Efavirenz use is associated with severe Vitamin D deficiency in a large, ethnically diverse, urban UK HIV cohort

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Background

- Vitamin D deficiency is associated with rickets, osteomalacia and other adverse health outcomes[1]
- High rates (29-52%) of Vitamin D deficiency have recently been reported in HIV patients[2,3] These studies also suggest an association between low Vitamin D levels and NNRTI use[2,3]

Objectives

To study the prevalence of, and risk factors for Vitamin D deficiency in a large, ethnically diverse, HIV cohort in London, UK

Methods

- Cross-sectional study conducted between June and December 2008
- Measurement of serum 25(OH)Vitamin D levels in addition to routine biochemistry in all consecutive adult HIV patients attending for routine follow-up.

25 (OH) Vitamin D status was defined as:
≥30 µg/L (≥75nmol/L): Optimal
<30 µg/L (<75nmol/L): Insufficient
<20 µg/L (<50nmol/L): Deficient
<10 µg/L (<25nmol/L): Severely deficient
< 4 µg/L: Undetectable

- Factors associated with severe Vitamin D deficiency (<10µg/L) were examined in multi-variate regression models
- To assess the potential effects of Vitamin D deficiency and specific antiretrovirals (ARVs) on bone turnover, we compared levels of Alkaline Phosphatase (ALP) according to Vitamin D level and ARV exposure in a subset of patients with normal aspartate trans-aminase (AST<50 IU/L) i.e. where ALP unlikely to be of liver origin.

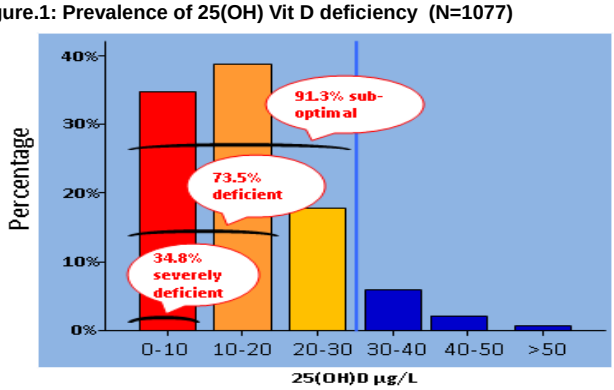
Results

- 1077 patients had 25 (OH) Vitamin D levels measured (Table 1)
- 35% of patients (375/1077) had severe Vit.D deficiency and only 9% (94/1077) had levels in the optimal range (Figure 1).

Table 1: Patient Characteristics (N=1077)

Age	**41 (IQR 36, 47)**
Female	**40.7%**
Black	**60.5%**
Current CD4 cells/mm3	**456 (IQR 328, 616)**
Nadir CD4 < 200 cells/mm3	**55%**
ARV naive	**12.4%**
Currently on HAART	**78.5%**
Currently on PIs	**24.2%**
Currently on NNRTIs	**53.8%**
Winter (October – December)	**33.4%**

Figure.1: Prevalence of 25(OH) Vit D deficiency (N=1077)



Risk factors for severe Vitamin D deficiency (Table 2)

•Black ethnicity (OR 2.7 (2.0-3.7)), winter season (OR 2.2 (1.6-3.0)), current Efavirenz (EFV) use (OR 1.9 (1.4-2.5)) and nadir CD4 count < 200 cells / mm³ (OR 1.5 (1.1-2.0)) were independent risk factors for 25(OH) Vit.D levels <10ug/L.

•We found no association with age, current CD4 count, eGFR, serum albumin or use of Nevirapine, Abacavir, Tenofovir or other NRTIs

Table 2: Risk factors for 25(OH) Vit D < 10 µg/L in HIV patients

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
All patients (N=1077)				
Black ethnicity	3.1 (2.3-4.1)	<0.001	3.4 (2.5-4.7)	<0.001
Female gender	1.4 (1.1-1.8)	0.02	0.8 (0.6-1.1)	ns
Winter season	2.0 (1.6-2.7)	<0.001	2.2 (1.6-2.9)	<0.001
CD4 nadir < 200	1.7 (1.3-2.1)	<0.001	1.4 (1.03-1.8)	0.03
Current HAART	1.6 (1.1-2.2)	<0.01	1.7 (1.2-2.3)	<0.01
Patients on HAART (N=845)				
Black ethnicity	2.7 (2.0-3.7)	<0.001	2.6 (1.8-3.7)	<0.001
Female gender	1.4 (1.0-1.8)	0.03	1.1 (0.8-1.5)	ns
Winter season	2.2 (1.6-3.0)	<0.001	2.1 (1.6-2.9)	<0.001
CD4 nadir < 200	1.5 (1.1-2.0)	0.01	1.4 (1-1.9)	<0.05
Current EFV use	1.9 (1.4-2.5)	<0.001	1.9 (1.3-2.7)	<0.001
Current PI use	0.7 (0.5-0.9)	0.01	0.9 (0.6-1.3)	ns

Clinical significance of EFV on Vitamin D

•Among Black patients with nadir CD4 cell counts <200 cells/mm3 tested in winter, the prevalence of severe Vit D deficiency was 59.5% on EFV vs. 51.4% on non-EFV HAART.

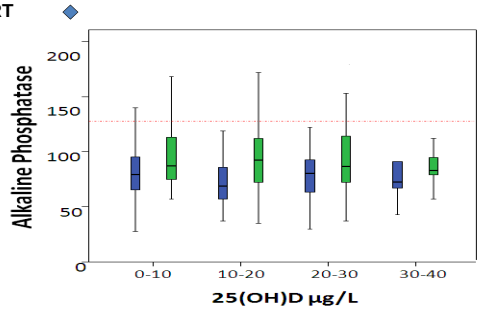
•Among white patients with nadir CD4 cell counts ≥200 cells/mm3 tested in summer the prevalence of severe Vit D deficiency was : 19.5% on EFV vs. 11.8% on non-EFV HAART.

Effect of ARVs on Alkaline Phosphatase (ALP)

•Patients on Tenofovir (TFV) had higher ALP levels than those on non-TFV HAART overall (ALP 93 [IQR 75, 115] vs. 79 [IQR 64, 97], p < 0.0001) and at every level of Vit.D (Figure 2).

•Patients on EFV also had higher ALP levels than those on non-EFV HAART (ALP 89 [IQR 70, 113] vs. 82 [IQR 68, 103], p=0.002) but this difference disappeared when patients on both TFV *and* EFV were excluded (ALP 80 [IQR 66, 104] vs. 77 [IQR 63, 95], p=0.07).

Figure 2: ALP levels by Vit.D level for patients on TFV ◆ compared to those on non-TFV HAART ◆



Conclusions

- Low Vitamin D levels are almost universal in this cohort
- Black ethnicity, winter and current Efavirenz use were the strongest risk factors for severe Vitamin D deficiency
- This study is the first to show an association between Efavirenz and low Vitamin D
- Efavirenz may alter Vitamin D homeostasis through CYP24 induction which catalyses the breakdown of 25(OH)D and active Vitamin D (1,25(OH)D) to inactive metabolites
- TFV is associated with higher ALP levels regardless of Vitamin D status
- The clinical implications of the potential synergy between Efavirenz and Tenofovir on Vitamin D and bone metabolism require further study

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