	0.19
Median CD4 count (μ/l)		356 (216-534)	376 (288-546)	360 (220-509)	0.13
Median viral load (log_{10} copies/ml)		2.5 (1.7 -3.6)	2.6 (1.7-3.8)	2.6 (1.7-3.5)	0.36
Median sample date		02/02 (12/98-12/05)	11/01 (11/98-7/04)	09/99 (1/98-10/02)	<0.0001
Median time from enrolment (months)		9 (0-23)	7 (0-23)	12 (3-29)	<0.0001

Results: *Factors Associated with Low 25OHD*

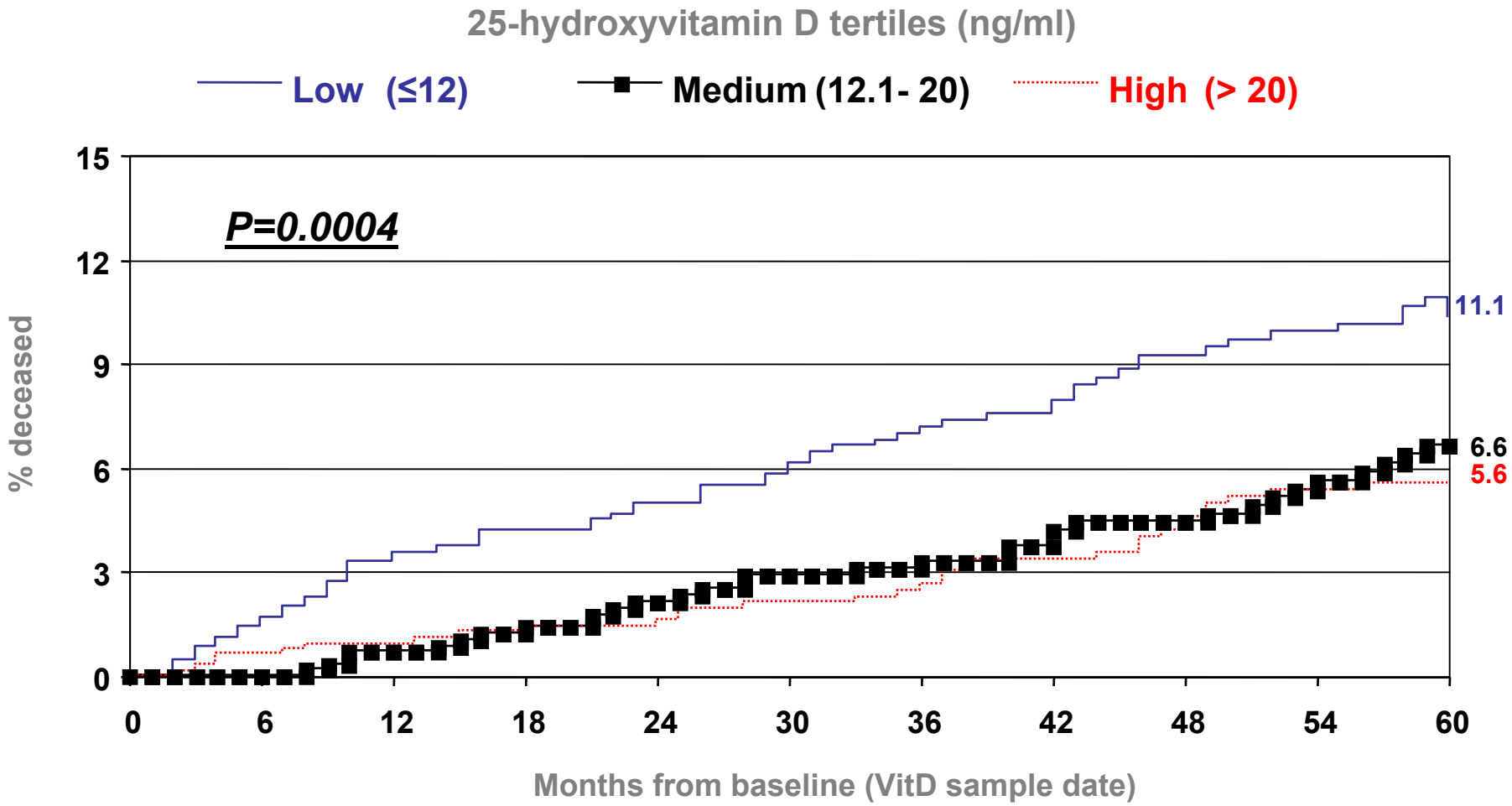
		Univariate			Multivariate		
		OR	95% CI	*P*	OR	95% CI	*P*
Ethnic origin	**White**	1.00			1.00		
	Other	1.83	1.41-2.37	0.0001	1.60	1.19-2.15	0.0017
HIV risk	**Homosexual**	1.00	-	-	1.00	-	-
	IDU	1.38	1.08-1.76	0.0099	1.65	1.26-2.15	0.0003
	Heterosexual	1.59	1.27-1.99	<0.0001	1.51	1.18-1.92	0.001
	Other	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	.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

Results: *Progression to AIDS (159 events)*



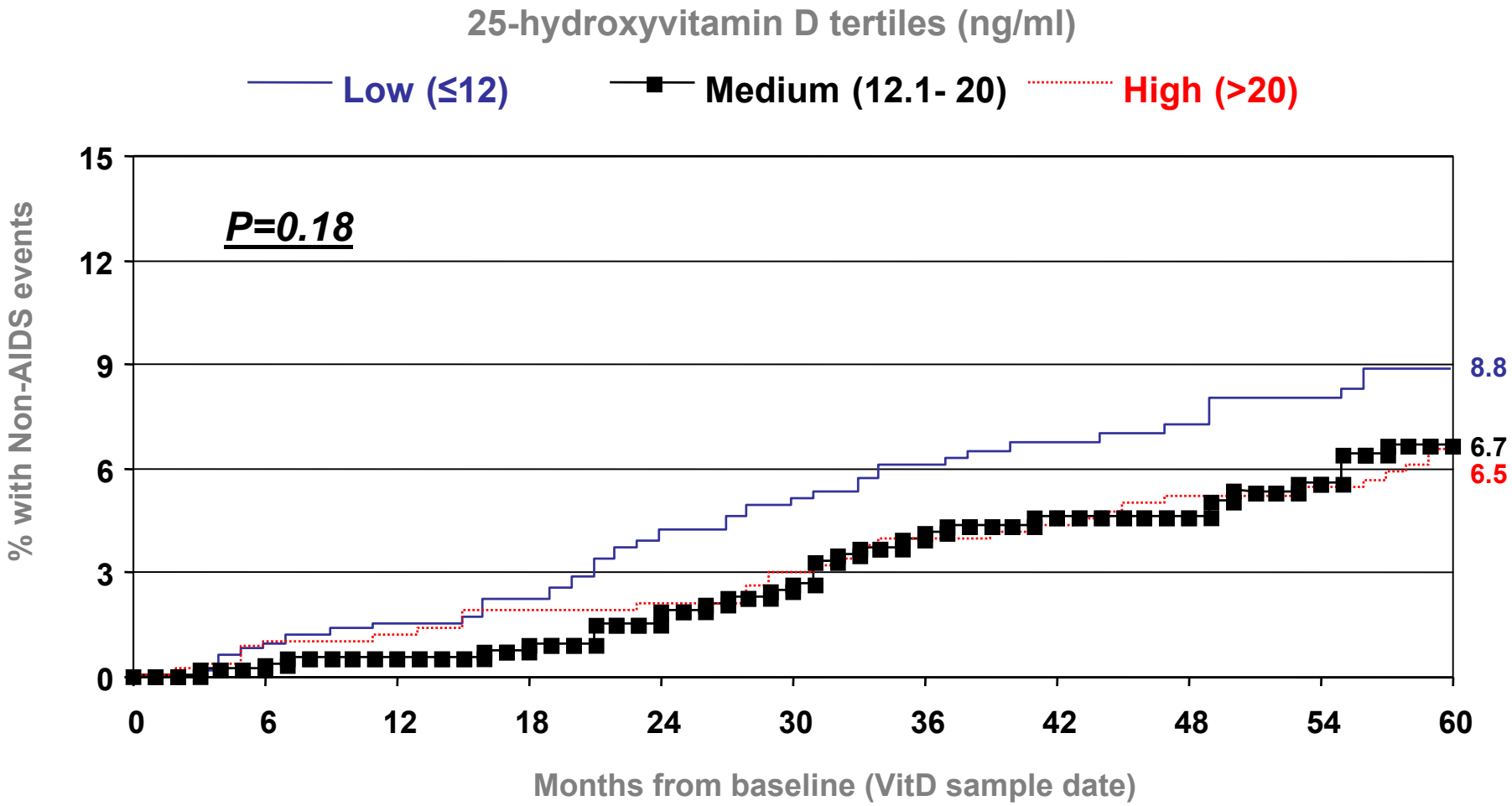
N Low	714	641	573	490	381	336
Medium	622	560	515	472	398	339
High	649	610	569	522	464	432

Results: *Progression to Death (188 events)*



N Low	714	654	591	518	410	363
Medium	622	574	530	485	414	353
High	649	616	579	438	478	445

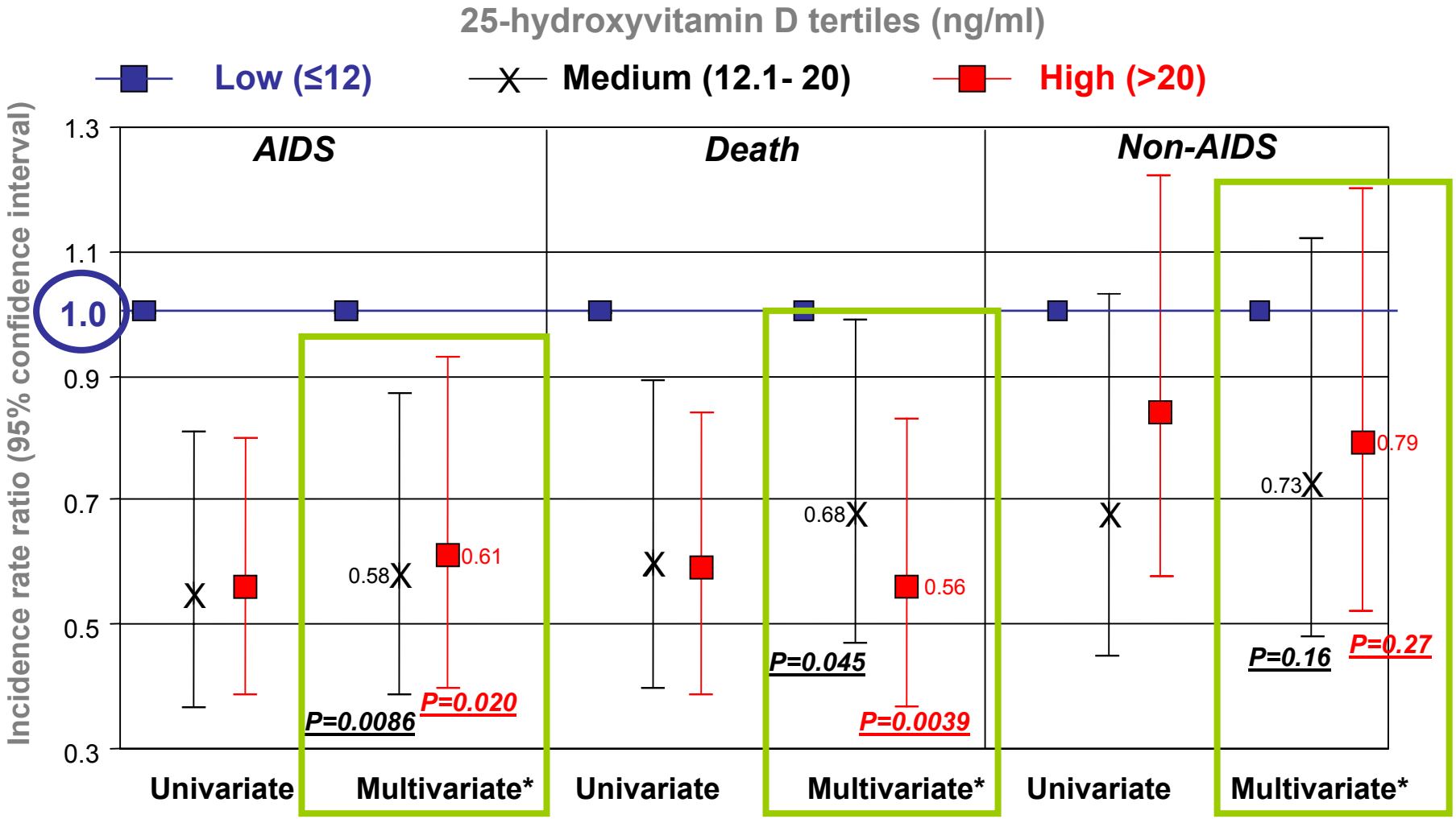
Results: *Progression to Non-AIDS Events (n=149)*



N Low	681	619	547	471	360	316
Medium	595	542	498	449	385	321
High	615	576	538	494	432	395

Results: *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, prior 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

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

Conclusion and Discussion (1)

- **Vitamin D insufficiency/deficiency common**
  - only 11% of patients with 25OHD ≥ 30 ng/ml

  … particularly in
  - non-white, non-MSM, older patients
  - more recent samples
- **Vitamin D deficiency at baseline associated with**
  - subsequent all-cause mortality and AIDS events in a large European population with standardized, well documented follow-up
  - independent of other prognostic factors
    - baseline and time-adjusted CD4 and HIV RNA, treatment, anaemia, eGFR

Conclusion and Discussion (2)

- **In line with study* in untreated HIV+ Tanzanian women, associating low vitamin D with:**
  - anaemia, clinical progression, death and MTCT
- **Main limitations:**
  - observational study
  - based on one measurement per patient
    - study with repeated vitamin D measurements ongoing
- **Intervention studies are warranted**

*Mehta S et al. *JID* 2009 and *PLoS ONE*, 2010

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