

Vaginal Flora May Affect HIV RNA Concentrations

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CHARLESTON, S.C. — Certain vaginal isolates affect the quantity of HIV RNA in cervicovaginal lavage, a study suggests.

Hydrogen peroxide-producing lactobacilli, for example, were associated with a significant decrease in cervicovaginal lavage (CVL) HIV RNA concentrations, and *Trichomonas vaginalis*, *Prevotella bivia*, and *Mycoplasma hominis*. Other anaerobes

were associated with increases in CVL HIV RNA concentrations, Jane Hitti, M.D., reported at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

Factors affecting the HIV RNA concentrations are important, because genital viral load is an important determinant of sexual and perinatal HIV transmission, she noted.

For the study, 38 HIV-positive women completed 163 study visits. Vaginal cul-

tures, CVL, and plasma were collected at each visit for HIV RNA quantitation. Of 163 CVL samples, 95 had detectable HIV RNA, and the levels correlated significantly with plasma HIV RNA levels, said Dr. Hitti of the University of Washington, Seattle.

After adjustment for log plasma HIV RNA, the log difference in CVL HIV RNA was significant for *H₂O₂* lactobacillus and *T. vaginalis*. Increased CVL HIV RNA concentrations were associated, although not significantly, with *M. hominis*, *P. bivia*, black

gram negative rods, *Candida albicans*, and bacterial vaginosis or indeterminate flora.

Also, CVL HIV RNA concentrations were increased with higher vaginal concentrations of IL-8 in this study.

Several vaginal isolates appear to directly influence CVL viral load, and the effects appear to be independent of plasma viral load, she concluded, noting that an antibiotic treatment trial is underway to determine whether treatment for bacterial vaginosis and associated infections will decrease genital viral load.

“A very logical next step would be looking at ways to augment endogenous lactobacilli and looking at what effects that has,” she said.

The prevalence of *H₂O₂*-producing lactobacilli is lower than what has been reported among HIV-negative women, even in the presence of bacterial vaginosis, she explained.

Treatment of osteoporosis Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX® (alendronate sodium) 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either FOSAMAX or placebo are presented in the following table.

	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX* % (n=196)	Placebo % (n=397)	FOSAMAX** % (n=3236)	Placebo % (n=3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

*10 mg/day for three years
**5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred. One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B1% of patients in either treatment group are presented in the following table.

	Once Weekly FOSAMAX		FOSAMAX	
	70 mg % (n=519)	10 mg/day % (n=370)		
Gastrointestinal				
abdominal pain	3.7	3.0		
dyspepsia	2.7	2.2		
acid regurgitation	1.9	2.4		
nausea	1.9	2.4		
abdominal distention	1.0	1.4		
constipation	0.8	1.6		
flatulence	0.4	1.6		
gastritis	0.2	1.1		
gastric ulcer	0.0	1.1		
Musculoskeletal				
musculoskeletal (bone, muscle, joint) pain	2.9	3.2		
muscle cramp	0.2	1.1		

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B2% of patients treated with either FOSAMAX or placebo are presented in the following table.

	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=109)	Placebo % (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Other studies with FOSAMAX® (alendronate sodium)

Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

	FOSAMAX 10 mg/day % (n=157)	FOSAMAX 5 mg/day % (n=161)	Placebo % (n=159)
	Gastrointestinal		
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to A2.0 mg/dL (0.65 mM) were similar in both treatment groups.

FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol)

In a fifteen week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of FOSAMAX PLUS D was similar to that of FOSAMAX once weekly 70 mg.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use with alendronate:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise and rarely, fever have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypercalcemia has occurred, generally in association with predisposing conditions.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, Information for Patients, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, Dental).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain).

Skin: rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

For more detailed information, please read the Prescribing Information.

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Smoking Linked To *G. vaginalis* And *M. hominis*

CHARLESTON, S.C. — Smoking has been linked with the occurrence of bacterial vaginosis, but a recent study further elucidating its effects on microvaginal flora suggests that smoking is particularly associated with heavy growth of *Gardnerella vaginalis* and *Mycoplasma hominis*.

“I think at this point, investigations are needed to determine if smoking should be considered a modifiable risk factor for bacterial vaginosis,” Harold C. Wiesenfeld, M.D., said at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

In the prospective cross-sectional study of 749 nonpregnant women, 56% were smokers, and most of them were daily smokers. Bacterial vaginosis was identified in 66% of the overall study population, compared with 69% of the smokers.

Heavy colonization with *G. vaginalis* was present in 72% of smokers vs. 64% of nonsmokers, and heavy colonization with *M. hominis* was present in 43% of smokers vs. 32% of nonsmokers.

Colonization with *H₂O₂*-producing lactobacilli was present in 33% of smokers vs. 41% of nonsmokers, said Dr. Wiesenfeld of the department of ob.gyn. and reproductive sciences at the University of Pittsburgh.

The women studied were recruited from an STD clinic, family planning clinics, and ambulatory gynecology clinics. All underwent a standardized interview and physical examination that included a Gram's stain, *Trichomonas vaginalis* culture, and semiquantitative cultures of vaginal fluid for aerobic and anaerobic organisms.

Additionally, cervical samples were cultured for *Neisseria gonorrhoeae* and tested by polymerase chain reaction for *Chlamydia trachomatis*.

Smoking in this study was not associated with gonorrhea, *C. trachomatis*, or *T. vaginalis* infection.

—Sharon Worcester