

# Multidrug-Resistant TB Persists Among Immigrants

BY HEIDI SPLETE  
Senior Writer

WASHINGTON — Cases of multidrug resistance in immigrant populations in the United States and links to the AIDS epidemic in Africa are attracting the attention of researchers.

“There is an erroneous assumption that tuberculosis has been eradicated,” Catherine D. DeAngelis, M.D., editor of the *Journal of the American Medical Association*,

said at a press briefing on tuberculosis sponsored by JAMA.

“In fact it is a big problem, and should be taken seriously,” she said.

Of note, 407 cases of multidrug-resistant tuberculosis (MDR-TB) with specific resistance to at least isoniazid and rifampin occurred in a study of 28,712 tuberculosis cases in California from 1994 to 2003, according to Reuben M. Granich, M.D., of the Centers for Disease Control and Prevention in Atlanta, and his colleagues.

**Cases of multidrug-resistant tuberculosis are highly complex and require 18-24 months of observed therapy to achieve recovery.**

Patients with MDR-TB were seven times more likely to have reported prior tuberculosis treatment, compared with those with non-MDR disease, Dr. Granich said at the press conference.

In addition, 83% of the MDR-TB patients were born outside the United States, which highlights the need for both international control and improved screening, said Dr. Granich.

Prior treatment for tuberculosis was the strongest risk factor for MDR-TB in his study.

“There are two ways to develop MDR-TB,” Dr. Granich said.

One is through noncompliance with the treatment regimen, and the other is via airborne transmission from one patient to another, he said.

Once infected, the average lifetime risk for developing tuberculosis is 10%, and the

risk is highest during the first 2 years after infection.

Most healthy people who are exposed to tuberculosis won't go on to develop the disease, and a person's state of health can modify the risk, Dr. Granich noted. For example, the risk of HIV/AIDS patients for developing tuberculosis increases significantly over that of a healthy person exposed to tuberculosis to an approximately 10% annual risk.

Of the 407 MDR-TB cases in Dr. Granich's study, 71 (17%) were resistant only to isoniazid and rifampin, and 86 (21%) were resistant to all four first-line drugs—isoniazid, rifampin, ethambutol, and pyrazinamide.

Most cases of tuberculosis are curable if patients are compliant and take the right medication for 6-9 months.

The “right medication” depends on the seropositivity of the patient's sputum sample, Dr. Granich said. However, cases of MDR-TB are highly complex, and require 18-24 months of therapy under the supervision of a specialist in order to achieve recovery, he noted.

The World Health Organization has stated goals of detecting 70% of new TB cases and successfully treating 85% of them, said Christopher Dye, D.Phil., at the press briefing.

The most significant barriers to achieving the goals set by WHO exist in Africa,

where the HIV epidemic has led to an increased vulnerability to tuberculosis, and in Eastern Europe, where tuberculosis rates doubled during the 1990s, and multidrug resistance is high due to low compliance.

Dr. Dye and his colleagues reported that, with the exception of Africa and Eastern Europe, WHO can achieve its goals with increased application of the Directly Observed Treatment Scheme (DOTS).

This public health strategy that includes gaining political commitment, detecting cases based on sputum smear microscopy, utilizing standard short-course therapy with supportive patient management, ensuring regular drug supplies, and standardizing systems for recording cases and reporting outcomes (*JAMA* 2005;293:2767-75).

“There is a major education job to be done in terms of keeping tuberculosis on the agenda,” he said.

Another study in the same issue of *JAMA* found that isoniazid reduced the odds of developing a primary case of tuberculosis in a highly vulnerable population—1,655 male gold miners in Orkney, South Africa, who had previously tested positive for HIV.

After adjustment for age, calendar date, and silicosis grade in 1,041 individuals, there was a 46% reduction in tuberculosis incidence with isoniazid.

Only nine patients discontinued the drug because of adverse events (*JAMA* 2005;293:2719-25).

**Ezetimibe:** The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

**Simvastatin:** Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses >40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

**Geriatric Use:** Of the patients who received VYTORIN™ (ezetimibe/simvastatin) in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

**ADVERSE REACTIONS:** VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated. Table 1 summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from 3 similarly designed, placebo-controlled trials.

**Table 1\***  
Clinical Adverse Events Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/ Organ Class Adverse Event	Placebo (%) n=311	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1234	VYTORIN** (%) n=1236
<b>Body as a whole – general disorders</b>				
Headache	6.4	6.0	5.9	6.8
<b>Infection and infestations</b>				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
<b>Musculoskeletal and connective tissue disorders</b>				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.5	3.0	2.0	2.3

\* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered.  
\*\* All doses.

**Ezetimibe:** Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: **Body as a whole – general disorders:** fatigue; **Gastrointestinal system disorders:** abdominal pain, diarrhea; **Infection and infestations:** infection viral, pharyngitis, sinusitis; **Musculoskeletal system disorders:** arthralgia, back pain; **Respiratory system disorders:** coughing.

**Post-marketing Experience:** The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

**Hypersensitivity reactions,** including angioedema and rash; increased CPK; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely in patients taking an HMG-CoA reductase inhibitor with ezetimibe, rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

**Simvastatin:** Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: **Body as a whole – general disorders:** asthenia; **Eye disorders:** cataract; **Gastrointestinal system disorders:** abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; **Skin and subcutaneous tissue disorders:** eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy.

**Musculoskeletal system disorders:** muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgia.

**Nervous system disorders:** dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial palsy), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances.

**Ear and labyrinth disorders:** vertigo.

**Psychiatric disorders:** anxiety, insomnia, depression, loss of libido.

**Hypersensitivity Reactions:** An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

**Gastrointestinal system disorders:** pancreatitis, vomiting.

**Hepatobiliary disorders:** hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma.

**Metabolism and nutrition disorders:** anorexia.

**Skin and subcutaneous tissue disorders:** alopecia, pruritus. A variety of skin changes (eg, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

**Reproductive system and breast disorders:** gynecostasia, erectile dysfunction.

**Eye disorders:** progression of cataracts (lens opacities), ophthalmoplegia.

**Laboratory Abnormalities:** elevated transaminases, alkaline phosphatase,  $\gamma$ -glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

**Laboratory Tests:** Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

**Concomitant Lipid-Lowering Therapy:** In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

**Adolescent Patients (ages 10-17 years):** In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use).

## Computer Keyboards Act as Bacteria Reservoir

BY BETSY BATES  
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LOS ANGELES — Computer keyboards and keyboard covers harbored vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* for more than 24 hours, during which time the bacteria easily spread to bare, and in some cases, gloved hands, a Northwestern University study has found.

The findings strongly suggest the need for health care providers to wash their hands after using computers, particularly in hospital settings and around immunocompromised patients, said Gary A. Noskin, M.D., an infectious disease specialist at Northwestern University and director of health care epidemiology and quality at Northwestern Memorial Hospital in Chicago.

Electronic patient records have ushered more computers into examining and patient rooms, heightening the importance of their role as a “viable reservoir for pathogenic bacteria,” in the words of the study presented in poster form at the annual meeting of the Society for Healthcare Epidemiology of America.

Investigators inoculated a number of standard computer keyboards and Dell computer keyboard covers with isolates of vancomycin-resistant *E. faecium* (VRE),

methicillin-resistant *S. aureus* (MRSA), and *Pseudomonas aeruginosa* (PSAE).

Samples obtained at various time intervals determined that both VRE and MRSA survived for 24 hours, while PSAE was less hardy, growing for 5 minutes on computer keyboard covers and 1 hour on computer keyboards.

Bacteria transmission to volunteers' hands increased with the number of times they touched the computer keyboards.

For example, MRSA resulted in recovery of bacteria on hands 92% of the time with 5 touches, versus 42% of the time after 1 touch of the computer keyboard.

Rates for VRE were 50% and 22% after 5 touches and 1 touch, and with PSAE, 18% and 9%, respectively.

Bare hands were more likely than were gloved hands to acquire VRE and MRSA, 67% versus 7%, and 80% versus 67%, respectively.

Investigators then conducted an experiment to see whether two quaternary ammonium-based germicides commonly used in health care settings could eliminate bacterial contamination on keyboards and keyboard covers.

Virex II 256 (Johnson Wax Professional, Sturtevant, Wisc.), when used as directed with a 10-minute dwell time, successfully disinfected both keyboards and keyboard covers.

Sani-Wipes (PDI, Upper Saddle River, N.J.), when used as directed and allowed a 5-minute dwell time, disinfected computer keyboards but failed to eliminate VRE and PSAE on computer keyboard covers.

Dr. Noskin and his associates recommended hand washing after contact with computers.

It is unknown how keyboards and keyboard covers should be disinfected, since there are “just no data” on how frequent germicide use might impact their durability, circuitry, and electronics, he said in a telephone interview following the meeting.

“On a practical level, keyboards and other environmental surfaces are never going to be sterile, so it's just very important for health care workers to wash their hands so the contamination is less relevant,” he said.

No industry funding was used for the study.

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