# Many HIV-Positive Women Fail to Get Pap Test

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Southwest Bureau

Los Angeles — Many women do not go for recommended Pap testing after being diagnosed with the human immunodeficiency virus, despite being at elevated risk for cervical cancer.

Chart reviews of 428 women at an urban HIV clinic found 48% had Pap tests within a year of enrollment at the clinic. Yet the clinic's physicians had referred all the women for testing, many of them repeatedly, Laurie C. Zephyrin, M.D., reported at the annual meeting of the Society for Gynecologic Investigation.

Those women who had other social factors or who tended to be sicker tended not to have their Pap tests. But they were referred. The primary care physicians were definitely doing their job in referring patients," said Dr. Zephyrin of the department of obstetrics and gynecology at Johns Hopkins University in Baltimore.

Guidelines call for Pap testing every 6 months in the first year after diagnosis with HIV, and once annually thereafter, according to Dr. Zephyrin. With so many women not being screened in the first year, she called for simplifying the health care delivery system to make tests more accessible at primary care sites.

"I really think there needs to be a reorganization of how we deliver care, particularly to women with conditions such as HIV," she said.

Dr. Zephyrin and her coinvestigators followed women who enrolled in a large urban HIV clinic affiliated with Johns Hopkins from January 1998 to November 2002. The population was predominantly African American and low income with a median age of 38. More than a third, or 36%, were intravenous drug users.

One in four patients had normal CD4 counts of at least 500. Dr. Zephyrin said more than 30% had "a diagnosis consistent with AIDS," as reflected in CD4 counts below 200.

About three-fourths of the women, 74%, were on highly active antiretroviral therapy (HAART).

The proportion that had a Pap test increased with time spent in the program.

**Compared with** women with normal CD4 counts, women with counts of 200-500 were 39% less likely to have a Pap test during the first year.

Nearly two-63%. thirds. were screened within 2 years and 75% were screened within 3 years. By the end of 6 years, 87% had at least one Pap test.

In the first vear, women were 37% more likely to have a Pap test and women

on HAART were 38% more likely, compared with their nonblack and non-HAART counterparts.

Dr. Zephyrin speculated that the patients receiving HAART were in the clinic more often and might have been more compliant.

Compared with women with normal CD4 counts, women with counts of 200-500 were 39% less likely to have a Pap test during the first year.

Similarly, intravenous drug users were 32% less likely than were those who were

Dr. Zephyrin reported that while 61% of Pap tests were normal, women who had been diagnosed with AIDS were four times more likely to have an abnormal Pap test result within the first year.

The clinic has 20 primary care physicians and six midlevel practitioners, according to Dr. Zephyrin. The staff was qualified to do Pap tests but often did not have the proper equipment and, therefore, referred patients to a gynecology clinic,

"You can't do the Pap test unless you have the stirrups and the speculum and a chaperone. The provider may be willing and able to do it, but cannot do it because of the system variables that are in place," she said.

"It becomes very challenging when you have to refer these women to other areas to get care. Because there is so much going on in their lives, making delivery of care as simple as possible will really allow them to get the screening they need," Dr. Zephyrin said.

She also questioned whether the guideline should be stratified to reduce the first year screening requirement from two tests to one for women with normal CD4 counts.



### **Brief Summary of Prescribing Information.**

For complete details, please see full Prescribing Information for NAMENDA.

### INDICATIONS AND USAGE

NAMENDA (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS
NAMENDA (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients

### PRECAUTIONS

Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

Neurological Conditions
Seizures: NAMENDA has not been systematically evaluated in patients with a seizure disorder. In clinical trials of NAMENDA, seizures occurred in 0,2% of patients treated with NAMENDA and 0,5% of patients treated

NAMENDA undergoes partial hepatic metabolism, but the major fraction of a dose (57-82%) is excreted unchanged in urine. The pharmacokinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.

### Renal Impairment

There are inadequate data available in patients with mild, moderate, and severe renal impairment but it is likely that patients with moderate renal impairment will have higher exposure than normal subjects. Dose reduction in these patients should be considered. The use of NAMENDA in patients with severe renal impairment is not recommended

# Drug-Drug Interactions

nvI-D-aspartate (NMDA) antagonists: The combined use of NAMENDA with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of NAMENDA on substrates of microsomal enzymes: In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on NAMENDA: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Coadministration of NAMENDA with The ACHE inhibitor donepezil HCI did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of departed the composition of the composition of

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCT2), triamterene (TA), cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of NAMENDA and HCTZ/TA did not affect the bioavallability of either memantine or TA, and the bioavallability of HCTZ decreased by 20%. Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate), and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

used with caution under these conditions. 
Carcinogenesis, Mutagenesis and Impairment of Fertility
There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks.
Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro S. typhimurium or E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells. se hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy Pregnancy Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended

which are 9 and 30 times, respectively, the maximum recommended human dose (MRHD) on a mg/m² basis). Slight maternal toxicity, decreased pup weights and an increased incidence of nonossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal

toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the postpartum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m² basis. There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Nursing Mothers

It is not known whether memantine is excreted in human breast milk Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

ere are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children ADVERSE REACTIONS

erience described in this section derives from studies in patients

with Alzheimer's disease and vascular dementia. Adverse Events Leading to Discontinuation: In placebo-controlled trials in which dementia patients received doses of NAMENDA up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the NAMENDA group as in the placebo group. No individual nt was associated with the discontinuation of treatment in 1% or more of NAMENDA-treated patients and at a rate greater than placebo

or more of NAMIENDA-treated patients and at a rate greater train placebo.

Adverse Events Reported in Controlled Trials: The reported adverse
events in NAMIENDA (memantine hydrochloride) trials reflect experience
gained under closely monitored conditions in a highly selected patient
population. In actual practice or in other clinical trials, these frequency
estimates may not apply, as the conditions of use, reporting behavior and
the types of patients treated may differ. Table 1 lists treatment-emergent
signs and symptoms that were reported in at least 2% of patients in
placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with NAMENDA than for those tre with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving NAMENDA and at a Higher Frequency than

Body System	Placebo	NAMENDA
Adverse Event	(N = 922)	(N = 940)
	%	%
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral		
Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Ha <b>ll</b> ucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in NAMENDA-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormal, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Vital Sign Changes: NAMENDA and placebo groups were compared with vital sign unlarges: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with NAMENDA. A comparison of superior and standing vital sign measures for NAMENDA and placebo in elderly normal subjects indicated that NAMENDA treatment is not associated with orthostatic changes.

Laboratory Changes: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with NAMENDA treatment.

ECG Changes: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with NAMENDA treatment.

Other Adverse Events Observed During Clinical Trials
NAMENDA has been administered to approximately 1350 patients with
dementia, of whom more than 1200 received the maximum recommended
dose of 20 mg/day. Patients received NAMENDA treatment for periods of dose of 20 mg/day, ratieffus received nameroa treatment on periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment.

Treatment emergent signs and symptoms that occurred during 8 controlled

clinical trials and 4 open-label trials were recorded as adverse events by

the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of

an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events — those occurring in at least 1/100 patients; infrequent adverse events — those occurring in 1/100 to 1/1000 patients. These adverse events are to necessarily related to NAMENDA treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Cardiovascular System: Frequent: cardiac failure. Infrequent: angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: Frequent: transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. *Infrequent* paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia

Gastrointestinal System: Infrequent: gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: Frequent: anemia. Infrequent: leukopenia.

Metabolic and Nutritional Disorders: Frequent: increased alkaline phosphatase, decreased weight. Infrequent: dehydration, hyponatremia aggravated diabetes mellitus.

Psychiatric Disorders: Frequent: aggressive reaction. Infrequent: delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paroniria, delirium, depersonalization, neurosis, suicide attempt.

**Skin and Appendages:** Frequent: rash. Infrequent: skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

Special Senses: Frequent: cataract, conjunctivitis, Infrequent: macula blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment

**Urinary System:** Frequent: frequent micturition. Infrequent: dysuria, hematuria, urinary retention.

## ADVERSE EVENTS FROM OTHER SOURCES

Memantine has been commercially available outside the United States since 1982, and has been evaluated in clinical trials including trials in patients with neuropathic pain, Parkinson's disease, organic brain syndrome page in swin reuning and spatistic bulk. The following adverse events of possible importance for which there is inadequate data to determine the causal relationship have been reported to be temporally associated with memantine treatment in more than one patient and are not described elsewhere in labeling: acne, bone fracture, carpal tunnel syndrome, claudication, hyperlipidemia, impotence, otitis media, thrombocytopenia

Impotence, ottlis media, thrombocytopenia.

ANIMAL TOXICOLOGY
Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in ordents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m² basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

Controlled Substance Class: Memantine HCl is not a controlled substance Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine. In a documented case of an overdosage with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

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