OSTEOPOROSIS MEDICATIONS

Drug	Dose	Metabolism	Efficacy	Interactions	Side Effects	Cost/Coverage
BISPHOSPHONATES						
Alendronate Fosamax® Fosavance® 70mg/2800IU 70mg/5600IU (Alendronate/Vitamin D3) (Merck)	*Prevention:* 5mg once daily *Treatment:* 10 mg once daily, OR 70mg once weekly *(1 hour prior to meals or other medications)*	Not metabolized by the liver; 50% excreted renally.	↑BMD in lumbar spine, femoral neck, and trochanter in women with <2.5SD below young peak adult bone mass with treatment dose over 3-4 years. ↓risk of vertebral, hip and non-vertebral fractures by 35-50% Studied in HIV population (at 70mg dose + calcium/vitamin D)[1,2,3]. Benefit in ↑BMD at 48 weeks, but studies not powered to detect ↓ fractures.	↓ absorption with food, antacids, iron, calcium ↑ GI side effects with NSAIDS, steroids	Nausea, abdominal pain, acid regurgitation, headache, constipation, diarrhea, esophagitis, ulceration	$10.06/month (70mg weekly) to $14.96/month (10 mg daily) ODB Blue Cross - special authorization (Fosavance® 70mg/2800 IU- not a benefit) NIHB-prior authorization
Etidronate Didrocal® (Warner Chilcott)	1 tablet daily (400 mg etidronate x14 days then calcium carbonate 500mg elemental x76 days) *1 hour prior to meals or other medications*	Not metabolized by the liver; 50% of absorbed dose is excreted renally. Unabsorbed etidronate is reported to be excreted intact via the feces (up to 99%)	↑BMD in the lumbar spine (1-2%) over 1 year ↓risk of vertebral fractures	↓ absorption with food, antacids, iron, calcium	Nausea, abdominal pain, acid regurgitation, headache, constipation, diarrhea, esophagitis, ulceration	$19.99/90 days (ODB) Blue Cross-regular benefit NIHB-regular benefit
Risedronate Actonel®	*Prevention/treatment:* 5mg once daily, OR	Not metabolized by the liver; up to	↑BMD (See Alendronate)	↓ absorption with food, antacids, iron, calcium	Nausea, abdominal pain, acid regurgitation,	$9.96/month (35mg once

Drug	Dose	Metabolism	Efficacy	Interactions	Side Effects	Cost/Coverage
(Aventis)	35mg weekly, OR 150mg once monthly *(1 hour prior to meals or other medications)*	80% excreted in the urine.	↓risk of vertebral, hip and non-vertebral fractures by 35-50%		headache, constipation, diarrhea, esophagitis, ulceration	weekly), $27.32/month (5 mg daily), $43.15/month (150 mg once monthly), ODB Blue Cross-special authorization (75mg/150mg not a benefit) NIHB-prior approval (75mg/150mg not a benefit)
Zoledronic Acid Aclasta® (Novartis)	*Treatment:* 5mg IV infusion once yearly	Not metabolized by the liver; 39 ± 16% excreted in the urine.	↑BMD (See alendronate) ↓risk of vertebral, hip and non-vertebral fractures by 40-70% Studied in HIV population.[4,5] Benefit in ↑BMD at 12 months, but not powered to detect ↓ fractures.	*Theoretical interactions:* - ↓ serum calcium with loop diuretics, aminoglycosides - nephrotoxicity with NSAIDs and other nephrotoxins (ie. Tenofovir, although no documented interactions).	Within first 3 days of infusion: fever, myalgia, flu-like symptoms, arthralgia and headache (resolve thereafter) ? risk of atrial fibrillation – not a confirmed association	$670.80/injection ($55.90/month) ODB Blue Cross-special authorization (only for Paget's disease) NIHB-prior authorization (only for Paget's disease)
ANABOLIC AGENTS						
Teriparatide Forteo® (Eli Lilly)	*Treatment:* 20mcg SC once daily x24 months	Metabolized via nonspecific proteolytic hepatic enzymes (no specific CYP metabolism information	↑BMD in lumber spine, femoral-neck and whole-body ↓risk of vertebral and non-vertebral fractures by 53-65%	↑ serum calcium with loop & thiazide diuretics Use with caution in digoxin patients - ↑serum calcium may predispose to digitalis toxicity.	Nausea, headache, arthralgia, leg cramps, dizziness, pain at injection site Transient hypercalcemia/	$1400/month (not covered via ODB) Blue Cross-not a benefit NIHB-not a

Drug	Dose	Metabolism	Efficacy	Interactions	Side Effects	Cost/Coverage
		available)			hypoparathyroidism Although no reports in humans, potential risk of osteosarcoma	benefit
ESTROGEN/SERMS						
Conjugated Estrogen Premarin® (Wyeth-Ayerst)	0.3mg or 0.625mg once daily	Metabolized by CYP3A4 (30%), glucuronidation	↑BMD in lumbar spine and hip over 2 years. ↓risk of vertebral, hip and total osteoporotic fractures. Should only be used as symptomatic therapy for relief of menopausal symptoms. Should be used in the smallest dose for the shortest duration.[6]	Avoid OC use if amprenavir, or unboosted fosamprenavir. In general, NNRTIs & boosted PIs have the potential to decrease oral contraceptive (OC) effectiveness (ethinyl estradiol/ norethidrone acetate/ norgestimate) mostly through induction of CYP 3A4 and/or glucuronidation – resulting in ↓ Cmax/AUC and potential for ↓ OC efficacy[7]. ARVs which may ↓ AUC of OC: ritonavir[8], lopinavir/r, nelfinavir, darunavir/r[9], tipranavir/r, efavirenz[10], nevirapine[11], rilpivirine[12] RTV & NFV[13] can ↑estrogen metabolism by ↑ glucuronidation which may decrease effectiveness [14,15] ARVs which may ↑ AUC and OC levels: atazanavir[16], amprenavir, indinavir. Delavirdine, saquinavir[17] and tenofovir result in no OC level changes. [18]	Abdominal pain, amenorrhea, breast tenderness, depression, diarrhea, edema, fatigue, mennoragia, pulmonary embolism, weight gain	$2.36/month (ODB) Blue Cross-regular beneft NIHB-regular benefit

Drug	Dose	Metabolism	Efficacy	Interactions	Side Effects	Cost/Coverage
				Please refer to the Oral Contraceptive and ARV Drug Interactions chart for more details ↓effect of warfarin Counteract effects of bromocriptine ↓metabolism of cyclosporine, TCA antidepressants		
Raloxifene Evista® (Eli Lilly)	60mg once daily	Extensive 1st pass metabolism in the liver to glucuronide conjugates; No reported CYP metabolism	↑BMD of several sites by ~2.5% over 1-2 years ↓risk of vertebral fractures	No documented ARV interactions with raloxifene, however, caution when use.[19-20] Cholestyramine ↓raloxifene absorption May alter the effects of warfarin (monitor INR)	Hot flashes, muscle cramps, weight gain, peripheral edema, myalgia, insomnia, breast tenderness, abdominal pain, vaginal bleeding ↑ risk of deep vein thrombosis, and pulmonary embolism (not associated with ↑ CV risk)	$27.51/month (ODB) Blue Cross-special authorization NIHB-prior approval
Monoclonal Antibody against RANKL						
Denosumab Prolia® (Amgen)	60mg sc every six months (self-administered injection)	N/A	↑BMD of several sites by 5.2-8.8% over 1-3 years ↓ risk of vertebral, hip and non-vertebral fractures in postmenoposal women	Interactions with other drugs have not been established.	Back pain, musculoskeletal pain, rash, constipation, infection (ie cellulitis), hypercholesterolemia, hypocalcemia	$450/dose (not covered via ODB) Blue Cross not a benefit NIHB not a benefit

Drug	Dose	Metabolism	Efficacy	Interactions	Side Effects	Cost/Coverage
CALCITONIN						
Calcitonin Calcimar® (Sanofi-Aventis), MiacalcinNS® (Novartis)	200IU intranasal once daily	Metabolized primarily in the kidneys and to a lesser extent in the blood and peripheral tissues	Stabilizes BMD in lumbar spine and hip ↓risk of vertebral fractures, and pain associated with acute vertebral fractures	No significant drug interactions reported	Rhinitis, nasal dryness, epistaxis Flushing, nausea, vomiting, dizziness (all usually subside spontaneously)	$64.69/month (ODB EAP) Blue Cross-special authorization (intolerant/failed etidronate) NIHB-prior approval (intolerant/failed bisphosphonate and raloxifene)
CALCIUM/VITAMIN D SUPPLEMENTATION						
Calcium Calcium carbonate: 500-1500mg (elemental calcium 200mg -600mg) (needs higher pH to be absorbed) Calcium citrate (elemental calcium 200-300mg)	1000-1500 mg elemental calcium daily (in divided doses) Note: use calcium citrate if patient on proton pump inhibitor.	Calcium is excreted renally. Unabsorbed calcium is excreted in the feces	↓bone loss ↑hip BMD & ↓fracture risk in combination with Vitamin D.[6,21]	↓absorption of bisphosphonates, phenytoin, tetracyclines, quinolones (space apart by >4 hours)	Constipation, flatulence, gastric distention	$8.99/350 tabs (generic 500mg calcium tablet) Blue Cross-not a benefit NIHB-regular benefit (calcium 500mg tab; 20mg/mL liquid; calcium 500mg/vit D 400IU tab)
Vitamin D 200-1000 IU tablets 400IU/mL liquid 400IU or 1000IU drops	600-2000 IU/day >2000 IU/day on recommendation of health care professional only (option for prescription strength Vitamin D2	Extensively metabolized by the kidney and liver. Excreted primarily in bile.	↑calcium absorption ↓bone loss ↑hip BMD & ↓fracture risk in combination with Calcium. ↓ risk of falls.[6]	Efavirenz may induce hepatic catabolism of 25(OH)D via the CYP450 system resulting in vitamin D insufficiency[22]. In one case, Vitamin D levels were decreased to below the limit	Metallic taste, in high doses can cause hypercalcemia or hypercalciuria	$9.97/500 tabs (Vit D 1000 IU tab) $7.99/bottle (Vit D 1000 IU/drop)

Drug	Dose	Metabolism	Efficacy	Interactions	Side Effects	Cost/Coverage
50,000 IU capsule (D-Forte)	50,000 IU weekly x 8 weeks to treat low vitamin D levels)			of detection (18nmol/L) after 18 months of treatment[23]. Tenofovir use may be correlated excessive renal phosphate and calcium losses and 1-hydroxylation defects of vitamin D[24,25] Phenytoin and phenobarbital may ↓effects of vitamin D Cholestyramine, mineral oil may ↓absorption of Vitamin D		Blue Cross-not a benefit (except IFH-400IU tab regular benefit) NIHB-regular benefit (drops, liquid, 400/800/1000 IU tablet; 50,000IU D2 capsule))

Legend: ***BMD****=Bone mineral density;* ***CYP****=Cytochrome P450;* ***NSAIDS****=Non-steroidal anti-inflammatory drugs;* ***NIHB-Non-Insured Health Benefits (Indian Affairs); ODB = Ontario Drug Benefit, IFH-Interim Federal Health***
Note: Blue Cross- includes AISH. SFI, IFH

References:

[1] Guaraldi, G. et al. Alendronate reduces bone resorption in HIV-associated osteopenia/osteoporosis. HIV Clinical Trials. 2004. 5:269-277.
[2] Mondy, K. et al. Alendronate, vitamin D, and calcium for the treatment of osteopenia/osteoporosis associated with HIV infections. Journal of Acquired Immune Deficiency Syndromes. 2005. 38: 426-431.
[3] McComsey, G. et al. Alendronate with calcium and vitamin D supplementation is superior to calcium and vitamin D along in the management of decreased bone mineral density in HIV. AIDS. 2007. 30: 2473-2482.
[4] Huang, J. et al. A double-blinded, randomized controlled trial of zoledronic therapy for HIV-associated osteopenia and osteoporosis. AIDS. 2009. 23: 51-57.
[5] Bolland, M. et al. Annual Zoledronate increases bone density in highly active antiretroviral therapy-treated human immunodeficiency virus-infected men: a randomized control trial. The journal of clinical endocrinology & metabolism. 2007. 92(4): 1283-1288
[6] Reid, R. et al. Menopause and osteoporosis Update 2009. SOGC Clinical Practice Guideline. 2009. 31: S1-S47.
[7] HIV Insite. Antiretroviral management charts and tables [online]. Available from URL: http://www.hivinsite.com/InSite?page=ar-00-00-02 [Accessed 2010 May 11]
[8] Ouellet, D. et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. British Journal of Clinical Pharmacology. 1998. 46:111-6.
[9] Sekar, V. et al. Pharmacokinetic interaction between ethinyl estradiol, norethindrone and darunavir with low-dose ritonavir in healthy women. Antiviral Therapy. 2008. 13. 563-569
[10] Carten, M. et al. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel, and efavirenz. Abstract. 2010. 17th Conference on Retroviruses and Opportunistic Infections.
[11] Mildvan, D. et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. Journal of the Acquired Immune Deficiency Syndrome. 2002. 29:471-477
[12] Crauwels, H. et al. Pharmacokinetic interaction study between TMC278, an NNRTI, and the contraceptives norethindrone plus ethinylestradiol. Abstract. 2009.

12th European AIDS Conference,
[13] Kerr, B. et al. Overview of in-vitro and in-vivo drug interaction studies of nelfinavir mesylate, a new HIV-1 protease inhibitor. Abstract. 1997. 4th Conference on Retroviruses
and Opportunistic Infections.
[14] Ouellet, D. et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. British Journal of Clinical Pharmacology. 1998. 46: 111-116.
[15] HIV Insite. Antiretroviral management charts and tables [online]. Available from URL: http://www.hivinsite.com/InSite?page=ar-00-00-02 [Accessed 2010 May 11]
[16] Tackett, D. et al. Atazanavir: a summary of two pharmacokinetic drug interaction studies in healthy volunteers. Abstract. 2003. 10th Conference on Retroviruses and Opportunistic Infections.
[17] Frohlich, M. et al. Oral contraception does not alter single dose saquinavir pharmacokinetics in women. British Journal of Clinical Pharmacology 2004. 57:244-252.
[18] HIV Insite. Antiretroviral management charts and tables [online]. Available from URL: http://www.hivinsite.com/InSite?page=ar-00-00-02 [Accessed 2010 May 11]
[19] Brown, K. et al. Drug interactions with new and investigational antiretrovirals. Clinical pharmacokinetics. 2009. 48(4): 211-241
[20] Dickinson, L. et al. Pharmacokinetics and drug-drug interactions of antiretrovirals: an update. Antiviral research. 2010. 85: 176-189.
[21] Tang, B. et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007. 370: 657-666.
[22] Dao, C. et al. Assessment of vitamin D levels among HIV-infected patients in the study to understand the natural history of HIV/AIDS in the era of effective therapy: SUN study. Abstract. 2010. 17th Conference on Retroviruses and Opportunistic Infections.
[23] Gyllensten, K. et al. Severe Vitamin D deficiency diagnosed after introduction of antiretroviral therapy including efavirenz in a patient living at latitude 59°N. AIDS. 2006. 20(14): 1906-1907.
[24] Fux, C. et al. Tenofovir use is associated with an increase in serum alkaline phosphatase in the Swiss HIV Cohort Study. Abstract. 2008. 15th Conference on Retroviruses and Opportunistic Infections.
[25] Mueller, C. et al. High prevalence of severe vitamin D deficiency in cART-naïve and successfully treated Swiss HIV patients. Abstract. 2010. 17th Conference on Retroviruses and Opportunistic Infections.

Amgen Canada Inc. Prolia® product monopgraph April 5, 2011. Available at . http://www.amgen.ca/Prolia_PM.pdf. Accessed June 28, 2011.