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St. John's Wort Alters Indinavir Metabolism

ABSTRACT & COMMENTARY

Synopsis: *In the current study, Piscitelli and colleagues conclude that concomitant use of St. John's wort results in significantly lower indinavir concentrations.*

Source: Piscitelli SC, et al. Indinavir concentrations and St. John's wort. *Lancet* 2000;355:547-548.

The hypericum extract of st. john's wort has gained popularity by many patients who seek alternative or herbal remedies for depression. Since hypericum has been considered relatively benign, it is important to elucidate any drug interactions that may be associated with its use. Due to recent reports that hypericum induces cytochrome P450 3A4 (CYP3A4) activity, the current study examined the possibility of a drug interaction between hypericum and a known CYP3A4 substrate, the protease inhibitor indinavir (Crixivan). The study, conducted in the research division of the National Institute of Allergy and Infectious Diseases, consisted of healthy volunteers (n = 8; 6 male, 2 female) older than 18 years who had a negative HIV-1 test. Subjects were excluded if they had smoked in the past year, received St. John's wort within 30 days, were allergic to indinavir, were pregnant or lactating, were receiving concomitant CYP450 substrates, or had persistent diarrhea or a history of malabsorption.

On day 1, fasting participants received 800 mg of indinavir orally every eight hours for a total of three doses in order to achieve steady state (based on a half-life of 1.8 hours, steady state should be achieved in 9 hours). The 800 mg given every eight hours is the usual dosage recommended for use in HIV disease. On day two, after a baseline indinavir serum concentration, a single 800-mg dose was given on an empty stomach, followed by blood indinavir serum concentrations collected at 0.5, 1, 2, 3, 4, and 5 hours after dosing.

On day 3, participants received 300 mg St. John's wort (0.3% standardized hypericin extract) three times daily with meals, for 14 days. On day 16 (day 14 of St. John's wort), subjects again received indinavir 800 mg orally every eight hours on an empty stomach. On day 17, sub-

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jects received 800 mg of indinavir in clinic with blood sampling before and serially for five hours after dosing.

Pharmacokinetic calculations showed that coadministration of hypericum resulted in significantly reduced concentrations of indinavir. The area under the curve for indinavir was reduced by 57% after therapy with St. John's wort ($P > 0.0008$), while the mean maximum concentration decreased from 12.3 mcg/mL to 8.9 mcg/mL. Thus, the results confirmed that concomitant use of St. John's wort results in significantly lower serum indinavir concentrations, presumably via induction of CYP3A4 (although induction of P-glycoprotein could not be ruled out).

COMMENT BY MICHAEL F. BARBER, PharmD

Currently, the hypericum extract of St. John's wort is not regulated as a drug by the FDA. As a result, patients often self-medicate with hypericum. Since hypericum is somewhat easily tolerated by most patients, its usage in and of itself probably poses minimal risks, providing that patients seek appropriate professional help if their depression continues, worsens, or they become suicidal. However, the use of hypericum can pose previously unforeseen risks due to drug interactions. The current report illustrates a drug interaction between St. John's wort and the protease inhibitor indinavir. The results of this research are important for several reasons. First, while hypericum previously has been shown to induce the hepatic enzyme CYP3A4 in vitro, confirmed reports of actual drug interactions involving hypericum lowering CYP3A4 substrates were lacking. The current report illustrates that the theoretical interaction between hypericum and the CYP3A4 substrate indinavir does result in lowering of indinavir serum concentrations. Second, while many drug interactions may not be of much significance, the decreases in indinavir concentrations are clinically significant since the efficacy of the indinavir against HIV may be compromised, leading to worsening of the disease, and possibly resistance of HIV to indinavir. Since this report involved healthy, noninfected patients, the exact consequences of a decrease in indinavir concentrations of this magnitude are not known; nonetheless, this is clearly a drug interaction that should be avoided. In order to minimize this drug interaction clinicians must be alert to any use of hypericum by patients and counsel them to consult with their physician or pharmacist before taking any product containing hypericum extract if they are taking indinavir. This situation is complicated by the fact that patients may not always be aware of any consumption of hypericum, since it is now available in such formulations as multivitamins and herbal teas. (*Dr. Barber is Assistant Professor of Clinical Sciences and Administration, University of Houston College of Pharmacy, Houston, TX.*) ❖

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Plague in Madagascar—Maybe Closer, Maybe Soon?

ABSTRACT & COMMENTARY

Synopsis: *Recent reports from both the highlands and port cities of Madagascar point to an ongoing epidemic of urban and sylvatic plague in Madagascar. Bubonic plague may be difficult to recognize clinically and progression to pneumonic plague not only increases mortality but also transmission to unwary contacts.*

Source: Ratsitorahina M, et al. Epidemiological and diagnostic aspects of the outbreak of pneumonic plague in Madagascar. *Lancet* 2000;355:111-113.

This report describes an outbreak of pneumonic plague in Madagascar, which occurred during

1997, when an index patient with secondary pulmonary disease infected a traditional healer and his family. Upward of 2000 cases of plague had been reported annually in Madagascar recently, but only a small percentage had been pneumonic. Most had been bubonic, but in October 1997 eight patients with suspected pneumonic plague were transferred to a provincial hospital for treatment with streptomycin.

Two methods were used to detect F1 antigen: an immunocapture enzyme-linked immunoassay (ELISA) and a dipstick assay from the Naval Medical Research Center in Bethesda, Maryland. The latter is a 15-minute one-step assay, which proved to be quite specific and rapid for F1 antigen detection (so-called fraction 1 glycoprotein surface antigen detection).

The index case was a woodcutter from a district 90 km north of the capital city of Antananarivo who initially presented with both fever and tender axillary adenitis. He consulted the traditional healer in his village as his course progressed over one day to clinical pneumonic plague, including chest pain, blood-stained sputum, and cough. He died the following morning but only after the healer had incised the patient's abdomen and sucked out some blood as part of the healing process. The healer became ill in three days and died within seven days; his wife and son followed soon after. Further exposures to the healer and at funeral ceremonies resulted in 18 cases, eight of whom died. The rate of infection in this remote, previously unexposed population was 8.4%, which represented a fairly good estimate of the risk of spreading pneumonic plague in these remote villages, having not seen plague for 50 years. Not all patients with pneumonic plague are expected to be bacteremic, hence, 10 patients, both treated and untreated, were tested for *Yersinia pestis* in sputum by culture and the organisms could be isolated from only two, whereas the F1 dipstick detected antigen in nine and the F1 ELISA detected antigen in eight.

This epidemic occurred in the remote central highlands of Madagascar, where plague is endemic, transmitted by oriental fleas living upon rats and shrews, the animal reservoirs. The use of F1 antigen assays as a mainstay for the diagnosis of suspected cases of pneumonic plague and for early chemoprophylaxis of infected contacts was evident in this outbreak.

COMMENT BY FRANK J. BIA, MD, MPH

No sooner had this report appeared in the *Lancet* early this year when Madagascar appeared in the popular press in a lead article written for the Science section of the *New York Times*.[1] The wreck of the flagship, *Adventure*, which had belonged to the infamous 17th century privateer, William Kidd, had just been located in waters just off Madagascar's east coast on the shores of Isle Ste Marie. This tropical isle and its inlets of sandy beaches was a perfect place for ships to be hauled ashore and turned on their sides to have barnacles scraped from the hull, a process known as careening—essential maintenance if pirate ships were to travel as fast as possible over open waters. Kidd took advantage of this anchorage when he turned his back on a royal commission from the British crown to fight piracy, and was transformed into a pirate himself. Ultimately, William Kidd was hanged twice in London during 1701 (the rope broke on the first try).

Yet one more reason for adventure travel to Madagascar—a destination with great allure. As a result, travel medicine consultants must become more aware of it. Forestry students, divers, archeologists, and bird watchers are among those who must be advised about the dangers posed by both urban and sylvatic plague in Madagascar. Yet, it wasn't always so.

Plague did not become established in Madagascar until the last great pandemic of 1894, which began in Hong Kong and spread rapidly over five continents. *Y. pestis* arrived in Madagascar during this third pandemic on ships from India, which appeared in November 1898. By 1921, plague had reached the high plateau regions, causing an outbreak of pneumonic plague in Antananarivo, then disappearing from seaports and becoming established at altitudes above 800 meters throughout this region.[2]

Silent until 1994, plague reappeared in epidemic form in neighboring regions such as Mozambique, Malawi, and India. Nor has this organism proven to be a particularly stable one, genetically speaking. In less than a century, the original strain that had been introduced into Madagascar has undergone chromosomal rearrangements, leading to the emergence of new ribotypes, based upon analysis of ribosomal RNA genes. It is not known what the selective advantage of such new variants may be and how they may relate to certain geographic environments, but Madagascar now has the distinction of harboring a particularly dangerous strain of *Y. pestis*.[3]

In 1995 a clinical isolate of this organism was recovered in Madagascar from a 16-year-old boy with an inguinal bubo, high fever, delirium, and prostration. The multi-drug-resistant organism, *Y. pestis* 17/95, carried a plasmid, which could be transferred by conjugation to other isolates of this organism. It carried resistance to antibiotics commonly used to treat plague such as streptomycin and the tetracy-

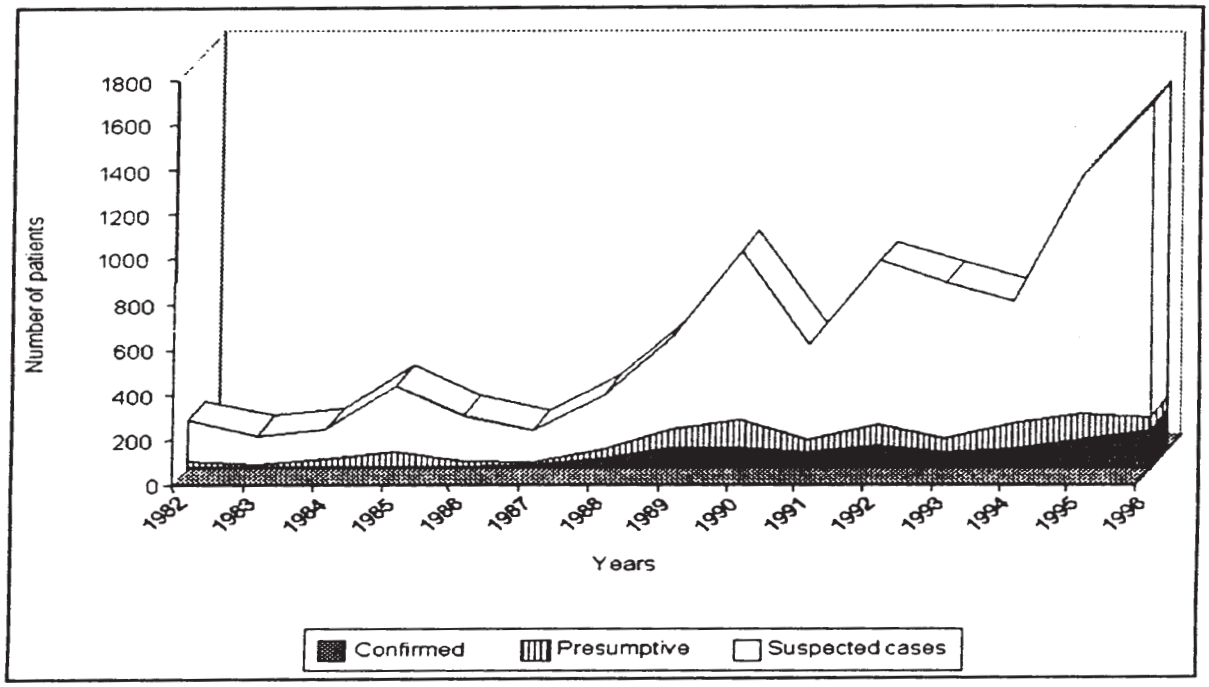
clines. In addition, the organism produced a beta-lactamase, mediating resistance to ampicillin and an acetyltransferase, causing resistance to chloramphenicol. It was not sensitive to sulfonamides, thus not allowing for synergy, but it retained sensitivity to trimethoprim, which may have accounted for this fortunate boy's recovery. This strain also retained sensitivity to the quinolones, cephalosporins, and other aminoglycosides. Madagascar's plague surveillance has been extensive, yet no such isolates had been identified between 1926 and 1995.

The appearance of multi-drug-resistant plague is an ominous event that could lead to an unpleasant emergency patient presentation in your office setting, as was recently reported by Dr. Martin Wolfe at his Travelers Medical Service in Washington, DC.[4] He treated a 47-year-old woman who had been working as a mammalogist in the La Paz District of Bolivia and had been placed on ampicillin in Bolivia for severe headache, chills, fever, myalgias, and swelling in her right axilla but without relief. Her axillary swelling increased to the point where she could no longer move her right arm effectively and Wolfe saw her on arrival in Washington at his office. He found her to be febrile with a 2.5-cm fluctuant lymph node in her right axilla. Immediate hospitalization and aspiration of the node revealed gram-negative bipolar organisms, which were evident on a Wayson stain. *Y. pestis* grew from cultures of the node aspirate and she recovered following a 10-day course of streptomycin, until now the standard drug for treatment of all isolates of this organism. The patient had been skinning rice rats as part of her work in Bolivia and then crushing their fleas with her fingers, the likely source of her infection. This case represented the first recognized imported plague into the United States since 1926—and surely not the last, as this emerging disease continues to reappear, but now with potentially altered antibiotic sensitivity patterns, as was the case in Madagascar.

Plague had never entirely disappeared from Madagascar after its introduction by steamboats from India in 1898, but only 20-50 cases per year were reported until 1989.[5] (*See Figure.*) Since then, a steady rise in the number of suspected plague cases has been reported, now reaching 800 to 1500 per year. No longer limited to the highland regions, plague has also reappeared in the northwest coastal town of Majunga. The introduction of both F1 antibody and F1 antigen immunodiagnostic tests has increased the number of confirmed cases two- to threefold because of their greater sensitivity. Perhaps analogous to the recent West Nile virus outbreak in New York City that was

Figure

Human Plague, Madagascar, 1982-1996



Source: Chanteau S, et al. *Emerg Infect Dis* 1998;4:101-104.

preceded by increased deaths among the city's crow population, every human outbreak of plague in Madagascar has been preceded by large numbers of rat deaths. Shrews are also infected with the vector flea, *X. cheopis*, and may be the reservoir for maintenance of plague between epidemics.

Travelers to endemic regions of Madagascar and other geographic foci of plague activity should be instructed regarding the presence of epizootic plague,[6] avoidance of sick or dead animals, and use of repellents and insecticides, gloves, and protective clothing. Prophylactic treatment with tetracycline for seven days (2 g/d) can be given to persons with close exposure to patients with pneumonic plague or with high-risk animal exposure. Doxycycline may be more efficacious than other tetracyclines, but there are no comparative evaluations among the tetracyclines. The role for the current killed whole-cell plague vaccine is limited and it does not fully protect against primary pneumonic plague. It requires three primary inoculations, and booster doses as frequently as every six months may be necessary.[6] Should a patient arrive on your doorstep with suspected plague, respiratory isolation is appropriate if pneumonic plague is suspect. The newer immunodiagnostic tests for F1 antigen detection should be considered and no assumptions regarding sensitivity of the organism to previously first-line agents such as streptomycin or chloramphenicol should be made if future reports from Madagascar or other endemic regions indicate spread of multidrug resistance. (*Dr. Bia is Professor of Medicine and Laboratory Medicine, Co-Director, Tropical Medicine and International Travelers' Clinic, Yale University School of Medicine, New Haven, CT.*) ❖

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African Trypanosomiasis and Acute Pulmonary Schistosomiasis in Travelers

ABSTRACTS & COMMENTARIES

Synopsis: *Two recent articles remind us that African trypanosomiasis and acute pulmonary schistosomiasis occur in travelers from developed countries.*

Sources: Sinha A, et al. African trypanosomiasis in two travelers from the United States. *Clin Infect Dis* 1999;29:840-844; Cooke GS, et al. Acute pulmonary schistosomiasis in travelers returning from Lake Malawi, sub-Saharan Africa. *Clin Infect Dis* 1999;29:836-839.

African Trypanosomiasis

Sinha and colleagues reported two travelers from the United States who contracted African trypanosomiasis during a recent safari trip in Tanzania. Both patients presented with fevers, sweats, chills, and myalgias. One patient recalled a painful fly bite six days prior to onset of her symptoms. The second patient recalled numerous tsetse fly bites and noted an expanding erythematous lesion on his right flank as well as an edematous swelling below the left lower lip. Both patients had been on malaria chemoprophylaxis. The first patient was diagnosed when the Giemsa-stained thin and thick malaria blood smears revealed trypomastigotes. The second patient was diagnosed by Wright's staining of a peripheral blood smear, which revealed trypomastigotes. The organisms were identified as *Trypanosoma brucei rhodesiense*, or the East African form of African trypanosomiasis. Cerebrospinal fluid (CSF) from both patients was examined and showed no parasites. Both patients were successfully treated with suramin.

COMMENT BY LIN H. CHEN, MD

Human African trypanosomiasis (HAT), or sleeping sickness, is endemic in sub-Saharan Africa and is caused by two subspecies of trypanosomes—*T.b. gambiense* and *T.b. rhodesiense*. Gambian HAT, also referred to as the West African form, occurs in western and central Africa, whereas Rhodesian HAT, the East African form, is endemic in eastern and southern Africa. Rhodesian HAT presents more acutely and progresses more rapidly. Sinha et al reported that since 1967, all cases of HAT occurring in U.S. travelers have been Rhodesian HAT, and most patients contract-

ed the disease during visits to game parks.

This disease is transmitted by tsetse flies. Acute presentations may include an inoculation chancre as well as nonspecific symptoms such as fevers, headaches, myalgia, malaise, and transient edema. The patients may develop weight loss, lymphadenopathy, and splenomegaly. Late-stage manifestations include somnolence, behavior change, stupor, and coma. Convulsions are more common in children. Left untreated, the disease is fatal.

The diagnosis of Rhodesian HAT is made by demonstration of trypanosomes in blood, chancre, or CSF. Because the degree of parasitemia is higher in Rhodesian HAT than in Gambian HAT, trypanosomes are easier to detect in blood; lymph node aspirates are rarely necessary. A CSF analysis should be done whenever HAT is established or suspected, and CSF should be examined for trypanosomes with "double centrifugation." The presence of parasites, CSF pleocytosis (WBC > 5/mm^3), or Mott cells (large globular inclusion-containing plasma cells) indicates late-stage disease. Treatment of early-stage Rhodesian HAT is with suramin, and with melarsoprol when there is central nervous system (CNS) involvement.

Acute Pulmonary Schistosomiasis

Cooke and colleagues reported four patients with acute schistosomiasis presenting to John Radcliffe Hospital in Oxford, England, in 1997. All four patients had been swimming in Lake Malawi. All four patients developed symptoms from two to eight weeks after swimming, including fevers, headaches, lethargy, cough, and urticarial rash. Laboratory evaluations were notable for eosinophilia with or without leukopenia, mild thrombocytopenia, and mild liver function abnormalities. Chest radiography and computerized tomography (CT) revealed pulmonary nodules. Only one patient was found to have *Schistosoma haematobium* in a stool sample, but all four patients had positive schistosomal serology. Although the enzyme-linked immunoassay (ELISA) did not identify the species specifically, the infections were acquired in the same area and were assumed to be *S. haematobium*. All were treated with a single dose of praziquantel 40 mg/kg. Three of the patients experienced transient exacerbation of symptoms, but all recovered.

COMMENT BY LIN H. CHEN, MD

Schistosomiasis occurs in tropical and subtropical areas of Africa, South America, the Middle East, and East Asia. *S. haematobium* is endemic in Lake Malawi in sub-Saharan Africa, where the four travelers from the United Kingdom acquired their infection. Acute schistosomiasis is associated more frequently with *S. japonicum* and *S. mansoni* infection, and is rarely observed during *S. haematobium* infection. The article by Cooke et al indicates that acute pulmonary schistosomiasis can occur with *S. haematobium* infections, and it will be interesting to see if similar presentations continue to appear.

Schistosomiasis is acquired in fresh water, through intact skin, when the human host comes into contact with the infectious cercarial larvae. The initial contact sometimes leads to a localized dermatitis. Acute schistosomiasis (Katayama fever) may develop 4-8 weeks after exposure, with symptoms of fever, sweats, chills, cough, and headaches. The pulmonary manifestation is speculated to be an immune response to the schistosomulae. Physical signs include lymphadenopathy, hepatosplenomegaly, and rash. Eosinophilia is a significant laboratory finding.

Detection of parasite eggs in stool or urine establishes the diagnosis, but may not be present early in the course. Biopsies of the rectum, intestine, liver, prostate, or bladder can make the diagnosis if parasite ova can be demonstrated. Serologic conversion can also establish the diagnosis of acute schistosomiasis. Praziquantel is the treatment of choice for schistosomiasis, and is well tolerated.

These two articles demonstrate that travelers from developed countries can contract African trypanosomiasis and acute pulmonary schistosomiasis during travel within endemic areas. Many of the patients reported in these two articles presented with nonspecific symptoms, but the patients' history of fly bite or swimming in Lake Malawi helped a great deal in determining the diagnoses. With increased tourism to Africa, travel medicine specialists need to consider these diagnoses in febrile travelers returning from endemic areas. (*Dr. Chen is Clinical Instructor, Harvard Medical School and Travel/Tropical Medicine Clinic, Lahey Clinic Medical Center, Cambridge, MA.*) ❖

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Correction

The article, "Peroneal Anatomy and UTIs in Women," in the March 1, 2000, issue of *Infectious Disease Alert* contained an error. The word *peroneal* should be *perineal* throughout. We regret any confusion this may have caused. ❖

CME Questions

24. Which of the following is true?

a. St. John's wort is a benign natural substance.
b. St. John's wort has been shown to increase levels of other drugs.
c. St. John's wort has been shown to decrease levels of other drugs.

25. Which of the following statements regarding human plague is true?

a. Pneumonic plague is generally not transmitted from person to person, but by septicemic spread from primary bubonic plague.
b. Most isolates of *Y. pestis* from Madagascar, India, and Mozambique are now resistant to the aminoglycosides.
c. Plague in Madagascar is no longer confined to the highland plateau, but has also appeared in coastal regions.
d. Resistant plague emerging from Madagascar would best be treated with a synergistic combination of folic acid antagonists consisting of sulfonamides and trimethoprim.
e. Fluoroquinolones will have no future role in the treatment of pneumonic plague.

26. Which of the following statements is *false*?

a. Infection with *Trypanosoma brucei rhodesiense* occurs in eastern Africa and causes a more acute disease than *Trypanosoma brucei gambiense*.
b. Acute schistosomiasis is usually associated with infection from *S. mansoni* and *S. japonicum* rather than *S. haematobium*.
c. When the diagnosis of African trypanosomiasis is being considered, one should perform a lumbar puncture to examine the CSF for parasites and WBCs.
d. Acute schistosomiasis should be considered in febrile patients with eosinophilia who report exposure to fresh water in Africa.
e. The history of a chancre from a tsetse fly bite should raise suspicion for possible schistosomiasis.

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UPDATES

By Carol A. Kemper, MD, FACP

Did West Nile Virus Survive the New York Winter?

Sources: Cooper J, et al. *MMWR Morb Mortal Wkly Rep* 2000:49:178-179; ProMED-mail. March 14 and 22, 2000. www.pro-medmail.org.

Mosquitoes that have survived the winter in New York in underground structures have been found to harbor bits of West Nile virus (WNV) RNA. A total of 67 pools of water containing dormant *Culex* spp. mosquitoes were analyzed, three of which yielded portions of envelope RNA, although the virus itself could not be isolated. It is hoped this may represent noninfectious viral particles, but there is concern that low titers of viable virus could escape detection. In another report, a redtail hawk that died in Connecticut two months ago had evidence of WNV infection, suggesting that low-level infection in the bird population may be occurring despite the cold weather.

These findings suggest that additional cases are likely with warmer weather. Plans are being stepped up in several states this spring to monitor potential hosts for infection along the Atlantic and Gulf coasts. Seropositive birds were found last summer in New Jersey, New York, and Maryland.

In the meantime, New Yorkers are being advised to wear long sleeves and plenty of insecticide should they venture outdoors, and to avoid areas of standing water. At least 69 New Yorkers became ill with WNV infection last year—seven of whom died. Recent data extrapolated from a serosurvey of residents in northern Queens, which is considered the epicenter of last year's outbreak, suggest that somewhere between 533 and 1903 people may have been infected with WNV last summer, representing ~2.6% of the residents in Queens. ■

Levofloxacin-Resistant Pneumococci

Source: Wortmann GW, Bennett SP. *Clin Infect Dis* 1999;29:1599-1600.

A 58-year-old man with a history of splenectomy was hospitalized in Washington, DC, with fever and sinusitis. He received levofloxacin, but became increasingly lethargic and died. Cultures of CSF yielded *Streptococcus pneumoniae* susceptible to penicillin but no zone of inhibition to levofloxacin was seen on Etest. This unfortunate case serves as a harsh reminder that a small percentage of *S. pneumoniae* are resistant to levofloxacin.

While resistance to the macrolides, clindamycin, trimethoprim-sulfamethoxazole, and tetracycline, is significantly increased in penicillin-resistant strains, it is important to recognize that the likelihood of quinolone resistance is independent of penicillin resistance. Therefore, no inference can be made regarding the susceptibility of a penicillin-sensitive strain of *S. pneumoniae* to the quinolones. Recent susceptibility data for the United States of 2752 clinical isolates collected between 1996 and 1997 found that, on the basis of MIC data, grepafloxacin was the most active agent against *S. pneumoniae*, followed by sparfloxacin, levofloxacin, ciprofloxacin, and ofloxacin in descending order of activity (Thornsberry C, et al. *Antimicrob Agents Chemother* 1999;43:2612-2623). Nonetheless, ~0.2% of strains were resistant to levofloxacin or grepafloxacin with an MIC more than 2.0 mcg/mL. However, a recent report from Hong Kong identified a 5.5% resistance rate to levofloxacin among multiple drug-resistant strains of pneumococci (Ho PL, et al. *Antimicrob Agents Chemother* 1999;43: 1310-1313). The newer quinolones should therefore not be used for cases of invasive or life-threatening streptococcal disease, irrespective of penicillin susceptibility data, unless their susceptibility to these agents has been predetermined. ■

Update on Rifamycins in HIV and TB

Source: *MMWR Morb Mortal Wkly Rep* 2000;49:185-189.

Patients concurrently infected with HIV and tuberculosis (TB) present complex care issues for clinicians, not the least of which are the selection of an optimal regimen for both diseases and the management of drug interactions. Earlier guidelines recommended against the use of rifampin in patients receiving protease inhibitors or the use of rifabutin in any patient receiving ritonavir or delavirdine.

Based on newer pharmacological data, the March 10 issue of *MMWR* presents newly modified recommendations for the use of rifamycins in HIV-infected patients. Rifampin can be used for the treatment of active TB in patients receiving an efavirenz- or ritonavir-containing regimen, or in patients receiving the combination of ritonavir and saquinavir. Rifabutin can be used in patients receiving efavirenz or ritonavir, but the dose should be increased to either 450 mg or 600 mg daily with the former agent and decreased substantially to 150 mg two or three times weekly with the latter. The dose of rifabutin does not require modification if used with saquinavir (soft gel) as a single agent.

The use of the rifamycins in patients receiving other antiretroviral regimens remains uncertain, but patients with active TB should generally receive a rifamycin-containing regimen whenever possible, even at the expense of more potent antiretroviral therapy. Should this not be possible, an antituberculous regimen containing no rifamycin can be considered. The *MMWR* also stated that the management of these patients requires the active input of a physician with expertise in the management of both of these diseases. ■