

# Undetectable HIV Doesn't Preclude Transmission

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BOSTON — Women on highly active antiretroviral therapy for human immunodeficiency virus whose plasma viral load is below detectable levels may continue to shed the virus intermittently in the genital tract, Dr. Susan Cu-Uvin said at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

“This finding means we cannot rule out

the possibility of continued risk of HIV transmission among women in whom the virus appears to be well controlled,” said Dr. Cu-Uvin of Brown University, Providence, R.I.

The advent of highly active antiretroviral therapy (HAART) has resulted in significant decreases in the replication of HIV in the blood of infected patients, and in so doing it has substantially reduced the associated morbidity and mortality of the disease, Dr. Cu-Uvin said.

“However, several studies have shown evidence of discordance between the RNA shedding of HIV in the blood and in the female genital tract, and when it comes to sexual transmission of HIV, the big player is the amount of genital tract viral load, not the plasma viral load,” she said. “Unfortunately, because the only commercially available tools for assessing HIV viral load are those that look at RNA shedding in plasma, we use plasma viral load as a surrogate for how infectious a given patient is, yet this may not always reflect what is happening in the genital tract.”

Dr. Cu-Uvin and colleagues sought to assess the pattern of HIV genital tract shedding among women already on HAART with sustained below detectable plasma viral loads. Of 55 women with HIV enrolled in an ongoing study of HAART, 49 with below detectable plasma viral load for at least 6 months were included in the analysis. Each of the women underwent serum plasma and genital tract sampling every 4

weeks for 12 weeks. Genital tract secretions were collected from the endocervix, ectocervix, and vagina in 40 of the women, and from the vagina only in 9 women who had previous hysterectomies. The lower limit of viral detection was 80 copies per milliliter for plasma and 3,300 copies per milliliter for the genital tract, Dr. Cu-Uvin noted.

The immune status of all of the patients was “generally good,” with a median CD4 count of 412 cells/mm<sup>3</sup>, said Dr. Cu-Uvin. In terms of demographics, 45% of the patients were African American, 35% were white, and 15% were Hispanic, and the median patient age was 45 years. An assessment for “classic” STDs showed not much gonorrhea, chlamydia, or syphilis, “which was not surprising, because the population was older,” Dr. Cu-Uvin said. All of the patients were positive for herpes simplex virus type 2, she noted.

Patients were grouped based on their genital tract HIV RNA patterns, Dr. Cu-Uvin explained. Nonshedders were those women with no evidence of detectable genital tract HIV during study visits. Indeterminate shedders had at least one episode of genital tract shedding with no available measurement prior to or following the episode. Women who had genital tract shedding between negative visits were described as intermittent shedders, and those who had at least two consecutive episodes of genital tract shedding were persistent shedders.

Of the 49 patients enrolled, 46 main-

tained below detectable plasma viral loads during the course of the study. “What was astonishing to us is that more than half of those women had some degree of detectable genital tract shedding,” Dr. Cu-Uvin said. Specifically, 26% of the women with sustained below detectable plasma viral load were indeterminate shedders, 18% were intermittent shedders, and 8% were persistent shedders, “despite being on HAART and having below detectable levels of virus in their plasma,” she said. Among the nine women with total hysterectomy, one demonstrated persistent shedding in the vagina, whereas the others were classified as nonshedders, she said.

Although logistic regression analyses showed the probability of detecting HIV RNA in the genital tract subcompartment was low when plasma viral load was below detectable levels, Dr. Cu-Uvin said, “it worries us that there are some women on antiretroviral therapy who have a very good response in the blood, who, if you look hard enough and at multiple time points, will have evidence of genital tract HIV RNA.”

What this means clinically, she said, is that the potential for sexual transmission of HIV exists even among women whose virus appears to be well controlled. “So, for example, when a woman on HAART comes to me and says she wants to have a baby, there is no way to assure her, even if she has a below detectable plasma viral load, that it's safe to have unprotected sex.”

## LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia\* (2% and <1%).\* Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). §Denominator used was for females only (N=490 Lexapro; N=404 placebo). Generalized Anxiety Disorder Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder\* (Lexapro (N=429) and Placebo (N=427)).

**Autonomic Nervous System Disorders:** Dry Mouth (3% and 5%); Sweating Increased (4% and 1%).

**Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%); Gastrointestinal Disorders: Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%).

**General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%).

**Musculoskeletal:** Neck/Shoulder Pain (3% and 1%).

**Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%).

**Urogenital:** Ejaculation Disorder†‡ (14% and 2%); Anorgasmia§ (6% and <1%); Menstrual Disorder (2% and 1%).

\*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). §Denominator used was for females only (N=247 Lexapro; N=232 placebo). Dose Dependency of Adverse Events The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. TABLE 4. Incidence of Common Adverse Events\* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125). Insomnia (4%, 7%, 14%); Diarrhea (6%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%); Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. Male and Female Sexual Dysfunction with SSRIs Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 5 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636)): Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Prapriam has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. Vital Sign Changes Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. Weight Changes Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. Laboratory Changes Lexapro 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 Lexapro treatment. ECG Changes Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) 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 (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. Other Events Observed During the Premarketing Evaluation of Lexapro Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular - Frequent: palpitation, hypertension. Infrequent: bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - Frequent: light-headed feeling, migraine. Infrequent: tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - Frequent: heartburn, abdominal cramp, gastroenteritis. Infrequent: gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - Frequent: allergy, pain in limb, fever, hot flushes, chest pain. Infrequent: edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - Infrequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - Frequent: increased weight. Infrequent: decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - Frequent: arthralgia, myalgia. Infrequent: jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - Frequent: appetite increased, lethargy, irritability, concentration impaired. Infrequent: jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruising, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female - Frequent: menstrual cramps, menstrual disorder. Infrequent: menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. \*% based on female subjects only. N= 905 Respiratory System Disorders - Frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. Infrequent: asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendage Disorders - Frequent: rash. Infrequent: pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - Frequent: vision blurred, tinnitus. Infrequent: taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - Frequent: urinary frequency, urinary tract infection. Infrequent: urinary urgency, kidney stone, dysuria, blood in urine. Events Reported Subsequent to the Marketing of Escitalopram - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, proclatemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

## MRSA Showing No Mercy in Skin Infections

BY ERIK GOLDMAN  
Contributing Writer

NEW YORK — Methicillin-resistant *Staphylococcus aureus* is now the most common cause of serious skin and soft-tissue infections in many communities throughout the United States, Dr. Mark Lebwohl said at the American Academy of Dermatology's annual Academy 2007 meeting.

“If you're getting cultures, you're seeing this, because it is definitely there,” said Dr. Lebwohl of the department of dermatology at Mount Sinai Medical Center, New York. “Where's it coming from? Everywhere!”

In one study he cited, methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for 72% of all skin and soft-tissue infections seen at a major medical center and affiliated outpatient clinics in Atlanta (Ann. Intern. Med. 2006;144:309-17). MRSA is particularly common among athletes, military personnel, homeless people, and intravenous drug users, but in reality, everyone is at risk, he stressed.

The bad news is that MRSA isn't just resistant to methicillin. It seems to be increasingly resistant to most antibiotics these days. “Unfortunately, vancomycin resistance is emerging in MRSA organisms. Erythromycin borders on worthless, as almost all MRSA strains are erythromycin-resistant,” he said.

Clindamycin is still effective in most communities around the country, but re-

sistance to this drug also is starting to show up. Between 10% and 15% of all MRSA strains identified in the cities of Atlanta and Baltimore and the state of Minnesota are resistant to clindamycin. In Chicago, the number is over 50% for infected adults, Dr. Lebwohl noted.

Fortunately, trimethoprim-sulfamethoxazole (Bactrim) still works almost everywhere. In Baltimore, though, 17% of MRSA strains have been found to be resistant to this drug as well.

All of this bad news might lead one to conclude that antibiotic therapy for MRSA is ultimately futile. A study published several years ago suggested that, when treating MRSA-infected skin and soft-tissue abscesses, there were no significant differences between allegedly effective and ineffective antibiotics, and that the key to treatment was incision and drainage (Pediatr. Infect. Dis. J. 2004;23:123-7).

Dr. Lebwohl cautioned against such antibiotic nihilism. “If there's no difference between the antibiotics, it's reasonable to ask: Why treat? But the point is, it is not the patient you are seeing that you worry about. It is the person you are not seeing: the patient's family members, neighbors, colleagues. MRSA can cause sepsis, coagulopathy, osteomyelitis. It can kill people. It is very serious. You need to use the right antibiotics, because in treating your patient properly you are also treating the whole community.”

Clindamycin and Bactrim are still good

options, as are doxycycline and minocycline, although they are not recommended for children. For adults, doxycycline and minocycline are the top choices, he said. Daptomycin (Cubicin) is also a good choice for deep-tissue infections, especially in the bones and joints (Curr. Med. Res. Opin. 2005;21:1923-6).

Dr. Lebwohl also had high praise for linezolid (Zyvox), a newcomer to the antibiotic front lines. MRSA seems to be very sensitive to this drug: A recent in vitro study of almost 3,400 MRSA isolates showed that all were sensitive to linezolid (Antimicrob. Agents Chemother. 2005;49:5024-32). Unfortunately, it is very expensive.

Generally, one should stay clear of quinolones and macrolides, as they are ineffective against MRSA at this point. Rifampin may seem to work at first, but resistance develops very quickly.

Dr. Lebwohl strongly advised colleagues to read and practice according to the Infectious Diseases Society of America's 2005 guidelines for the management of skin and soft-tissue infections (Clin. Infect. Dis. 2005;41:1373-406). He also advocated routine culture and sensitivity testing. The more information physicians can gather about the infections they are confronting, the more intelligently they can choose the antibiotic therapy.

Over the past year, Dr. Lebwohl has been a consultant for a number of drug companies, including Galderma (clindamycin) and Pfizer (doxycycline).