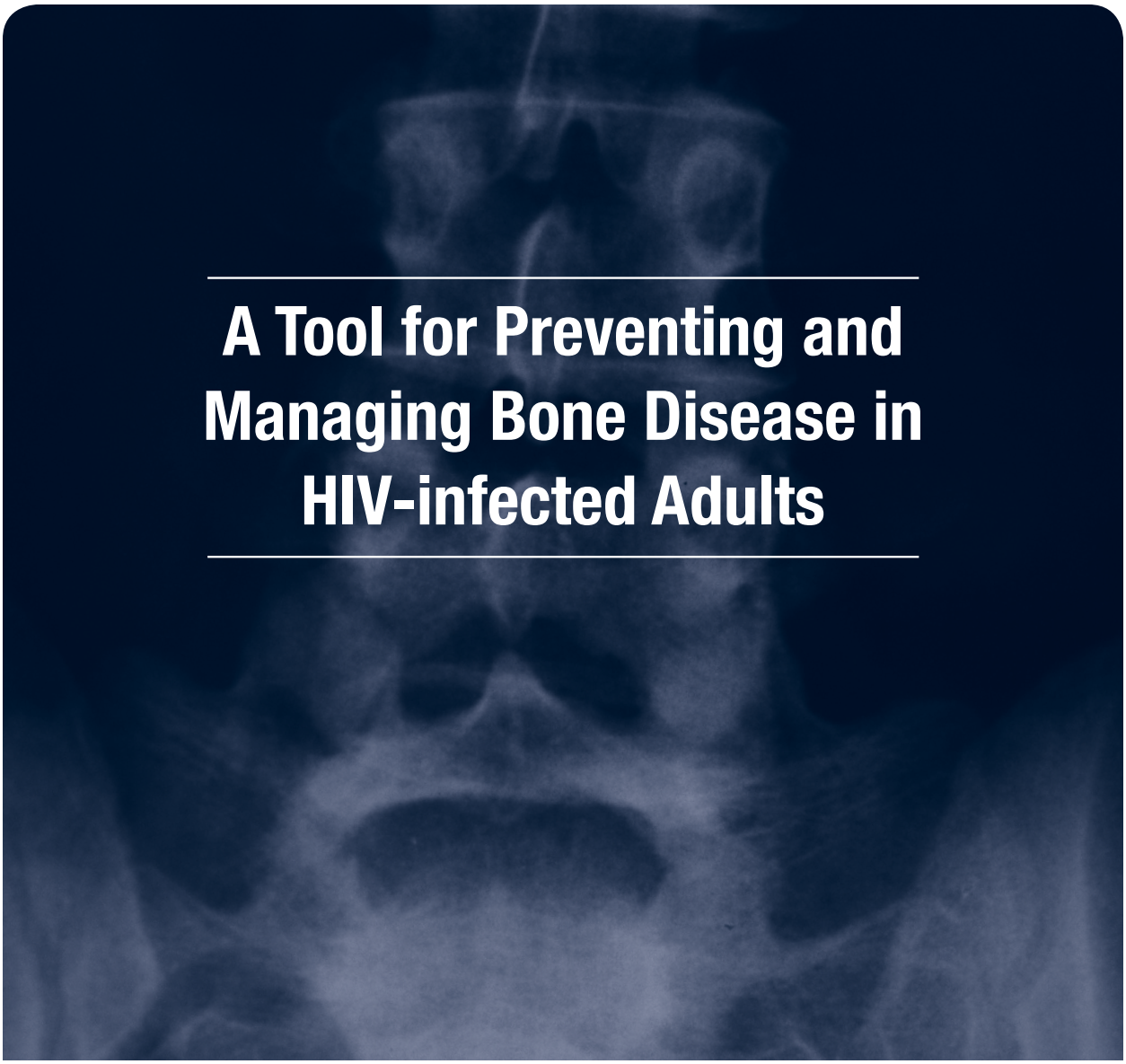

A Tool for Preventing and Managing Bone Disease in HIV-infected Adults

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1 Risk Factors for Fractures/Bone Loss

Patient Characteristics

- Age ≥ 50 y.o.
- History of fragility fracture
- Vertebral Fracture (radiographic or occult)
- Parental Hip Fracture history
- Low body weight (< 60 kg)
- Major weight loss of 10% after age of 25 years old
- Sedentary lifestyle
- Caucasian, East Asians
- Premature menopause (< 45 y.o.)
- Post-menopausal women

Diseases/Disorders

- Chronic kidney disease (CKD)
- Chronic viral hepatitis
- Endocrine – hypogonadism, hyperthyroidism, primary hyperparathyroidism, adrenal insufficiency, Type 1 and 2 diabetes
- HIV factors – lower extremity neuropathy (↑ risk falls), lipoatrophy, low nadir CD4, longer duration of HIV infection
- Malabsorption – celiac disease, inflammatory bowel disease
- Rheumatoid arthritis

Nutrition

- Inadequate calcium intake
- Malnutrition
- Vitamin D deficiency

Substances

- Alcohol abuse (> 3 units/day): 1 unit = 8-10 g of alcohol (285 mL of regular beer, 30 mL of spirits, 120 mL of wine, or 60 mL of an aperitif)
- Cigarette smoking
- Opiate use

Medications

- Anti-androgen therapy
- Anticoagulants – chronic heparin, warfarin
- Anticonvulsants – e.g. phenytoin, phenobarbital, carbamazepine; valproate
- Antiretrovirals (ARVs) – tenofovir disoproxil fumarate (TDF) can impact BMD; boosted protease inhibitors (PIs) (e.g. ritonavir-boosted atazanavir, lopinavir and darunavir), especially when combined with TDF can impact BMD; efavirenz is associated with vitamin D deficiency
- Aromatase inhibitors
- Chemotherapy
- Glucocorticoids (> 3 months in past year at a prednisone-equivalent dose > 5.0 mg/day)
- Medroxyprogesterone, depo (Depo-Provera®)
- Pre-formed retinol (vitamin A) supplements > 10,000 IU/day
- Proton pump inhibitors (PPIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Thiazolidinediones (glitazones)

2 Patient Assessment

LEGEND:
BMD – bone mineral density
DXA – dual-energy x-ray absorptiometry

Initial Screening Assessment (prior to BMD Scan)

- Screen post-menopausal women and men ≥ 50 y.o. for risk factors
- In HIV+ patients ≥ 50 y.o., consider measuring height every 1-2 years (ideally with a stadiometer)
  - ≥ 2 cm loss in height could indicate a vertebral fracture
  - significant height loss should be investigated radiographically
- Assess history and risks for falls in the past year

Indications for initial BMD (DXA) testing in HIV patients

- History of fragility fracture (any age)
- Post-menopausal women and men ≥ 50 y.o. (particularly if they have ≥ 1 additional risk factor for fracture) *(see Risk Factors)*
- Men 40-49 y.o. or premenopausal women ≥ 40 y.o. with intermediate or high risk stratification via Frax® (> 10% 10-year risk of major osteoporotic fracture); *Note: If femoral neck BMD is not available, check yes in 'secondary osteoporosis' box in Frax® tool when performing calculation*
- Consider repeating BMD screening every 2-5 years in patients with major risk factors where therapy is not warranted yet

Fracture Risk Assessment (post BMD scan)

- A T-score (for postmenopausal women and men ≥ 50 y.o.) and/or Z-score (if < 50 y.o.) is reported in BMD reports
- Generally, a T-score ≤ - 2.5 indicates osteoporosis, however decisions regarding therapy are based on 10-year fracture risk; Z-scores are not used to diagnose osteoporosis
- There are two scoring systems used to predict the 10-year risk of fracture in osteoporosis therapy-naïve patients. These are validated in the non-HIV population:

1) CAROC System
   - BMD reports in Canada use the CAROC system; validated in patients > 50 y.o.
   - 10-year probability risk of fracturing is reported as low (< 10%), moderate (10-20%) and high (> 20%)

2) FRAX® Algorithm
   - Considers additional risk factors, but generally correlates well with results from the CAROC system
   - Validated in Canada in patients > 40 y.o. and can use as an additional tool
   - Calculates the 10-year probability (%) of major fracture and hip fracture
   - Can be used without BMD as an initial screen to assess for fracture risk
   - HIV+ US adults median age 43 y.o.- FRAX® 10-year fracture probability ≥ 3% significantly associated with elevated fracture risk (Battalora, 2017)

Rule-out secondary causes of low BMD (Review history and physical exam)

BLUE ITEMS: When ruling-out secondary causes, it is recommended to order these tests initially.

- **Suggested Laboratory Tests:**
  - Complete blood count, blood chemistries, serum creatinine, phosphate, alkaline phosphatase (ALP), calcium corrected for albumin
    *Corrected Ca = measured Ca (mmol/L) + { (40 – albumin (g/L))*0.02}*
  - Vitamin D deficiency → 25(OH) Vitamin D
  - Hyperparathyroidism → Parathyroid hormone (PTH), Calcium
  - Subclinical Hyperthyroidism → Thyroid stimulating hormone (TSH)
  - Hypogonadism → Males: Free Testosterone (measured before 10 AM)
  - Phosphate wasting → See FEP04*
  - Rule-out osteomalacia → See Definitions
  - Idiopathic Hypercalciuria → 24 hr Urinary Ca
  - Celiac Sprue → Tissue Transglutaminase
  - Multiple Myeloma → Serum Protein Electrophoresis
  - Mastocytosis → Serum Tryptase
- **Antiretrovirals (ARVs):**
  - In those with low BMD, a Hx of fragility fracture or osteoporosis, consider other ARVs instead of TDF* and PIs (e.g. abacavir, lamivudine, tenofovir alafenamide (TAF) and raltegravir may ↑ BMD. Elvitegravir or dolutegravir may also be considered [data limited])
  - Consider avoiding efavirenz due to ↓ vitamin D concentrations
  - **Fractional Excretion of Phosphate (FEPO4):*
  - Used to assess PO4 wasting from TDF. Obtain a fasting urine and serum phosphate (PO4) at the same time as a urine and serum creatinine (Cr)
  - *FEPO4 (%) = (UPO4/SPO4) ÷ (UCr x 1000/SCr) x100* (Cr in SI units)
  - FEPO4 < 20% is generally acceptable; > 20% indicates tubular dysfunction/phosphate wasting

3 Treatment

Who to Treat?

HIGH RISK

- CAROC System: High risk (> 20%)
- FRAX® Algorithm: Major fracture risk > 20% or hip fracture risk ≥ 3%

MODERATE RISK

- CAROC System: Moderate risk (10-20%)
- Initiating therapy is a clinical decision that depends on the presence of additional significant risk factors and careful evaluation for such risk factors is recommended. Consider delaying bisphosphonates and modify ARVs to a bone-sparing regimen *(See Patient Assessment- Secondary Causes)*. Repeat BMD after one year to reassess need for therapy
- Plain X-rays of thoracic and lumbar spine can be useful to evaluate for subclinical vertebral fracture; if present, treatment is strongly encouraged

LOW RISK

- General preventative measures only; reassess in 5 years

TREATMENT

- Treat any identified secondary causes of osteopenia, including avoidance of medications associated with bone loss *(see Risk Factors)*
- Correct existing vitamin D deficiency and ensure adequate vitamin D and calcium intake *(see Prevention)*
- Encourage smoking cessation and limit alcohol consumption
- Assess fall risk and refer to physiotherapy if there have been any falls
- *First-line therapies for the prevention of fractures in the general population:*

  Postmenopausal women:
  - Prevent vertebral, non-vertebral and hip fractures - *alendronate, risedronate, *zoledronic acid, denosumab, hormone therapy (if vasomotor symptoms also present)

  Men:
  - *Alendronate, risedronate, *zoledronic acid

  *Preferred agents; studied in HIV+ patients; denosumab not recommended in HIV+ *(See Osteoporosis Medications)*
- *Duration of Therapy:* Long term use of bisphosphonates has been associated with atypical fractures and osteonecrosis of the jaw. The optimal duration of bisphosphonate use has not been established. Some clinicians are considering a drug holiday after 3 to 5 years of bisphosphonate use in patients who are at low risk of fracture. Consider repeat BMD 1-2 years after stopping treatment. Avoid drug holiday if previous fragility fracture, hip T-score ≤ -2.5, or high fracture risk

MONITORING

- The goal of therapy is to prevent further bone loss and/or increase the BMD and remain fracture free
- CAROC and FRAX® tools are not validated to monitor changes in fracture risk in patients on therapy
- Monitor BMD 1-2 years after starting therapy to evaluate drug efficacy
- The interval for monitoring can be increased to every 3-5 years once results are stable
- A decrease in BMD at one year may be considered significant and warrants further investigation (e.g. adherence to therapy, how medication is taken/ absorbed, consider other secondary causes of osteoporosis)

EXAMPLES OF WHEN TO REFER TO AN OSTEOPOROSIS SPECIALIST

- Evidence of phosphate wasting and low BMD
- Patients who fail first-line therapy
- Younger patients with a history of fragility fracture

Osteoporosis Medications

LEGEND: sc – subcutaneous • BMD – bone mineral density • CVD – cardiovascular • DR – delayed-release

Drug	Trade names	Treatment dose	Side effects	Comments
Bisphosphonates				
alendronate ¥	Fosamax®, generics 5, 10, 70 mg tabs 70 mg/75 ml oral solution Fosavance® 70 mg/2800 IU vit D_3 70 mg/5600 IU vit D_3	70 mg once weekly 10 mg daily one tab once weekly	GI upset, dyspepsia, diarrhea, muscle/joint pain RARE: esophagitis, ulcers (esophageal, gastric), osteonecrosis of the jaw, atypical fractures	• Take 30-60 minutes before the first food, beverage or medication with full glass of water • Do not lie down for 30 minutes after taking • Safety with CrCl<35 ml/min unknown • Preferred 1st-line in HIV+
risedronate	Actonel®, generics 5, 35 mg tabs 150 mg tabs Actonel DR 35 mg	35 mg once weekly 5 mg daily 150 mg monthly DR: 35 mg weekly with food	GI upset, dyspepsia, diarrhea, muscle/joint pain RARE: esophagitis, osteonecrosis of the jaw, atypical fractures	• Take 30 minutes before the first food, beverage or medication with full glass of water • Do not lie down for 30 minutes after taking • DR form to be taken with food (breakfast) • Safety with CrCl<30 ml/min unknown
etidronate	Didrocal®, generics	Cyclic: 400 mg/day x 14 days, then calcium carbonate (500 mg elemental) x 76 days	GI upset, dyspepsia, diarrhea, muscle/joint pain	• Etidronate tablets should be taken on empty stomach 2 hours before or after eating
zoledronic acid ¥	Aclasta® 5 mg/100 ml IV solution	5 mg IV infusion once yearly	Acute phase reaction after injection (2-3 days) – fever, flu-like symptoms, muscle/joint pain RARE: osteonecrosis of the jaw, atypical fractures, acute renal failure, hypocalcemia	• 30 minute infusion • Safety with CrCl<35 ml/min unknown (avoid use) • Caution with use of other nephrotoxins (e.g. tenofovir DF (TDF), NSAIDS)
Selective Estrogen Receptor Modulators (SERMS)				
raloxifene	Evista®, generics 60 mg tabs	60 mg daily	Hot flashes, leg cramps, thromboembolic events	• Can be taken with or without food
Hormone Therapy				
oral estrogens: *conjugated estrogens* *17-estradiol* ***transdermal estrogens:*** *17-estradiol*	Premarin® generics Estrace® EstroGel® gel Divigel® 0.1% gel Climara® patch Estradot® patch, generics	0.3 – 0.625 mg PO daily* 0.5 – 1 mg PO daily 1-2 pumps daily (0.75 mg/actuation) 0.5 – 1 mg daily 25 – 50 µg daily, applied once weekly 25 – 50 µg daily, applied twice weekly	Headache, nausea, water retention, breast tenderness, vaginal bleeding, thromboembolic events	• Possible increased risk of breast cancer • Cardiovascular risk depending on age and CVD risk factors • Potential for interactions with certain antiretrovirals. Consult a current reference for additional information • *0.625 conjugated estrogen dose or equivalent is required for fracture reduction • Women with a uterus will need to be on progesterone therapy for endometrial protection while on estrogen
Monoclonal antibodies against RANKL (receptor-activated nuclear factor-κB ligand)				
denosumab	Prolia® 60 mg sc injection	60 mg sc injection every six months	Hypocalcemia, cellulitis, back/limb pain, arthralgias, hypercholesterolemia, rash/eczema RARE: infections, osteonecrosis of the jaw	• Self administered • Increased risk of infections, safety in HIV patients is unknown (avoid in HIV+)
Anabolic agent (recombinant parathyroid hormone)				
teriparatide	Forteo® 20 µg (per dose) sc pen	20 µg sc daily	Dizziness, orthostatic hypotension, leg cramps RARE: hypercalcemia	• May decrease pain from vertebral fractures • Osteosarcoma reported in rats, though no reports in humans. Avoid if patient is at risk of osteosarcoma • Indicated for a maximum of 18 months duration. Antiresorptive therapy required post-teriparatide to maintain BMD gains

¥Best evidence in the HIV population with similar BMD increase as general population, but no fracture prevention data.

4 Prevention

General Preventative Measures

- Evaluate/treat modifiable risk factors
- Smoking cessation
- Alcohol – limit use
- Limit sodium intake to < 2300 mg daily
- Limit caffeine intake to < 400 mg daily (e.g. coffee 95-200 mg/cup; tea 50 mg/cup; cola 30-55 mg/can)
- Weight bearing exercise – 30 minutes 3 days/ week and resistance training
- Fall assessment and prevention; balance and gait exercises
- Calcium and vitamin D supplementation

Calcium

Calcium Supplementation in Adults- Recommended Daily Allowance (RDA)

Age (years)	Daily Calcium Requirement
19-50	1000 mg
50 +	1200 mg
Pregnancy or lactating women 18 +	1000 mg

Note: When possible, it is recommended to get the majority of calcium via dietary sources. In general, calcium supplements should be spaced apart from integrase inhibitor ARVs as recommended for each drug.

Oral Calcium Salts

Calcium Salt	Elemental Calcium (%)
Calcium acetate	25.3
Calcium carbonate	40
Calcium citrate	21
Calcium glucoheptonate	8
Calcium gluconate	9
Calcium lactate	13

Examples of Oral Calcium Products

Calcium Salt	Product Examples	Elemental Calcium
Calcium carbonate	Generic Products OS-CAL	500 mg 500 mg + 1000 IU Vitamin D_3
Calcium carbonate	Caltrate®	600 mg
Calcium lactate, gluconate and carbonate	Calcium Sandoz Forte® Calcium Sandoz Gramcal®	500 mg 1000 mg
Calcium citrate	Citracal Regular®	500 mg + 400 IU Vitamin D_3
Calcium lactogluconate	Wampole Liquid Calcium®	300 mg/15 mL solution

Note: Calcium is best absorbed when given in doses ≤ 500 mg/dose (elemental). When possible, dietary sources of calcium are recommended rather than taking supplements.

Examples of Dietary Sources of Calcium

Food Product	Qty	Calcium (mg)
Dairy Products		
Buttermilk	250 mL	300
Cheese	245 mg	200-250
Cottage Cheese, 1-2%	250 mL	150
Ice cream - soft serve	1 cone	232
Milk – whole, 2%, 1%, skim	250 mL	300
Yogurt – plain, 1-2%	175 mL	332
Yogurt – Frozen	250 mL	218
Yogurt – Fruit-flavoured	175 mL	200
Other beverages		
Orange juice – fortified	250 mL	300
Rice/Soy/Almond/Coconut beverages-fortified	250 mL	300

Food Product	Qty	Calcium (mg)
Other foods		
Almonds, dry roast	125 mL	186
Beans, white	250 mL	191
Broccoli	125 mL	33
Figs	10	150
Oatmeal – instant, fortified	32 g (1 pouch)	150
Orange	1 med.	50
Salmon, with bones (canned)	105 g	240
Sardines, with bones (canned)	55 g	200
Soybeans, cooked	250 mL	170
Tofu, with calcium sulphate	84 g	130

4. PREVENTION CONTINUED

Vitamin D

Vitamin D Supplementation in Adults – Recommended Daily Allowance (RDA)

Age (years)	Daily Vitamin D Requirement
19-50	600 IU (400-1000 IU)
50 +	800 IU (800-2000 IU)
Adults with osteoporosis	800 IU (800-2000 IU)

NOTE: Daily doses up to 2000 IU can be safely taken without medical supervision. **Routine supplementation for all Canadian adults year round is recommended.**

Vitamin D Forms and Examples of Oral Products

Chemical Name	Product Examples	Indication/Comments
Calciferol Vitamin D group	General Term	
Ergocalciferol Vitamin D_2 (plant, native form) 40 IU= 1 mcg	D-Forte® (50,000 IU/capsule)* Osto- D2® (50,000 IU/capsule)*	Less potent than vitamin D_3
Cholecalciferol Vitamin D_3 (animal) 40 IU= 1 mcg	Calciferol® (400 IU/tablet) Euro-D® (10,000 IU/capsule)* Generics (400, 1000/IU tablet) Wampole Liquid Vitamin D (1000 IU/15 mL)	Preferred supplement More potent than vitamin D_2
Calcitriol 1,25-diOH vitamin D (kidney)	Calcijex® (calcitriol 1.0 or 2.0 mcg/mL injectable)* Rocaltrol® (calcitriol 0.25 or 0.50 mcg/ capsule)* One-Alpha® (alfacalcidol 0.25 or 1.0 mcg/ capsule; 2 mcg/mL oral solution and injectable)*	Chronic renal failure Most active form of vitamin D Renal hydrolysis not required to activate calcitriol Prescription products for renal disease only

*Prescription required. Note: **Calcidiol** is 25(OH) vitamin D and circulates in blood in this form. This is the lab test used when ordering vitamin D concentrations.

Examples of Dietary Sources of Vitamin D

Food Product	Qty	Vit. D (IU)
Eggs – yolk	1	25
Cod liver oil	5 mL	450
Fish	90-100 g	Ranges depending on fish spp.
Mackerel		310
Salmon		250-1000
Sardines		250
Tuna		236
Margarine	5 mL	60
Milk - fortified with Vit D_3	250 mL	100
Orange juice – fortified	250 mL	100
Soy/Almond/Coconut beverages – fortified	250 mL	120-180

4. PREVENTION CONTINUED

Vitamin D Deficiency

Who to screen for vitamin D deficiency?

- Patients with recurrent fractures, hip fracture, low BMD, osteoporosis
- Patients with a history of falls
- Consider testing: patients with dark skin, dietary deficiency, malabsorption, little sun exposure, obesity, CKD, efavirenz use

NOTE: Routine screening is unnecessary in most healthy adults at low risk for vitamin D deficiency (e.g. < 50 y.o., with no osteoporosis or conditions affecting vitamin D absorption or action)

What to order?

- Serum 25-hydroxyvitamin D [25(OH)D] (i.e. calcidiol)

Classification of Vitamin D Status

Serum 25(OH)D Concentration (nmol/L)	Category
< 25	Vitamin D deficiency
25-75	Vitamin D insufficiency (suboptimal)
> 75	Desirable vitamin D status
> 250	Potential toxicity

Conversion (conventional to SI units):
25(OH)D ng/mL x 2.5 → nmol/L

Examples of Oral Vitamin D Replacement Therapy in Adults with Vitamin D Deficiency

Replacement Therapy*
25(OH)D insufficiency → Vitamin D_3: 2000 IU daily for 12 weeks
25(OH)D deficiency → Vitamin D_2: 50,000 IU once weekly for 8-12 weeks

*Dosing Tips:

- Generally, 25(OH)D concentrations ↑ by 1.0 nmol/L per 40 IU (1 ug) of vitamin D_3 given daily
- Calculate daily replacement dose and decide on the best administration schedule

Sample calculation:

- If the baseline 25(OH)D level is 10 nmol/L and target is 75 nmol/L, then calculate as follows:
  - 75-10= 65 nmol/L; 65/1= 65; 65 x 40 IU= 2600 IU of Vitamin D_3 daily → round up to 3000 IU daily x 8 weeks
- This calculation assumes that 25(OH)D concentrations ↑ by 1.0 nmol/L per 40 IU of Vitamin D_3

Monitoring

- Repeat 25(OH)D levels after about 3-4 months of adequate supplementation
- *Goal of Therapy:* 25(OH)D level > 75 nmol/L (optimal)
- Do not repeat serum concentrations if an optimal concentration is achieved
- *Maintenance Therapy:* Continue with RDA dosing once optimal concentrations are achieved

Definitions

Fragility Fracture: Fracture that occurs spontaneously or following a minor trauma (e.g. falling from standing height).

Osteopenia: Decreased bone mineral density (BMD). T-score between -2.5 and -1 SD (for postmenopausal women and men ≥ 50 y.o.); Z-score ≤ -2 SD (indicates low BMD if < 50 y.o.).

Osteoporosis: Low bone mass, deterioration of bone/altered bone strength leading to an increased risk of fracture. T-score ≤ -2.5 SD (for postmenopausal women and men ≥ 50 y.o.); Z-score ≤ -2 SD (indicates low BMD if < 50 y.o.).

Osteomalacia: Impaired bone mineralization, often caused by severe vitamin D deficiency; accompanied by muscle weakness, bone pain, stiffness, bone fracture; treated with vitamin D, calcium +/- phosphate, not bisphosphonates; most important differential diagnosis for low BMD.

T-Score: Refers to the number of standard deviations a person's BMD varies from the mean BMD of a young normal reference mean with peak bone mass (25-30 y.o.). This value has been validated in post-menopausal women and men > 50 y.o. as a predictor of fracture risk.

Z-Score: Refers to the number of standard deviations a person's BMD varies from the mean BMD (matched for age, gender and ethnicity).

CAROC System: Risk Assessment Tool developed by a "Joint initiative of the Canadian Association of Radiologists and Osteoporosis Canada." www.osteoporosis.ca/multimedia/pdf/CAROC.pdf

FRAX®Algorithm: World Health Organization (WHO) Fracture Risk Assessment Tool. The FRAX®algorithm was developed by the WHO and gives a 10-year probability of the risk of fracture (hip, clinical spine, forearm, hip and/or humerus). The tool has been validated for use in Canada and a number of other countries. www.shef.ac.uk/FRAX/

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