For patients with vitamin D deficiency, what is the appropriate replacement dose?

Evidence-Based Answer

Both ergocalciferol (vitamin D2) 1,000 IU and cholecalciferol (vitamin D3) 1,000 IU are equally effective in raising 25-hydroxyvitamin D levels [25(OH) D]. Oral replacement with 50,000 IU weekly for 6 weeks is more effective than parental replacement with a single dose of 300,000 IU at 3 months out, with no difference at 6 months (SOR: **C**, disease-oriented evidence).

An RCT of 68 adults aged 18 to 84 years compared once-daily oral 1,000 IU vitamin D2 with daily oral 1,000 IU vitamin D3 to determine if D3 was more effective than D2 in maintaining levels of 25(OH)D over 11 weeks.[1] Sixty percent of the patients were vitamin D deficient (<20 ng/mL) and 87% were insufficient <30 ng/mL. Both forms of vitamin D elevated the 25(OH) D levels by about the same amount (D2: from 17 to 26 ng/mL; D3: from 20 to 29 ng/mL; no *P* value provided). Subjects were followed for only 11 weeks at the end of winter.

An open-labeled RCT of 92 subjects (mostly middle-aged women) evaluated whether high-dose parenteral D3 was as effective as oral D3 in treating hypovitaminosis D and maintaining normal levels.[2] The study compared single-dose 300,000 IU intramuscular (IM) D3 with the same total dose oral D3 given as 50,000 IU in 6 doses over 3 months. While both treatments raised 25(OH)D levels at 3 months the oral group showed a significantly larger delta change from baseline than the IM group (90 vs 59 nmol/L; *P*=.03). By 6 months, no differences were noted in change in serum levels between groups (52 vs 62 nmol/L; *P*=.32) Both treatment routes achieved normal 25(OH)D levels at 3 months that were sustained at 6 months of follow-up. This trial was limited by the small size and short length of study.

Current evidence-based guidelines from the Endocrine Society suggest 50,000 IU of either vitamin D2 or D3 weekly for 8 weeks (or the equivalent of 6,000 IU daily) be given until a blood level of 25(OH) D >30 ng/mL is achieved.[3] Maintenance therapy should then be continued with 1,500 to 2,000 IU daily. The guideline states obesity, malabsorption syndromes, and tobacco smoking adversely affect vitamin D absorption, requiring larger doses to treat deficiency and maintain normal levels of vitamin D.

Courtney Stroble, MD
Anne M. Proulx, DO, FAAFP
Wright State University FMR
Dayton, OH

1. Holick MF, et al. *J Clin Endocrinol Metab.* 2008; 93(3):677–681. **[STEP 2]**
2. Zabihiyeganeh M, et al. *Clin Endocrinol (Oxf).* 2013; 78(2):210–216. **[STEP 2]**
3. Holick MF, et al. *J Clin Endocrinol Metab.* 2011; 96(7):1911–1930. **[STEP 4]**

What is the prognosis for newborns with congenitally acquired HIV?

Evidence-Based Answer

Infants with congenital HIV infections have lower morbidity and mortality rates when started on immediate antiretroviral therapy (ART) compared with delayed ART treatment (SOR: **A**, systematic review of RCTs). Infants who start early ART in the 3 months after birth have reduced morbidity and mortality even in the first year of life (SOR: **B**, single RCT).

Among untreated congenitally HIV-infected newborns, 50% progress to AIDS or death by age 2.[1] Advancements in treatment have led to 90% of HIV-infected children reaching the age of 10 in high-income countries. However, in low- and middle-income countries only 23% of HIV-infected children have access to treatment.

A Cochrane systematic review analyzed 5 RCTs (N=1,124) that investigated when to initiate ART, what treatment to start, and whether regimens should be switched.[1] Participants (age <24 months) received nevirapine (NVP, a non-nucleoside reverse transcriptase inhibitor) or lopinavir (LPV, a protease inhibitor) for 1 to 2 years.

Early treatment, compared with no treatment, was associated with a 75% reduction in mortality and disease progression (1 trial, N=377; HR 0.25; 95% CI, 0.12–0.51). Patients with NVP regimens had a higher risk for treatment failure (2 trials, N=411; HR 2.0; 95% CI, 1.5–2.8) than patients with LPV treatments. However, LPV is more expensive, needs refrigeration, and comes only in a bitter-tasting liquid form.[1]

A retrospective trial compared the effect of starting any ART regimen (N=210) before or after 3 months of age in HIV-positive infants.[2] Deferred treatment

was associated with increased risk of progression over 58 months (HR 3.0; 95% CI, 1.2–7.9).

All of the studies were consistent with World Health Organization (WHO) guidelines for antiviral treatment in infants and children.[3] WHO indicates that ART should start immediately upon confirmed diagnosis of HIV in infants (<12 months old) irrespective of clinical or immunological stage. If no testing is available, ART should still be initiated in infants with clinically diagnosed severe HIV-related infections.

[Editor's note: There have now been case reports of infants being cured of HIV with very early, aggressive ART. This field is changing rapidly. Stay tuned.]

Krishnan Narasimhan, MD
Ethan Kellogg, MS
Lalita Kaul, PhD, RD, LD, LN
Howard University College of Medicine
Washington, DC

1. Penazzato M, et al. *Cochrane Database Syst Rev.* 2012, (7):CD004772. **[STEP 1]**
2. Goetghebuer T, et al. *AIDS.* 2009; 23(5):597–604. **[STEP 3]**
3. World Health Organization. *Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a Public Health Approach: 2010 Revision.* http://www.who.int/hiv/pub/paediatric/infants2010/en/. Accessed April 23, 2014. **[STEP 3]**

Does the use of vaginal misoprostol increase the success rate of IUD insertion (or decrease pain during insertion) in nulliparous patients?

Evidence-Based Answer

No. Misoprostol has no effect on the success of intrauterine device (IUD) insertion or pain during insertion. Misoprostol may cause minor adverse effects as well (SOR: **A**, consistent RCTs).

A 2012 RCT compared misoprostol (400 mcg either vaginal or buccal per patient preference, with 94% choosing intravaginal) with placebo self-administered 3 to 4 hours before an appointment for IUD insertion in 108 nulliparous women.[1] Outcomes measured were pain on a 100-mm visual analog scale (VAS), with 0 being no pain and 100 being the worst pain imaginable, and healthcare provider assessment of ease of insertion, also on a 100-mm scale.

This study found no significant difference in pain during insertion (58 mm with misoprostol vs 57 mm with placebo; *P*=.74). Significantly more pain was noted in the misoprostol group before insertion (17 vs 4.7 mm; *P*=.003). No difference was reported in provider perception of ease of insertion (25 vs 27 mm; *P*=0.64).[1]

A 2011 double-blinded RCT compared 400 mcg vaginal misoprostol with placebo 3 hours before attempted IUD placement in 270 parous or nulliparous women.[2] The primary outcome was failed insertion. After dropouts in both groups, 102 women and 97 women remained in the misoprostol and placebo groups, respectively. No difference was noted in failed insertion in the misoprostol group compared with the placebo group (2 vs 1; risk ratio [RR] 1.9; 95% CI, 0.2–21). Adverse effects such as headache, nausea, and shivering were more frequent in the misoprostol group (57% vs 42%; RR 1.3; 95% CI, 1.0–1.7), although all adverse effects were reported as mild. Pain during insertion did not differ between groups (46 mm misoprostol group vs 40 mm placebo on a 100-mm VAS; *P*=.14).

Another RCT compared 400 mcg buccal misoprostol with placebo given 90 minutes before IUD insertion in 40 nulliparous women.[3] Of the 35 patients who completed the study, all had an IUD successfully placed on the first attempt. Three patients in the placebo group required mechanical dilation to complete the insertion. No difference was noted for patient-reported pain in the misoprostol arm compared with the placebo group (65 vs 55 mm on a 100-mm VAS; *P*=.83). The misoprostol group reported more nausea (29% vs 5%; *P*=.05) and cramping (47% vs 16%; *P*=.04).

A 2007 single-blind RCT compared oral diclofenac 100 mg PO with sublingual misoprostol 400 mcg + diclofenac 100 mg 1 hour before the procedure in 80 patients who had no history of vaginal deliveries and desired copper IUD.[4] Two insertion attempts failed in the control group versus none in the misoprostol group (no *P* value provided). Pain during insertion was measured using a 10-point VAS and was similar in both groups (averaging 7 for misoprostol vs 6.5 for placebo; *P*=.2).

Carrie Pierce, MD
Kate Rowland, MD, MS
Advocate Illinois Masonic FMR
Chicago, IL

1. Swenson C, et al. *Obstet Gynecol.* 2012; 120(2):341–347. **[STEP 2]**
2. Dijkhuizen K, et al. *Hum Reprod.* 2011; 26(2):323–329. **[STEP 2]**
3. Edelman AB, et al. *Contraception.* 2011; 84(3):234–239. **[STEP 2]**
4. Sääv I, et al. *Hum Reprod.* 2007; 22(10):2647–2652. **[STEP 2]**