

# Guideline for the management of vitamin D deficiency in HIV positive children: screening, treatment and prevention

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**Date of preparation:** February 2011 Version SMH/CF for 20,000 unit capsules

**Date reviewed:** February 2014

**Next review:** February 2016

## Content:

1. Algorithm for the management of vitamin D deficiency.
2. Summary of guidelines
3. Full guidelines

## 2. SUMMARY

Vitamin D is required for skeletal and non-skeletal health including bone mineralization, innate immunity and cardiovascular health [1]. Both HIV infection and vitamin D deficiency are associated with reduced bone mineral density (BMD), increased risk of tuberculosis, and cardiovascular disease [1-3]. Vitamin D levels of  $\leq 25$  nmol/L ( $\leq 10$   $\mu\text{g/L}$ ) are associated with rickets and osteomalacia [4] and levels of  $>75$  nmol/L (30  $\mu\text{g/L}$ ) are required for maximal BMD [5]. children. Highly Active Anti-Retroviral Therapy (HAART) has brought long term survival and maximising bone health in children is increasingly important as this population reach adult life.

**Screening:** Annual autumn screening is recommended since children with HIV in the UK have a high prevalence of vitamin D deficiency. survey (n=131) found that vitamin D deficiency is common in children with perinatally acquired HIV: 83.2% had insufficient levels ( $<50$  nmol/L,  $<20$   $\mu\text{g/L}$ ), 48.9% were deficient ( $<25$  nmol/L,  $<10$   $\mu\text{g/L}$ ), and 30.5% had undetectable vitamin D levels ( $<15$  nmol/L,  $<6$   $\mu\text{g/L}$ ) [6].

## Treatment

Vitamin D deficiency is safely and effectively treated with inexpensive supplements.

i) **Children  $>6$  yrs can be treated with short courses of high dose colecalciferol (Vitamin D3)** in order to reduce daily pill burden. Recheck vitamin D levels at next clinic appt.

**$>6$  yrs: Vit D  $<25$  nmol/L ( $<10$   $\mu\text{g/L}$ ) = 40,000 units/day for 6 days (Total 240,000 units)**

**$>6$  yrs: Vit D 25-50 nmol/L (10-20  $\mu\text{g/L}$ ) = 40,000 units/day for 3 days (Total 120,000 units)**

ii) **Alternative daily dosing: if  $<6$  yrs or colecalciferol caps, (Vitamin D3) not available (as per RCPCH)**

Category	Vitamin D dose and frequency	Duration
Up to 6 months	1,000 - 3000 units daily	4-8 weeks
6 months-12 years	6000 units daily	4-8 weeks
12-18 years	10,000 units daily	4-8 weeks

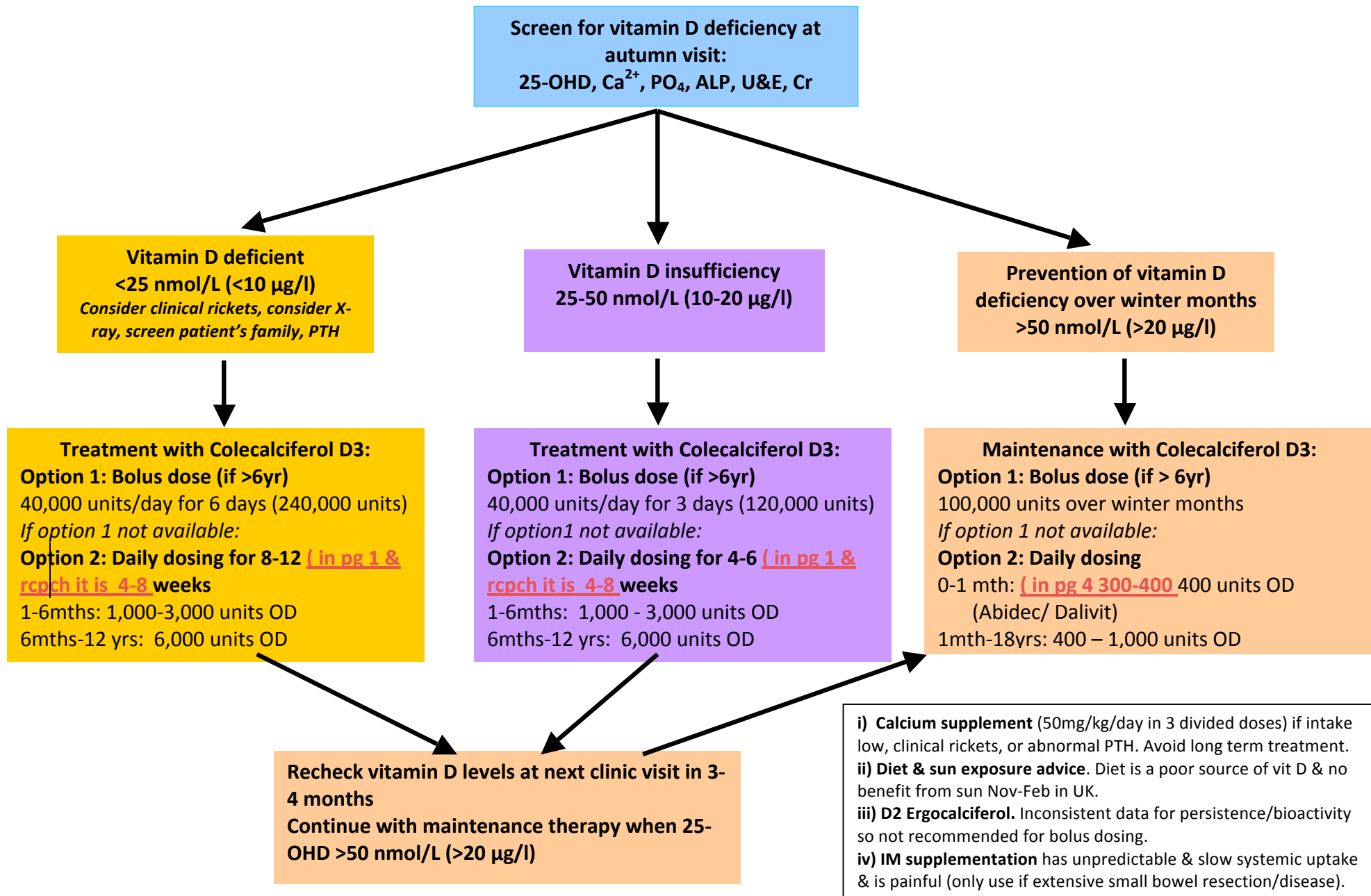
**Prevention:** i) In children  $>6$  yrs a single maintenance dose of 100,000 units of colecalciferol, (Vitamin D3) during the winter months is recommended to prevent vitamin D deficiency.

ii) If  $<6$  yrs or capsules of colecalciferol (Vitamin D3) not available (as per RCPCH guidelines)

<b>Category</b>	<b>Dose and frequency</b>	<b>Preparations</b>
Newborn up to 1 mth	300-400 units daily	Abidec, Dalivit, 'Healthy Start' Vitamins
1 month to 18 years	400 units–1,000 units daily	Over the counter preparations

400 units=10 µg of colecalciferol

## Guideline for the management of vitamin D deficiency in HIV positive children



### 3. Full guideline for the management of vitamin D deficiency

**Background:** Both HIV infection and vitamin D deficiency are associated with low bone mineral density [1, 3]. Plasma 25(OH)D levels of <25 nmol/L (<10 µg/L) are associated with rickets and symptomatic osteomalacia [4]. In one study 86% of children with vitamin D levels <20 nmol/L (<8 µg/L) had rickets [7]. There has been a rise in the incidence of rickets in the UK with highest levels in children of Afro-Caribbean origin [8]. Other reported effects of vitamin D deficiency (<50 nmol/L, <20 µg/L) include impaired immunity (especially to TB), and increased risk of cardiovascular disease, cancer, IDDM, cognitive impairment and multiple sclerosis (reviewed in [4]). Current WHO and UK guidelines recommend that all children <5 years of age and those with recognised risk factors receive vitamin D supplementation ([www.healthystart.nhs.uk](http://www.healthystart.nhs.uk)) [9].

A survey found that vitamin D deficiency is common in children with perinatally acquired HIV infection in the UK with almost half being vitamin D deficient (48.9% had levels <25 nmol/L, <10 µg/L) and about a third (30.5%) having undetectable vitamin D levels (<15 nmol/L, <6 µg/L) [6]. Children with HIV infection have lower bone mass compared to healthy controls [3] and the combined effects of HIV infection and vitamin D deficiency are not known. HAART has brought long term survival and maximising bone health in childhood and adolescence is important as this population reach adult life.

#### **i) Screening for vitamin D deficiency in HIV positive children**

Children with HIV infection in the UK are at high risk of vitamin D deficiency. Risk factors for vitamin D deficiency include:

African/South Asian ethnicity (pigmented skin reduces sunlight induced vitamin D synthesis by 99% [10]).

Age: infancy or adolescence (periods of maximal growth, less risk if bottle fed)

Poor diet (especially vegetarian/vegan)

Clothing which limits sunlight exposure or avoidance of sunlight

P450 enzyme inducing drugs (NNRTI use, rifampicin, phenytoin)

Winter season

Obesity (sequestration of vitamin D in fat)

Malabsorption

Renal/liver impairment

Alcohol abuse

#### ***Recommended investigations at Autumn screening:***

All children with HIV:

- Annually 25(OH)D [Total 25(OH)D / Calcidol] (min 1.3 mL clotted or heparin bottle). To be measured sooner if Ca low or if the child is symptomatic.
- 3 monthly U&E, Ca, PO<sub>4</sub>, LFTs
- Parathyroid hormone [PTH] (min 1.3 mL EDTA bottle): in symptomatic children (skeletal abnormality, bone pain, muscle weakness and poor growth) and annually for children taking tenofovir.

## **ii) Treatment of vitamin D deficiency in HIV positive children**

**Aim:** To reach a serum level of 25(OH)D >75 nmol/L (30 µg/L) to improve bone health in adult life. There is a significant reduction in intestinal calcium absorption when 25(OH)D levels are <75 nmol/L (30 µg/L) [11] and maximal BMD is achieved with 25(OH)D levels between 90-100 nmol/L [5].

### **1) if 25(OH)D level <25 nmol/L (<10 µg/L) or PTH >6.4 pmol/L:**

Consider clinical rickets (widened epiphyses, bowed legs/wide-based gait, floppiness and irritability) and in older children enquire regarding symptoms of bone pain, muscle weakness and poor growth. Consider X-ray if symptomatic. Consider referral to paediatric endocrinologist if clinical rickets/abnormal X-ray, low Ca, or growth failure and screen other family members for vitamin D deficiency.

Short course bolus dosing of vitamin D (option 1) is recommended in children >6 years in order to reduce daily pill burden.

**Option 1: Short course** (>6 yrs) = 40,000 units of colecalciferol/day for 6 days (Total 240,000 units)

*If Option 1 is not available (<6 yrs or D3 colecalciferol capsules not available)*

**Option 2: Daily dosing** with colecalciferol, D3

Category	Vitamin D dose and frequency	Duration
Up to 6 months	1,000 - 3000 units daily	8-12 weeks
6 months-12 years	6000 units daily	8-12 weeks
12-18 years	10,000 units daily	8-12 weeks

**Both treatment options should be followed by prophylaxis.**

### **2) if 25(OH)D level 25-50 nmol/L (10-20 µg/L):**

Enquire regarding clinical symptoms as above.

**Option 1: Short course** (>6 yrs) = 40,000 units colecalciferol, D3/day for 3 days (Total 120,000 units)

*If Option 1 is not available – (<6 yrs or D3 colecalciferol capsules not available)*

**Option 2: Daily dosing** with colecalciferol, D3,

Category	Vitamin D dose and frequency	Duration
Up to 6 months	1,000 - 3000 units daily	4-6 weeks
6 months-12 years	6000 units daily	4-6 weeks
12-18 years	10,000 units daily	4-6 weeks

**Both treatment options should be followed by prophylaxis.**

### **3) if 25(OH)D level >50 nmol/L (>20 µg/L):**

Continue with prophylaxis for winter months as per below.

#### **4) Monitoring following treatment**

Children with 25(OH)D levels of <50 nmol/L (<20 µg/L) who have received treatment should have repeat 25(OH)D levels, U&E, Ca, PO<sub>4</sub>, and LFTs at the next clinic visit. Repeat dosing may be required.

#### **5) Calcium supplementation**

Any child with clinical rickets, with an abnormal PTH or with low Ca levels should receive calcium supplements for the first few weeks of therapy. Some experts recommend that all children treated for vitamin D deficiency should receive calcium supplements for the first few weeks (50mg/kg/day in 3 divided doses) [4]. Long term calcium supplementation should be avoided as it is usually unnecessary, unpalatable and reduces compliance.

#### **iii) Rationale for therapy:**

**1) Safety:** Vitamin D has a very high therapeutic index and is thus extremely safe. Serum 25(OH)D levels of 250 nmol/L (100 µg/L) have been reported following sunlight exposure and therapy with no adverse effects. The normal range is 25 to 120 nmol/L. Toxicity is thought to require serum levels over 500 nmol/L (200 µg/L) [12].

**2) Choice of supplement:** Colecalciferol, D<sub>3</sub>, is preferable although ergocalciferol, D<sub>2</sub>, may be used for daily dosing. Colecalciferol, D<sub>3</sub>, is almost twice as effective as ergocalciferol, D<sub>2</sub>, in raising and maintaining 25(OH)D levels [13, 14]. Increase in serum 25(OH)D was 70% (1.7 times) greater with cholecalciferol, D<sub>3</sub>, supplementation compared to ergocalciferol supplementation [14]. Serum 25(OH)D levels rapidly decrease after Day 3 in ergocalciferol, D<sub>2</sub>, treated patients compared to levels that are maintained for up to 30 days in cholecalciferol treated patients [13].

**3) Route of supplementation:** Vitamin D supplementation should be given via the oral route if possible. Data suggests that intramuscular dosing is unpredictable with very slow systemic uptake resulting in a very slow increase in 25-OHD levels so that maximal levels are only reached after a couple of months [13]. Intramuscular injections also cause pain and distress. The IM route should only be used if there is extensive small bowel resection/disease.

**4) Dosing regime:** Both daily and intermittent vitamin D dosing regimens safely and effectively increase and maintain serum 25-OHD levels. Studies have shown that compliance is poor with daily dosing of vitamin D and this is likely to be the case in HIV positive children who already have a large daily pill burden. Thus short bolus doses are recommended in children >6yrs.

**5) RCPCH guidelines:** Our guideline advocates bolus dosing because: i) children with HIV already have a very high pill burden and problems with adherence and ii) bolus dosing is safe and effective. The RCPCH guideline states that it would be possible to multiply the daily dose by 30 if compliance is a concern. Daily dosing is in line with RCPCH guidelines.

#### **iv) Prophylaxis of vitamin D deficiency**

The Department of Health recommends a daily supplementation of vitamin D for formula fed infants over 6 months of age taking less than 500ml of formula/day and for children between 1 and 5 years of age (see [www.healthystart.nhs.uk](http://www.healthystart.nhs.uk)). Children of African/Caribbean, or Asian origin living in the UK and those with reduced sun exposure are at increased risk and should receive supplementation. Children with HIV are at high risk of vitamin D deficiency and should receive prophylactic vitamin D over winter months.

**Option 1: Annual prevention:** A dose of 100,000 units of colecalciferol during the winter months is a safe and effective alternative to daily dosing in children >6 yrs of age. A randomized controlled trial of vitamin D prophylaxis in HIV infected children found that 100,000 units given at 2 monthly intervals was safe and effective [15]. Treated children had a mean monthly 25(OH)D level of 81 nmol/L compared to 55 nmol/L in the placebo group [15]. The study concluded that higher doses or more frequent dosing was required since 75% of the children had at least 1 monthly 25-OHD level <75 nmol/L [15].

*If option 1 is not available or for children <6yrs the alternative is daily prophylaxis-*

**Option2: Daily prophylaxis:**

Abidec or Dalivit contain 400 units (10 µg) of colecalciferol in 0.6 mL and may be given once daily as prophylaxis for children <5years.

Category	Dose and frequency	Preparations
Newborn up to 1 month	300-400 units daily	Abidec, Dalivit, Baby D drops and 'Healthy Start' Vitamins
1 month to 18 years	400 units–1,000 units daily	Over the counter preparations

**v) Preparations of vitamin D**

Doses of vitamin D are expressed in 'units' of antirachitic activity: 400 units = 10 microgram.

**1) Multivitamin preparations:**

**Abidec®** Chefaro UK, Huntingdon, Cambridgeshire

**Dalivit®** LPC Pharmaceuticals Ltd, Luton, Bedfordshire

0.6ml provides 400 units/day of colecalciferol. Suitable for preventing vitamin D deficiency in babies and children, but beware of prolonged high-dose therapy due to vitamin A toxicity.

**2) Solutions/Liquids:**

**Colecalciferol liquid 3000 units/mL**

**Ergocalciferol liquid 3000 units/mL**

Ergocalciferol can be used interchangeably with colecalciferol for daily dosing. Ergocalciferol is a second line choice if colecalciferol is unavailable.\*

Neither colecalciferol or ergocalciferol liquids are licensed medicinal products in the UK but both are usually available from UK 'specials' manufacturers. However, there are long-term

intermittent supply problems with many vitamin D-containing preparations. For this reason, it may be necessary for alternative preparations to be used instead.

### **3) Tablets/capsules:**

Alternative preparations containing vitamin D:

**Colecalciferol capsules 50,000 units** pack of 100 (Named patient imported from Germany via Mawdsleys Unlicensed Medicines, Unit 4 Crompton Road Business Park, Crompton Road, Doncaster, DN2 4PW Tel: (0)1302 553000 Fax: (0)1302 553003 <http://www.mawdsleys.co.uk/unlicensedMedicines.asp>).

**Colecalciferol capsules 20,000 units** (Dekristol; MIBE, Brehna, Germany, imported by IDIS World Medicines, Surrey, KT13 8DB Tel: 01923 824 000, [idis@idispharma.com](mailto:idis@idispharma.com)).

### **4) Calcium and vitamin D combination preparations (e.g. Adcal D<sub>3</sub> tablets 600mg calcium + 400 units colecalciferol)**

These are unsuitable for treating vitamin D deficiency because they contain sub-therapeutic quantities of vitamin D and may also result in hypercalcaemia. They may be used for prophylaxis of vitamin D deficiency if calcium supplements are also required.

### **5) Alfacalcidol and calcitriol**

Not recommended for treatment of vitamin D deficiency unless severe renal or liver impairment is present.

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