A novel replacement and maintenance regimen for vitamin D deficient HIV positive patients

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Aim

To prospectively evaluate a novel vitamin D replacement protocol to correct and maintain normal vitamin D levels in individuals with HIV infection.

Background

Vitamin D promotes calcium and phosphate homeostasis via regulation of uptake in the small intestines, thus having a central role in bone metabolism.[1] Vitamin D deficiency is a risk factor for osteoporosis and evidence is emerging that other complications such as cancer, chronic infections, cardio-vascular, inflammatory and metabolic disorders may be more prevalent in deficient individuals.[2]

Cross-sectional studies have indicated that the prevalence of vitamin D deficiency among HIV-infected individuals may be as high as 73%, and that certain anti-retrovirals, particularly Efavirenz, have been linked with vitamin D deficiency.[3] Whilst acknowledging that evidence for the clinical impact of vitamin D supplementation in HIV is lacking,[4] many clinicians recognise that this may become an important issue in the future and it has become common practice to test and replace vitamin D as part of HIV management. However, the best strategy for doing this is not clear. We aimed to devise and test the efficacy and safety of a novel protocol for vitamin D replacement in the HIV outpatients setting.

Methodology – protocol development

Several cohort studies have been conducted in HIV-negative subjects regarding the correction and maintenance of Vitamin D deficiency without inducing toxicity or unwanted side-effects (table 1).

Table 1: Existing protocols/evidence for replenishment in HIV-negative subjects

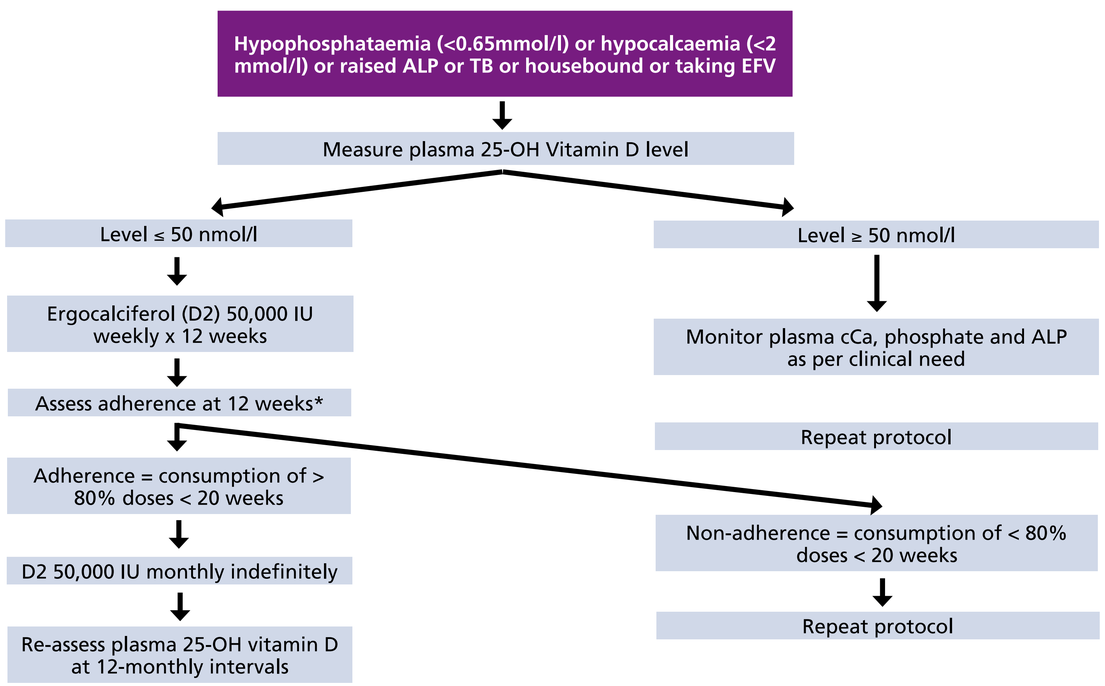
First author	Population	Vitamin D (VD) maintenance/ Correction	Protocol	Outcome Vitamin D level (nmol/l)
Malabanan (1998)[5]	Adults > 50 years	Correction	Ergocalciferol 50,000IU weekly x 8 weeks	≥ 50
Pepper (2009)[6]	VA cohort (67 ± 12 years)	Correction	Group 1: Ergocalciferol 50,000IU weekly x 4 weeks + 50,000IU monthly x 5 months	Baseline 27.5, Post-treatment 62.5
			Group 2: 50,000IU monthly x 6 months	Baseline 52.5 Post-treatment 75
			Group 3: 50,000IU 3 times weekly x 6 weeks	Baseline 42.5 Post-treatment 115
Lappe (2007)[7]	Post-menopausal women	Correction	Ergocalciferol 800-2800 IU plus 1400 – 1500mg calcium citrate daily	Increased levels by 24.5
Chung (2011)[8]	Meta-analysis	Correction	Ergocalciferol 50,000 IU x 4 weeks	≥ 50
Chung (2011)[8]	Meta-analysis	Maintenance	Ergocalciferol 50,000 IU monthly x 20–24 weeks	≥ 50

Ergocalciferol (vitamin D2) treatment, in a weekly dose of 50,000 IU, has been shown to lead to restoration of body stores of vitamin D over eight to twelve weeks in HIV-negative persons. Thereafter, a maintenance dose of 1000-2000 IU ergocalciferol daily or 10,000 IU weekly is usually adequate. It is advised that combined calcium and vitamin D preparations should be avoided in the long term because the calcium component is usually unnecessary, makes for unpalatability, and reduces adherence.[2]

In devising our protocol (figure 1) we used the above data, in conjunction with advice from a local rheumatologist and taking into account the following important additional factors:

- cost (1 ergocalciferol 50,000 IU costs 50p in-house),
- pill burden (to limit impact on adherence) and
- timing/duration of supplementation in relation to monitoring visits (hence twelve weeks of supplementation).

Figure 1: Birmingham Heartlands vitamin D replacement protocol



*In the original protocol vitamin D levels were measured at twelve weeks. After the success of the correction phase of the protocol was demonstrated testing at this stage was deemed unnecessary and the protocol was altered.9

Methodology – protocol evaluation

Adults attending the Birmingham Heartlands HIV service between July 2010 and July 2011 were screened for vitamin D deficiency if one of a number of indicator conditions was present (table 2).

Table 2: Indications for vitamin D testing

1. Significant hypocalcaemia (corrected calcium < 2.0 mmol/L)
2. Significant hypophosphataemia (<0.65 mmol/l)
3. Raised alkaline phosphatase (especially if GGT is normal)
4. Musculoskeletal syndrome of unclear cause
5. Patients undergoing treatment for mycobacterial disease, including TB (please only give vitamin D supplement once TB treatment has been initiated)
6. Patients who are housebound or institutionalised
7. Patients on Cytochrome P450 interacting HAART (especially Efavirenz)

Patients were excluded if they had end-stage renal or liver disease or were pregnant. If deficient (<50 nmol/l), subjects were prescribed 50,000 IU ergocalciferol weekly for 12 weeks (correction phase) followed by the same dose at monthly intervals thereafter (maintenance phase). Vitamin D levels were re-assessed at or around the end of the correction phase (mean 14 weeks, n=78). Upon confirmation of a normal range vitamin D test patients were commenced on 50,000 IU ergocalciferol monthly for six months and plasma vitamin D re-tested after this phase (mean 32 weeks, n=53). Any patient with a low plasma vitamin D after receiving the 12-week dosing repeated the protocol. Serum alkaline phosphatase, phosphate and corrected calcium levels were also monitored to assess changes and monitor for signs of vitamin D toxicity.

Adherence data was collected through one to one interview with dieticians and pill counts.

Statistical analysis was performed using SPSS version 19. Friedman's 2-way ANOVA and related samples Wilcoxon Signed Rank Test were used to compare variables against plasma vitamin D levels.

Results

247 out of 1017 patients met the testing criteria. Of these, 238 subjects (96%) had 25-hydroxy-vitamin D levels <50 nmol/L. 106 of these received a prescription for weekly ergocalciferol and had one or more follow-up vitamin D level. Table 3 shows baseline demographics and table 4 shows baseline and follow-up vitamin D data.

Table 3: Baseline demographics of vitamin D deficient patients who received a prescription

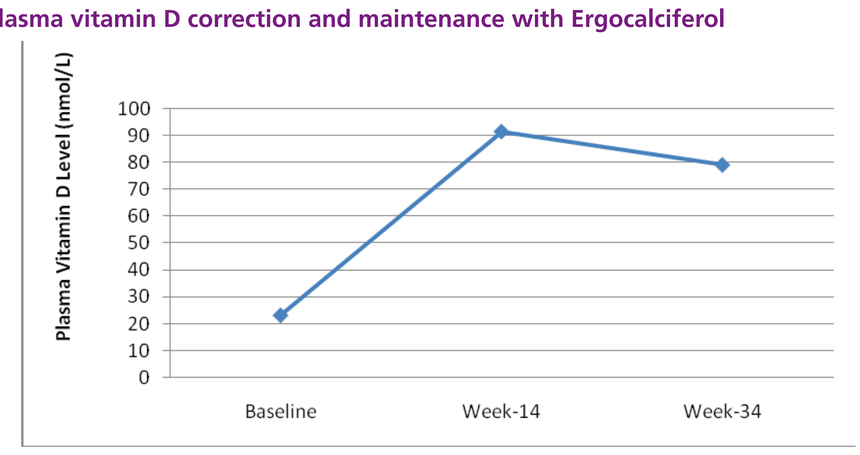
Demographic	Number (%)
Average age (years)	41.5 (range 23-69) (n = 106)
Males (%)	46 (43)
Afro-Caribbean (%)	71 (67)
Caucasian (%)	32 (30)
South Asian (%)	3 (3)

Table 4: Baseline and follow-up vitamin D levels

	Median vitamin D level (nmol/l)	Number tested	P-value
Baseline	22.8 (IQR 14.8 - 31.5)	106	
Week 14	84.5 (IQR 63 - 111)	78	<0.05
Week 32	72.3 (IQR 55.4 - 87.7)	53	<0.05

A rise of 61.7 nmol/L (p<0.05) was observed between baseline and week-14 (figure 2). 88.4% of patients' vitamin D were normalised after the correction phase and 80.3% remained corrected after twelve weeks of the maintenance phase.

Figure 2: Plasma vitamin D correction and maintenance with Ergocalciferol



No patients experienced toxicity or had elevated corrected calcium levels. The main identified reason for ongoing vitamin D deficiency was poor adherence and was significantly associated with vitamin D status at 12-weeks (p = 0.026; n = 31).

Conclusions

- **Using this vitamin D protocol, 96% of patients tested were deficient.**
- **A twelve week course of vitamin D 50,000 IU weekly effectively corrected vitamin D levels in approximately 90% of patients.**
- **A subsequent monthly dose of 50,000 IU maintains vitamin D levels above 50 nmol/l in >80% of patients.**
- **Further work is needed to determine:**
  - **the cost-effectiveness of testing and treating versus treating alone (given that a vitamin D test costs £75),**
  - **the need for long-term replacement,**
  - **the clinical necessity of vitamin D replacement and**
  - **whether targeted screening is more effective than widespread screening.**

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