Vitamin D Insufficiency in AIDS-Associated Kaposi's Sarcoma in Zimbabwe

KM Erlandson[1], I Gudza[2], S Fiorillo[1], B Ndemera[2], RT Schooley[3], L Gwanzura[2], M Borok[2], TB Campbell[1]

1. University of Colorado, Aurora, CO USA;
2. University of Zimbabwe College of Health Sciences, Harare, Zimbabwe; 3. University of California San Diego, San Diego, USA

ABSTRACT

Objectives: Low 25-hydroxyvitamin D (25[OH]D) has been associated with progression of some malignancies. The activated form of vitamin D may slow tumor growth in vitro, and topical vitamin D may slow cutaneous KS in persons with localized KS. We hypothesized a high prevalence of 25(OH)D deficiency among persons with AIDS-KS in Zimbabwe, and that baseline 25(OH)D would be associated with AIDS-KS progression.

Methods: 90 antiretroviral naive participants were enrolled in a prospective study of antiretroviral therapy for treatment of AIDS-KS in Harare, Zimbabwe. Co-formulated abacavir, lamivudine, and zidovudine was initiated in all subjects. Chemotherapy or radiation was provided at the discretion of the provider. Subjects were followed for 96 weeks. 25(OH)D was measured from stored plasma samples at study entry and dichotomized as insufficient (<75 nmol/L) or adequate (≥75 nmol/L). Relationship between 25(OH)D and HIV or AIDS-KS clinical response was described by Spearman correlation coefficient for continuous variables and odds ratios and 95% confidence intervals (CI) for dichotomous variables.

Results: Samples were available from 85 participants. Median 25(OH)D was 73 (56-89) nmol/L; 45 (53%) had insufficient levels. 25(OH)D insufficiency was associated with higher baseline plasma HIV-1 RNA (4.7 [4.3-5.0] versus 4.5 [3.9-4.9] $\log_{10}$ copies/mL; p=0.04), and baseline 25(OH)D correlated with log change in plasma HIV-1 RNA (r=0.34, p=0.009). No correlation was detected between baseline 25(OH)D and change in CD4+ count (r=0.05, p=0.64), plasma herpes human virus (HHV)-8 DNA (r=0.06, p=0.60), or peripheral blood mononuclear cell HHV-8 DNA (r=-0.12, p=0.26). Similarly, baseline and change in CD4+ count, plasma or peripheral blood mononuclear cell HHV-8 viral load were not significantly different between subjects with adequate or insufficient 25(OH)D (all p≥0.4). Adequate 25(OH) D was not significantly associated with KS clinical response (OR 0.6; CI 0.2, 1.9; p=0.40), KS-IRIS occurrence (0.4; 0.2, 1.9; p=0.40), chemotherapy initiation (1.2; 0.5, 2.8; p=0.68), radiation initiation (0.6; 0.2, 1.5; p=0.24), or death (0.5; 0.1, 1.9; p=0.30). Odds ratios and significance remained unchanged after adjustment for baseline HIV-1 viral load and CD4 count.

Conclusions: Vitamin D insufficiency was common among Zimbabweans with AIDS-KS. Although we detected a relationship between 25(OH)D levels and plasma HIV-1 RNA responses, baseline 25(OH)D was not associated with other virological, immunological or clinical outcomes during treatment of AIDS-KS. This study does not support a role for vitamin D supplementation in AIDS-KS treatment.

BACKGROUND

- **Acquired immunodeficiency syndrome-related Kaposi's sarcoma (AIDS-KS) is the most common tumor in Zimbabwe**
- **Without antiretroviral therapy (ART), AIDS-KS is associated with >85% mortality; with ART, clinical response is still <20%**
- **Low vitamin D is associated with progression of some cancers, particularly those of rapidly proliferating tissue (ex. oral-gastrointestinal tract)**
- ***In vitro*, vitamin D analogues inhibit growth of KS transformed cell lines**
- **Mice with implanted KS tumors treated with vitamin D analogues had slowing of tumor growth**
- **A topical, synthetic vitamin D receptor agonist led to improvement in 4 of 8 males with cutaneous KS**

- **We hypothesized that a high prevalence of vitamin D deficiency would be found in Zimbabweans with AIDS-KS, and that low baseline vitamin D would be associated with AIDS-KS treatment response.**

METHODS

- **Retrospective analysis of data & specimens from a study of 90 subjects with AIDS-KS initiating co-formulated abacavir, lamivudine, and zidovudine**
- **Subjects were recruited from the Parirenyatwa Hospital Kaposi Sarcoma Clinic in Harare, Zimbabwe between June 2003-May 2005 & followed for 96 weeks**
- **Clinical response was defined as complete or partial resolution of KS at week 96; KS-IRIS as KS progression <12 wks after ART with ↑of >50 in baseline CD4 count**
- **Plasma from study entry was assayed for 25-hydroxyvitamin D (25[OH]D) and dichotomized as insufficient <75 nmol/L (<30 ng/mL) or sufficient ≥75 nmol/L; or 3 groups of ≤ 50, >50 but <75 and ≥ 75 nmol/L**
- **Statistical tests included chi-square and fisher's exact test; odds ratios for dichotomous and Spearman's rank correlation for continuous variables; and logistic regression models (adjusted for CD4 and HIV-1 RNA)**

RESULTS

- **Median 25(OH)D= 72.5 (IQR 56.3-88.8) nmol/L**
- **45 (53%) had 25(OH) <75 nmol/L (17were ≤ 50 nmol/L)**
- **40 (50%) had 25 (OH) ≥ 75 nmol/L**

Table 1. Demographic and clinical characteristics

Characteristic	*Insufficient 25(OH)D N=45*	*Sufficient 25(OH)D N=40*	*P value*
Demographics			
Age	38 (33-45)	36 (31-43)	0.4
Gender (female)	14 (31)	12 (30)	0.9
BMI	22 (20-23)	22 (19-24)	1.0
Disease stage			
Stage 4 KS	23 (51)	17 (43)	0.4
ACTG T1	38 (84)	33 (83)	0.8
Baseline laboratory			
Hemoglobin	11 (9.4-11.9)	11.3 (10.3-12.6)	0.2
CD4+ count	117 (76-208)	141 (70-222)	0.5
HIV-1 VL (log)	**4.7 (4.3-5.0)**	**4.5 (3.9-4.9)**	**0.04**
HHV-8 plasma VL (log)	2.9 (2.1-3.5)	2.8 (1.8-3.4)	0.4
HHV-8 PBMC VL (log)	3.2 (2.4-4.4)	3.5 (2.5-4.1)	0.8
96 week change[a]			
⬆ in CD4+ count	85 (21-291)	105 (30-202)	0.8
⬇ in HIV-1 VL (log)	**1.9 (1.3-2.4)**	**1.3 (0.8-1.9)**	**0.04**
⬇ in HHV-8 plasma VL (log)	0.5 (0-1.5)	0.4 (0-1.5)	0.8
⬇ in HHV-8 PBMC VL (log)	0.9 (-0.4-2.3)	1.0 (0-2.0)	0.9

Median and intraquartile range or number and percentage are reported for each variable; BMI: body mass index; KS: Kaposi Sarcoma; ACTG T1: AIDS Clinical Trials Group Tumor 1 Staging; VL: viral load; HHV-8: Human Herpes Virus 8; PBMC: peripheral blood mononuclear cells. a. week 96 or last available results

RESULTS

Figure 1. Flowchart of Study Participants

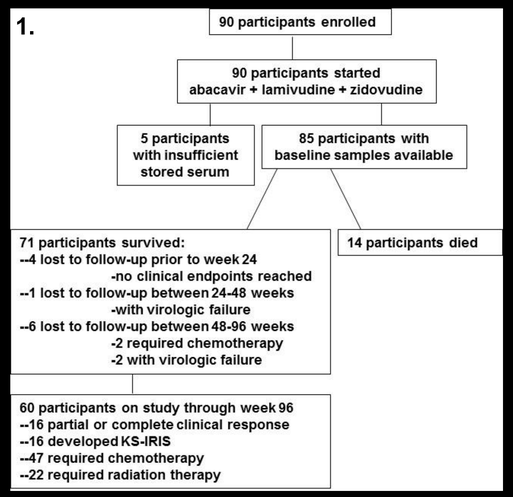


Figure 2. Change in CD4, HIV-1 VL, and HHV-8 VL (by PBMC or plasma) were similar across 25(OH) D categories

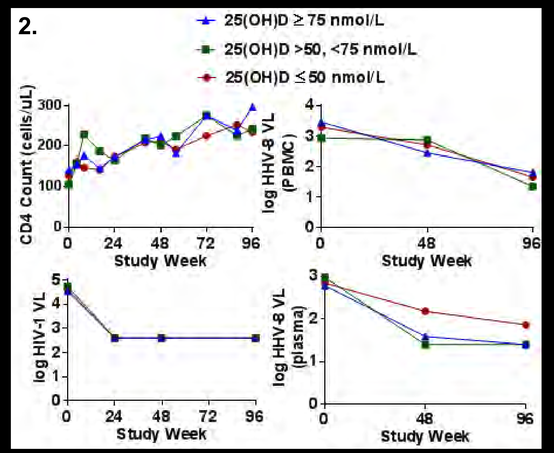


Figure 3. Changes in HIV-1 RNA but not CD4+ count or HHV-8 VL (not shown) correlated with baseline 25(OH)D

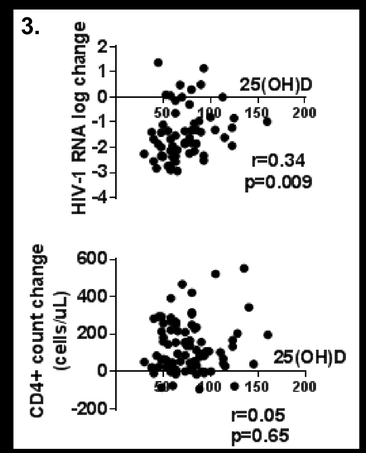


Figure 4. Odds of favorable clinical outcomes did not differ by 25(OH)D <75 or ≥75 nmol/L

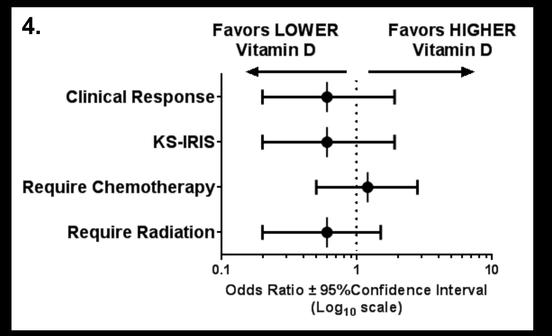
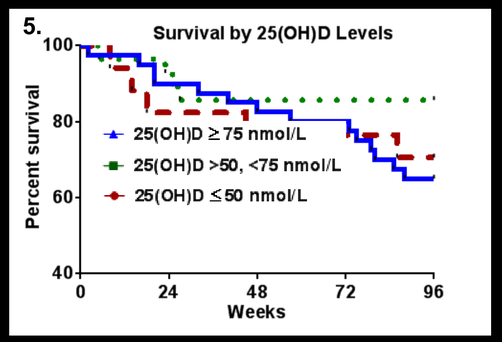


Figure 5. Survival at week 96 did not differ by 25(OH)D category



SUMMARY/CONCLUSIONS

- **Vitamin D insufficiency (<75 nmol/L or <30 ng/mL) occurred in more than 50% of Zimbabweans with AIDS-KS starting ART**
- **Lower vitamin D was associated with a greater decline in HIV-1 viral load**
- **No significant associations were detected between vitamin D and change in CD4+ lymphocyte count, HHV-8 viral load, improved clinical response, frequency of KS-IRIS, need for chemotherapy or radiation, or survival at 96 weeks**
- **Limitations of the study include the small sample size and the assessment of vitamin D only at baseline**
- **This study does not support a role for vitamin D supplementation in AIDS-KS treatment**

Contact: Kristine M Erlandson; kristine.erlandson@ucdenver.edu; University of Colorado-Anschutz Medical Campus, Aurora, CO
Funding: GlaxoSmithKline/ViiV Healthcare, NIH T32 A1007447-1, and the John A. Hartford Foundation