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INSIDE

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Relationship between Tenofovir-Associated Renal Dysfunction and HAART Regimen

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University School of Medicine

Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for Boehringer-Ingelheim and GSK.

Synopsis: *Treatment with TDF plus PI/r was associated with a greater decline in renal function over 48 weeks compared with TDF + nnRTI-containing regimen.*

Source: Goicoechea M, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis*. 2008;197:102-108.

THIS STUDY FROM THE CALIFORNIA COLLABORATIVE TREATMENT Group examined renal function over time in 146 patients included in the CCTG 578 prospective, randomized clinical trial of therapeutic drug monitoring (TDM). Creatinine clearance (CrCl) was estimated using the Cockcroft-Gault (C-G) equation and the unabbreviated Modification of Diet in Renal Disease (MDRD) equation. Decreases in C-G estimates of CrCl were not significantly different among the 3 groups during the first 24 weeks of therapy. However, at 48 weeks, patients receiving TDF+PI/r had a greater decline in CrCl than did the TDF+nnRTI group (-13.9 vs-6.2 mL/min/year by C-G and -14.7 vs-4.5 by MDRD). The rates of decline in CrCl between the TDF+nnRTI and non-TDF-treated patients were similar. Among the TDF-treated patients, tenofovir plasma concentration was not associated with change in CrCl over time.

COMMENTARY

This is an important paper, with significant clinical relevance, which sheds some light in the direction of the increasingly-recognized issue of TDF-related nephrotoxicity. Tenofovir has been a very

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important advance in the construction of better-tolerated and more durable antiretroviral regimens. Numerous studies have now shown the superior efficacy and superior long-term tolerability of TDF-containing ARV regimens over zidovudine (AZT)-containing nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbones. However, this advance has come at some cost. While clearly less nephrotoxic than Gilead Science's earlier nucleotide analogue, adefovir dipivoxil, it soon became apparent to treating clinicians that occasionally severe nephrotoxicity (with or without renal tubular acidosis) could be seen with TDF, as well as with adefovir.

Nucleotide analogues are actively transported into renal tubular epithelial cells from the basolateral border by organic anionic transporter proteins (OAT-1), then excreted out the tubular border by the ubiquitous efflux pumps, MRP-2, and possibly MRP-4. Ritonavir has been shown to be an inhibitor of MRP-2, thus accounting for potential increased renal tubular intracellular concentrations of tenofovir, resulting in potential nephrotoxicity. The lack of correlation between overall plasma levels of tenofovir and change in renal function suggests that PI/r is not affecting intestinal absorption of tenofovir and systemic exposure.

The CCTG is to be commended for looking at this important issue. It is my perception that Gilead Sciences often chooses to be in denial regarding the toxicities of their nucleotide analogue RTIs. While TDF is an excellent drug which I prescribe everyday to my patients, wider recognition of its potential nephrotoxicity, and better characterization of particular patients at risk for this toxicity, could be done by more in-depth analysis of the company's drug safety database. Greater knowledge of the types of patients at highest risk for TDF-related nephrotoxicity would serve to increase the appropriate use of this agent.

(Some of the readers of *Infectious Disease Alert* might be interested in a few Pharma insider anecdotes about Gilead Sciences for whom I worked from late 1997 until early 1999. While this company doesn't quite qualify for "Evil Empire" status, a few Darth Vader types work there. During my first week on the job there, Dr. Steve Barriere, the head of drug safety, started receiving a handful of adverse event reports of proximal renal tubular acidosis in patients being treated with adefovir. Steve coined the term, "Fanconi-like syndrome," which we were later ordered by management to change to "proximal renal tubular dysfunction" since the former term sounded too scary. We later received some very disturbing serious adverse event reports of acute renal failure requiring hemodialysis in patients who had adefovir continued in the presence of RTA. Steve and I immediately asked Dr. Mike Wulfsohn, the company's lead biostatistician, to perform a blinded A vs B analysis of all on-going Gilead-sponsored trials of ADV. Mike quickly pulled the data together and demonstrated that, at 24 weeks, using a number of criteria, 46% of group A vs only 5% of group B patients had developed nephrotoxicity. I later drafted a letter to Dr. Carla Petinelli, the Division of AIDS Medical Officer, informing her of this. Because of the sensitivity of this communication, it required approval at a VP level before going outside the company. My draft came back from this VP with 46% crossed out and "approximately one-third" written in. I unsuccessfully argued that even with my limited knowledge of higher mathematics you couldn't round off 46% to "one-third," but you could round that up to "one-half." Seeing that I was losing the argument, in a career-enhancing move, I told the VP, "You can take my name off the 'expletive deleted' letter, then and shove it up your a__!!" I tried to argue that we should put the recently initiated US expanded access program on hold. The project team concurred that we should definitely not start an expanded access program in Europe. A few weeks later, I hired another physician, who was personal friends with both the VP and the CEO, to help work on the project.

As her boss, I had to sign off on travel, so I was confused why she was requesting a business class ticket to Europe when the project team had just decided to not start an expanded access program in Europe due to the

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ASSOCIATE PUBLISHER: Lee Landenberger.

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Leslie Hamlin,
Managing Editor, at (404) 262-5416, or
e-mail to leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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safety issues. This resulted in a somewhat tense confrontation between us, but was resolved by management, who decided the next day to have her report directly to the VP instead of me. Shortly after this, they stopped inviting me to my own project team meetings! I hung in there for several more months hoping for Gilead to see the light, but eventually started looking for another job. On my last day at Gilead, I insisted on giving a brief PowerPoint presentation to the entire clinical research group entitled "Principles of Disciplined Drug Development," where I detailed all the mistakes I felt Gilead made in the development of adefovir and why I was sure that FDA Division of Antiviral Drug Products would never approve adefovir for HIV. The VP was still sure that, in his words, "We're going to jam this drug down the FDA's throat!" Gilead submitted their NDA several months after I left the company, and adefovir became the only antiretroviral agent ever to be rejected for approval by FDA. I was bitter about my experience there and for a brief time even considered informing the Chairman of the Board of my concerns about Gilead management. I wisely reconsidered this, since the Chairman of the Board, Donald Rumsfeld, later became my boss for four military deployments to Iraq and Afghanistan. He probably would have just told me, "Dean, you know you go to war with the antiretroviral agent you have, not the one you'd like to have!" ■

A New Class of Antiretrovirals: Isentress® (Raltegravir)

ABSTRACT & COMMENTARY

By Lian Chang, PharmD Candidate, Jessica C. Song, MA, PharmD, and John O'Brien, PharmD

Lian Chang is PharmD Candidate, University of the Pacific, Jessica C. Song is Pharmacy Residency Coordinator, University of the Pacific, and John O'Brien is Clinical Pharmacist Specialist, Santa Clara Valley Health and Hospital System

Lian Chang, Jessica C. Song, and John O'Brien report no financial relationships relevant to this field of study.

OVER THE PAST DECADE, TREMENDOUS PROGRESS HAS been made to increase the tolerability of treatment regimens and to reduce the pill burden for HIV-1 infected patients. However, many potential areas for improvement exist for optimizing the treatment of HIV-1 infected patients. These areas include the development of new agents with activity against highly-resistant HIV strains, and new agents that are not associated with the adverse events seen in established regimens (ie, lipoatrophy, dyslipidemia, insulin resistance, renal and liver toxicities, and central nervous system effects).[1]

In September 2007, maraviroc (Selzentry), the first CCR5 co-receptor antagonist, was approved by the FDA.[1] Shortly thereafter, in October 2007, approval was granted for the first HIV-1 integrase inhibitor raltegravir (Isentress).[1,2] With the approval of these new agents, highly treatment-experienced HIV-1 patients now have access to novel classes of drugs, with minimal propensity towards conferring HIV resistance. This article will review the pharmacology of raltegravir and discuss the resistance patterns and pivotal clinical studies highlighting this new antiretroviral agent.

Management of Treatment-Experienced Patients

According to the 2008 DHHS (US Department of Health and Human Services), HIV treatment guidelines for adults and adolescents should contain at least two, preferably three, fully active agents.[3] The two most common types of combination therapy in treatment-naïve patients are NNRTI (nonnucleoside reverse transcriptase inhibitor)-based (1 NNRTI + 2 NRTI [nucleoside reverse transcriptase inhibitor]) and PI (protease inhibitor)-based (1 or 2 PI + 2 NRTI) regimens.[3] *Table 1* shows the DHHS-recommended agents for initial therapy in treatment-naïve patients. The goal of treatment is to achieve an undetectable viral load of HIV-1 RNA < 50 copies/mL (goal at Santa Clara Valley Medical Center (SCVMC, San Jose, CA) is < 75 copies/mL).

Antiretroviral (ARV) treatment failure is not uncommon, and is defined as a viral load of > 400 copies/mL after 24 weeks, > 50 copies/mL after 48 weeks, or a repeated detected viral load after prior virologic suppression.[3] Healthcare providers should evaluate adherence history, medication intolerance, suboptimal pharmacokinetics, and drug resistance, all of which may contribute to treatment failure.[3]

A new treatment regimen should be designed for the treatment-experienced patient based on treatment history and resistance testing results. Ideally, a genotypic drug resistance test should be obtained while the patient is taking the failing ARV regimen (or within four weeks of treatment discontinuation).[3] A coreceptor tropism assay should also be performed to deter-

Table 1

Antiretroviral Components Recommended for Treatment of HIV-1 Infection in Treatment-Naive Patients3

To Construct an Antiretroviral Regimen, Select One Component from Column A + One from Column B

	Column A (NNRTI or PI options)		Column B (Dual NRTI options)
Preferred Components	**NNRTI** Efavirenz[a] **OR** **PI** -Atazanavir = ritonavir -Fosamprenavir = ritonavir -Lopinavir/ritonavir[b] (conformulated) (2x/day)	**Preferred Components**	Tenofovir/emtricitabine[c] (coformulated) **OR** Abacavir/lamivudine[c] (coformulated)
Alternative Components	**NNRTI** Nevirapine[d] **OR** **PI** -Atazanavir[c] -Fosamprenavir -Fosamprenavir = ritonavir (1x/day) -Lopinavir/ritonavir (coformulated) (1x/day) -Saquinavir + ritonavir	**Alternative Components**	**OR** -Zidovudine/lamivudine[c] (coformulated) -Didanosine = (emtricitabine or lamivudine)

[a]Efavirenz is not recommended for use during the 1st trimester of pregnancy or in sexually-active women with childbearing potential who are not using effective contraception.

[b]The pivotal study that led to the recommendation of lopinavir/ritonavir, one of the first-line PI components was based on twice-daily dosing. A smaller study has demonstrated similar efficacy with once-daily dosing, but also showed a higher incidence of moderate-to-severe diarrhea with the once-daily regimen (16% vs 5%). Also, once-daily dosin may not suffice for patients with viral loads > 100,000 copies/mL.

[c]Emtricitabine may be used in place of lamivudine and vice versa

[d]Nevirapine should not be initiated in women with CD4 count > 250 cells/mm^3 or in men with CD4 count > 400 cells/mm^3 due to increased risk of symptomatic hepatic events in the patients.

[e]Atazanavir must be boosted with ritonavir if used in combination with efavirenz or tenofovir.

mine whether a CCR5 inhibitor (maraviroc) may be added to raltegravir in order to maintain at least two fully active drugs in the new regimen.[1]

While adding a singly, fully active agent in a new regimen is not recommended to prevent the risk of rapidly developing resistance, it may be done in some clinically deteriorating patients, because even transient decreases in HIV RNA and/or transient increases in CD4 T-cell count have been shown to provide clinical benefits.[3] Discontinuing or briefly interrupting therapy (even with ongoing viremia) may quickly lead to drug resistance and treatment failure; therefore, it is not recommended.

Table 2 summarizes the ARV classes with newly approved drugs in treatment-experienced patients.

Pharmacologic Properties of Raltegravir

Raltegravir acts by inhibiting the strand transfer step (catalyzed by the integrase enzyme) that allows the insertion of reverse transcribed DNA into the host cell DNA.[4,5] Inhibiting this essential step limits the ability of the virus to replicate and infect new host cells. Raltegravir is used in combination with other antiretrovirals for the treatment of HIV-1 in highly treatment-experienced adults who have evidence of viral progression and viral strains resistant to multiple antiretroviral agents.[3] It is administered orally as a 400 mg tablet given twice daily with or without food and does not require boosting with ritonavir.[1] In practice, PIs are boosted with ritonavir to achieve

Table 2

Antiretroviral Classes with Newly Approved Drugs in Treatment-Experienced Patients

Class	Drug Name	Clinical Status	Pivotal Clinical Studies	Comments
Entry Inhibitors	Maraviroc[a] (Selzentry®)	FDA-approved	Phase IIb/III studies (MOTIVATE I & II)[12,13]: (N = 601, MOTIVATE I; N = 475, MOTIVATE II) triple-class, treatment experienced patients with mean age of 45 years, 90% males, median CD4 cell count of 150-180 cells/mm^3 and a mean HIV viral load of ~ 65,000 copies/mL. Results: 24-week results showed significantly better virologic responses over 24 weeks with maraviroc-treated patients (45.6%-48.5% of twice-daily dosing arm patients achieved viral loads < 50 copies/mL) compared with placebo-treated patients (20.9%-24.6% of patients achieved viral loads < 50 copies/mL; $P < 0.0001$)	-Maraviroc should be considered for use in treatment-experienced patients who have only R5 virus and who are naive to CCR5 inhibitors. -Usual dose range: 150-600 mg bid
Integrase Inhibitor	Raltegravir (Isentress®)	FDA-approved	Phase III studies (BENCHMARK I & II)[4,5] (total N = 699) triple-class, treatment-experienced patients, failed current ARVs, with detectable viremia Results: 24-week results showed significantlybetter virologic responses with raltegravir-treated patients (63% of patients achieved viral loads < 50 copies/mL) compared with placebo-treated patients (34% of patients achieved viral loads < 50 copies/mL) when added to OBT.	-Raltegravir should be considered for use in treatment-experienced patients who are naive to integrase inhibitors -Usual dose: 400 mg bid
NNRTI	Etravirine (TMC-125)	FDA-approved	Phase III studies (DUET I & II)[14,15] (N = 612 in DUET I; N = 591 in DUET II) triple-class, treatment-experienced patients with at least one NNRTI-associated resistance mutation and at least 3 primary PI mutations,failure of current ARV regimen. All patients received darunavir with low-dose ritonavir, along with investigator-selected NRTIs. Enfuvirtide was considered as an optional agent. Results: 24-week results showed significantly better virologic patients (56%-62% of patients achieved viral loads < 50 copies/mL) compared with placebo-treated patients (39%-44% of patients achieved viral loads < 50 copies/mL; P = 0.005 in DUET I; P = 0.0003 in DUET II)	-Expanded access program available since July 2007 -Usual dose: 200 mg bid with food

[a]The entry inhibitors are a heterogeneous group that includes agents that act at several stages in the entry process. Maraviroc is a CCR5 antagonist
OBT-optimized background therapy (a regimen of active antiretroviral agents tailored to individual patients, selected by their physicians as most likely to be of benefit); ARV-Antiretroviral

Table 3

Pharmacologic Properties of Isentress® (Raltegravir)[2]

Brand/Generic	**Isentress® (Raltegravir)**
Classification	Human Immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI)
Mechanism of Action	Selectively inhibits the strand transfer step that allows integration of reverse transcribed DNA into host cell DNA
Indications (FDA labeled)	Isentress® is indicated in combination with other antiretroviral agents for treatment of HIV-1 in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.
Pharmacology (young, healthy adults); Dose 400 mg twice daily	**Elimination half-life (h):** 9 **T_{max} (h):** 3 **Protein bound (%):** 83% **Metabolism:** Primarily hepatic glucuronidation via UGT1A1 **Excretion:** Feces (51%, as unchanged drug); Urine (32%; 9%, as unchanged drug)
How Supplied/Storage	**Oral:** pink, oval-shaped, film coated 400 mg tablets with "227" on one side **Storage:** at 15°C to 30°C (59°F to 86°F)
Dosage and Administration	**Adults:** 400 mg by mouth twice daily, with or without food **Pediatrics:** Safety and efficacy in children less than 16 years of age have not been established
Dosage Adjustment	**Renal Impairment:** No dose adjustment is necessary **Hepatic Impairment:** No dose adjustment is necessary for mild-to-moderate hepatic impairment
Monitoring Parameters	-Viral load, CD4 count -Resolution/improvement of HIV-related symptoms
Contraindications	There are no known contraindications
Warnings/Precautions	-Immune reconstitution syndrome resulting in an inflammatory response to an indolent or residual opportunistic infection may occur -Myopathy and rhabdomyolysis have been reported; use with caution in patients with risk factors for CK elevations and/or skeletal muscle abnormalities -Inhibitors or inducers of UGT1A1 glucuronidation -Safety and efficacy have not been established in children < 16 years of age
Adverse Effects	**Adverse events of all intensities occurring in ≥ 10%:** diarrhea (16.6%), nausea (9.9%), headache (9.7%), fever (4.9%)
Drug/Food Interactions	-Isentres® is not a substrate, inhibitor, or inducer of CYP450 isoenzymes. It is eliminated mainly by the UGT1A1 mediated glucuronidation pathway. -Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of Isentress®; caution should be used with the recommended dose of Isentress® -Similar to rifampin, tipranavir/ritonavir reduces Isentress® concentrations. This is not clinically significant; no dose adjustment of Isentress® is necessary -Atazanavir, a strong inhibitor of UGT1A1, increases Isentress® plasma concentrations. This is not clinically significant; no dose adjustment of Isentress® is necessary -Isentress® may be administered without regard to food
Pregnancy Category	**C**, to monitor fetal outcomes of pregnant women exposed to Isentress® call 1-800-258-4263
Lactation	Breast-feeding is not recommended while taking Isentress®. HIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV
Overdose/Toxicity	**S/Sx:** Doses as high as 1600 mg single dose and 800 mg twice daily multiple doses showed no evidence of toxicity. **Tx:** Includes general supportive care (ie, remove unabsorbed drug from GI tract, monitor for clinical changes, etc.). The extent to which Isentress® is dialyzed is unknown.

adequate plasma drug concentrations and to prevent resistance to PIs. Unfortunately, ritonavir has many drug-drug interactions, and it can induce significant medication intolerance in susceptible patients.

In studies, raltegravir was generally well tolerated. The most commonly reported adverse effects included diarrhea (16.6%), nausea (9.9%), headache (9.7%), and fever (4.9%).[2] Grade 2-4 creatine kinase elevations were observed in patients receiving raltegravir (~2% , which is comparable to that of daptomycin[6] and rosuvastatin[7]). Myopathy and rhabdomyolysis have been reported, although the causality is unknown.[2] Healthcare providers should assess the risk factors for these two conditions, such as the co-administration of medications (ie, statins) also known to cause these conditions.

Raltegravir is metabolized by UGT1A1-mediated glucuronidation.[2] It is neither a substrate, inhibitor, nor inducer of the CYP450 enzymes.[2] Thus, it is expected to have no substantial interactions with drugs metabolized by the CYP450 system, including most PIs and NNRTIs. Concomitant usage of drugs that are strong inducers of UGT1A1 (eg, rifampin, efavirenz, tipranavir/ritonavir, rifabutin) may result in reduced plasma concentrations of raltegravir, and must be used with caution.[2,3] However, data show that strong inhibitors of UGT1A1 (eg, atazanavir) may be co-administered with raltegravir without dose adjustment.[2] Furthermore, no dose adjustment is required for renal and hepatic impairment.[2]

Table 3 summarizes the key pharmacologic properties of raltegravir.

Resistance Patterns/Clinical Studies of Raltegravir

The approval of raltegravir was based on 24-week data from two identical, randomized, double-blind, placebo-controlled, phase III BENCHMRK (I & II) studies. These studies included 699 treatment-experienced HIV-1 patients who were 16 years or older and had documented resistance to at least one drug in each of the three antiretroviral classes (NRTIs, NNRTIs, PIs).[4,5] The results at 24 weeks showed that subjects who received raltegravir 400 mg twice daily plus optimized background therapy (OBT) were roughly twice as likely to achieve a viral load below 400 copies/mL and 50 copies/mL than those receiving OBT plus placebo (75.5% vs 39.3% and 62.6% vs 33.3%, respectively).[4] The mean increase in CD4+ cell counts was also higher in the treatment arm than in the control arm (89 cells/mm2 vs 35 cells/mm^2). These efficacy results were supported by 48-week analysis of a double-blind, phase II dose-ranging trial.[8,9]

As seen with the NNRTIs and many of the antimicrobial drug classes, development of resistance to one integrase inhibitor often confers cross-resistance within its own class. Limited data show that there are two distinct pathways that confer resistance in this class: N155H and Q148K/R/H.[10] Elvitegravir, another HIV-1 integrase inhibitor, is in the late-stages of clinical development.[11] One study analysis consisting of two patients who switched from elvitegravir/ritonavir to raltegravir after virologic failure showed no significant reductions in HIV-1 RNA, suggesting some cross-resistance between raltegravir and elvitegravir.[11]

Conclusion

As the first integrase inhibitor to be approved in its class, raltegravir offers much hope for current HIV-infected patients who have exhausted other treatment regimens. Since raltegravir does not undergo biotransformation by the CYP450 system and does not require to be boosted with ritonavir, this drug eliminates many of the issues concerning drug-drug interactions and current adverse drug reactions attributed to protease inhibitors. Furthermore, raltegravir has recently been approved by the AIDS Drug Assistance Program (ADAP) in November 2007, and no longer requires the SUPPORT program. As always, healthcare providers must enforce patient medication adherence to maintain efficacy with the current antiretroviral therapeutic options. ■

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S. maltophilia: A Multi-Resistant Nosocomial Pathogen

ABSTRACT & COMMENTARY

By Robert R. Muder, MD

Hospital Epidemiologist, Pittsburgh VA Medical Center

Dr. Muder does research for Aventis and Pharmacia.

STENOTROPHOMONAS MALTOPHILIA (FORMERLY KNOWN as *Pseudomonas maltophilia*, *Xanthomonas maltophilia*) is a motile, gram-negative bacillus that is widely distributed in nature, particularly in water and soil. It rarely causes disease in healthy hosts, but it can be a particularly troublesome pathogen in highly compromised, hospitalized patients. The most serious infections caused by *S. maltophilia* are catheter-related bacteremia and pneumonia.[1] Central venous catheters are the most frequent source of bacteremia; malignancy, neutropenia, and receipt of broad spectrum antimicrobial therapy are notable risk factors. *S. maltophilia* bacteremia often presents as "breakthrough" bacteremia, that is, occurring while the patient is receiving antimicrobials.

The other typical infection caused by *S. maltophilia* is hospital-acquired pneumonia, particularly in patients receiving mechanical ventilation; pneumonia is the second most frequent source of bacteremia. It should be noted, however, that *S. maltophilia* often colonizes the sputum of ventilated patients without pneumonia; differentiating infection from colonization in a patient with underlying pulmonary pathology may be problematic. Approximately 10% of

patients with cystic fibrosis are colonized with *S. maltophilia*; the incidence of colonization increases with the duration of the illness. It is not clear that colonization of cystic fibrosis is itself an independent predictor of disease severity.

S. maltophilia may cause infection at a variety of other sites. Ocular infections, including keratitis and endophthalmitis, may occur after ophthalmologic surgery. Soft tissue infections occur after contamination of wounds with soil. Among hospitalized patients, isolation of *S. maltophilia* from wounds typically represents colonization rather than infection. A notable exception are neutropenic patients, in whom *S. maltophilia* may cause severe soft tissue infection, often with associated bacteremia.[2] *S. maltophilia* is an occasional cause of endocarditis in patients with prosthetic heart valves or a history of intravenous drug abuse.[3]

Treatment of *S. maltophilia* infection is problematic due to the organism's intrinsic resistance to multiple classes of antimicrobials.[4] It possesses two separate βeta-lactamases, a zinc containing penicillinase and a cephalosporinase. Nearly all isolates of *S. maltophilia* are highly resistant to carbapenems. Resistance to third generation cephalosporins and anti-pseudomonal penicillins is variable. Interestingly, many isolates are susceptible to ticarcillin/clavulanate, but nearly all are resistant to piperacillin/tazobactam.

S. maltophilia isolates frequently have drug efflux pumps that mediate resistance to multiple classes of antimicrobials, including βeta-lactams, aminoglycosides, and quinolones. Susceptibility to the latter two classes of agents is highly variable. MICs to newer agents, such as moxifloxacin and gatifloxacin, tend to be lower than to older agents, such as ciprofloxacin and levofloxacin. Historically, trimethoprim-sulfamethoxazole has been highly active against *S. maltophilia*. Recent surveillance data show an increase in resistance,[5] so that susceptibility of trimethoprim-sulfamethoxazole can't be assumed. Limited data indicate that *S. maltophilia* is usually susceptible to tigecycline, although clinical experience is lacking.

In vitro studies have identified a number of antimicrobial combinations with synergistic activity against *S. maltophilia*. Trimethoprim/sulfamethoxazole and ticarcillin/clavulanate are synergistic, and may demonstrate in vitro synergy, even if the isolate is resistant to both combinations. Synergy between quinolones and third generation cephalosporins has also been documented.

As *S. maltophilia* tends to cause infection in highly compromised patients, and is often resistant to multiple classes of agents, appropriate therapy can be challenging. Although data from clinical trials is lacking, observational data from series of patients with bacteremia suggests that multi-drug treatment is associated with lower mortality than single agent treatment.[4] Candidates for multi-drug therapy include neutropenic patients, patients with bacteremia, and patients with hospital-acquired pneumonia. Combination therapy should consist of one βeta-lactam agent, such as a third generation cephalosporin or ticarcillin/clavulanate (NOT piperacillin/tazobactam) plus either trimethoprim/sulfamethoxazole or a quinolone. The choice of individual agents should be based on the results of in vitro testing. Tigecycline is an option if high level resistance or allergy to other agents exists.

Less severe infection, such as UTI or uncomplicated soft tissue infection, can usually be managed with a single agent. Trimethoprim-sulfamethoxazole is the preferred agent if the isolate is susceptible. It is probably best to avoid quinolone monotherapy since emergence of quinolone resistance on therapy can occur. ■

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CME Question

16. Two blood cultures obtained from a febrile, neutropenic patient are positive for Stenotrophomonas maltophilia. Pending the results of susceptibility studies, an appropriate initial treatment regimen would be;

a. meropenem

b. meropenem + gentamicin
c. ciprofloxacin
d. ciprofloxacin + piperacillin/tazobactam
e. trimethoprim/sulfamethoxazole + ticarcillin/clavulanate.

17. Which of the following is correct?
a. Tenofovir is entirely excreted by glomerular filtration.
b. Ritonavir coadministration may lead to increased concentrations of tenofovir in renal tubules.
c. Tenofovir is a nucleoside analog.
d. Tenofovir-containing regimens have repeatedly been shown to be inferior to zidovudine-containing regimens.

18. Which of the following is correct?
a. Raltegravir inhibits entry of HIV into the cell.
b. A coreceptor tropism assay should always be performed before prescribing raltegravir.
c. Raltegravir must always be administered with ritonavir.
d. Raltegravir is neither a substrate, inhibitor, nor induce of the CYP450 enzymes.

19. Which of the following is correct regarding *Stenotrophomonas maltophilia*?
a. It is a Gram positive organism.
b. It is a common cause of meningitis.
c. Most are resistant to imipenem and meropenem.
d. Most are resistant to trimethoprim-sulfamethoxazole.

Answers: 16. (e); 17. (b); 18. (d); 19. (c)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Angiostrongylus cantonensis

UPDATES

By Carol A. Kemper, MD, FACP

CDC Flu Update

CDC New Conference, February 8, 2008.

In a news conference February 8, 2008, officials from the CDC announced that preliminary data suggest there is a mismatch between circulating influenza virus in the United States this winter and this year's influenza vaccine. Curtis Allen and Joe Bresee, the Branch Chiefs for epidemiology, CDC Influenza Division, told reporters that 93% of circulating Influenza B virus, and up to 21% of circulating Influenza A virus, may not match the current vaccine. Thus far, 197 Influenza isolates have been characterized, including 53 Influenza A/H3N2, 101 Influenza A/H1N1, and 43 Influenza B virus. Forty of the 43 Influenza B virus cases (93%) are from a lineage distinct from the B/Malaysia-like component of the 2007-2008 vaccine, so the vaccine will provide no cross protection for Influenza B. The circulating Influenza A/H3N2 virus is predominately A/Brisbane/10/2007, which is antigenically similar to the current A/Wisconsin component in this year's vaccine, so there should be some cross-protection provided by this year's vaccine.

The flu season started out slowly this year, but cases have begun to escalate fairly rapidly the last few weeks. Officials urged people to continue to receive this year's vaccine, despite the apparent mismatch of 2 of the 3 components, as it still provides good protection for the predominant circulating Influenza A strain, as well as some likely cross protection for the less common Influenza A strain.

Physicians are reminded to be on the alert for MRSA superinfection in patients with the flu; last year, 15 of 73 influenza-related deaths (21%) were the result of MRSA infection.

The 5th Human Malaria

Source: Cox-Singh J, et al. *Plasmodium knowlesi* malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis*. 2008;46:165-171.

Following the deaths of four previously healthy individuals in Malaysia, from what was initially believed to be *Plasmodium malariae* between 2004-2005, and an outbreak of symptomatic malaria secondary to *Plasmodium knowlesi* in a northwestern state of Borneo, Cox-Singh and colleagues set about to determine the incidence of *P. knowlesi* infection in humans from the Malaysia peninsula and Malay Bornea.

P. knowlesi is believed to be an "Old World" infection, predominately infecting certain primate species, although it is permissive to humans under certain environmental circumstances. The potential for human-to-human transmission exists, and gametocytes have been observed in human blood specimens. A limitation to more widespread human infection with this plasmodium species is its mosquito vector, *Anopheles latus*, which has a limited habitat in forested areas in parts of Borneo and the South Pacific. Human infection due to *P. knowlesi* has been identified in persons from China, Thailand, and Burma (although, as data suggest, the identification of this organism by microscopy may be frequently mistaken, as *P. knowlesi* morphologically resembles *P. malariae*). Unlike *P. malariae*, which takes a relatively benign course in humans, with low grade parasitemia, *P. knowlesi* multiplies rapidly and quickly leads to high level parasitemia, similar to *P. falciparum*.

Cox-Singh et al examined 960 blood spots collected and archived from unselected patients hospitalized with malaria throughout Malaysia between 2001-2006. DNA was extracted, and nested PCR speciation assays were compared with the results of microscopy. Routine microscopy had identified *P. vivax* in 45% of the these patients, *P. malariae* in 33%, *P. falciparum* in 23%, and *P. ovale* in 0.2%. In contrast, nested PCR demonstrated that 266 of the 960 (28%) subjects in Sarawak hospitals, 41 of 49 (84%) of cases in Sabah district, and all 5 cases from Pahang, Peninsular Malaysia were infected with *P. knowlesi*. In Sarawak, Malay Borneo, 5.5% of the cases were due to mixed infection with *P. knowlesi* and other plasmodium species. Only 4 cases were PCR+ for *P. malariae*. Of the 312 cases initially identified by microscopy as *P. malariae* in Sarawak, 228 were PCR+ for *P. knowlesi*; most of the rest were due to *P. falciparum* or *P. vivax*, suggesting that microscopic identification of these organisms is frequently flawed.

The four fatal cases presented with parasite loads ranging from 75,000 to 765,000/µl, with significant thrombocytopenia and hepatorenal dysfunction. The patients died

within 2 hrs to 13 days of presentation. Only *P. knowlesi* DNA was detected from their blood samples.

These data conclusively demonstrate that *P. knowlesi* is not only responsible for human cases of malaria in Malay Borneo but is quite common, and may result in life threatening disease. Treatment of these cases should be prompt and aggressive, similar to that for *P. falciparum*.

More on XDR-TB: Did DOT do it?

Source: Pillay M, Sturm AW. Evolution of the extensively drug-resistant F15/LAM4/KZN strain of *Mycobacterium tuberculosis* in KwaZulu-Natal, South Africa. *Clin Infect Dis*. 2007;45:1409-1414.

EXPERTS ESTIMATE THAT FEWER than 5% of MDR-TB isolates around the world are actually recognized, due to a dirth of laboratory capability and surveillance in many poorer countries. Few programs have the capacity to do even basic smears and cultures, let alone susceptibility testing to first line agents; testing to second line agents is limited to a handful of specialized laboratories, and testing for certain agents is difficult and non-standardized (capreomycin). As a result, experts are concerned that many cases of MDR- and XDR-TB are being missed, with the potential for public health disaster. Already more than 400 cases if XDR-TB have been recognized in South Africa, which are overwhelming health facilities caring for patients with TB. Attempts to contain the spread of this infection by forcibly isolating patients with drug-resistant disease failed miserably last year, when patients escaped a locked facility to return home to their families. It is suspected that many other XDR-TB cases remain undetected; other patients with HIV infection may die too quickly for their infection to be recognized.

A recent effort to screen for drug-resistant isolates in Botswana identified 100 cases of multidrug-resistant disease, and two cases of XDR-TB.

Because KwaZulu-Natal has been considered "ground zero" for many of the identified cases of XDR-TB, Pillay and Sturm examined resistance patterns of isolates from this area from 1994 to 2005. The majority of XDR-TB cases appear to be due to single strain of *M. tuberculosis* (F15/LAM4/KZN). This strain was detected as early as 1994, when it was responsible for a number of cases of MDR-TB. Over the years, resistance to additional agents was identified, and Pillay and Sturm tracked the evolution of resistance in this strain, with the step-wise occurrence of resistant to seven different drugs, beginning with isoniazid-ethambutol and isoniazid-rifampin-resistant strains, to the sequential addition of resistance to ethambutol, streptomycin, ethionamide, thiacetazone, capreomycin, kanamycin/amikacin, and finally fluoroquinolones. The first XDR-TB strain was recognized in 2001 in South Africa.

Sadly, Pillay and Sturm believe that the creation of this super-bug coincides with the initiation of directly-observed, therapy-based and directly-observed, therapy-plus-based programs in this part of the country. This strategy, though well-meaning, was intended to prevent the spread of drug-susceptible strains, as well as limit the occurrence of drug-resistant strains by ensuring adherence to therapy. It was hoped that those few patients who were non-compliant, or who did not complete their 6-month treatment course, would have insufficient exposure to drug to promote resistance. However, this strategy did not include drug susceptibility testing for second line agents; for strains exhibiting resistance to first line agents, patients were treated with empiric alternate agents, such as ethambutol and cycloserine, combined with pyrazinamide or kanamycin. As a result, patients were unwittingly treated with only one or two active agents.

Thus, MDR-resistant strains already present at low levels in 1994, began showing evidence of further resistance to ethambutol and ethionamide in 1997, kanamycin in 1999, and fluoroquinolones in 2000. Re-treatment strategies with the empiric addition of streptomycin to the standard 4-drug regimen in patients who had interrupted their therapy further cemented the evolution of resistance to the predominant XDR strain today, but also probably explains a divergence in XDR isolates now in circulation.

This evolution of drug resistance occurred at the same time more persons were infected with HIV, resulting in a greater number of susceptible and contagious individuals. There is also some data that the F15/LAM4/KZN strain may be more transmissible than other strains.

Not only does this report reinforce the idea of evolutionary imperative, but reinforces the dire public health need for laboratory support, trained personnel, and a better treatment plan in the global fight against drug-resistant TB. Given the eventuality that more of these isolates will make their way to the United States, if you suspect MDR or XDR-TB in persons from southern African or the former Soviet Republics, contact your local public health department. Newer molecular technologies, such as the Deakon PCR for INH/rifampin resistance, are available for use, and can quickly provide information direct from sputum specimens well before the results of culture are available. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

FDA Heightens Warnings on Chantix

In this issue: *Stop smoking drug Chantix rates stronger warning from FDA; Type 2 diabetes surgery on the way?; Vytorin study inconclusive; Influenza A virus found resistant to Tamiflu; FDA actions.*

The FDA has strengthened its warning on the stop smoking drug varenicline (Chantix). Last November the agency issued an Early Communication regarding reports of changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior in patients taking the drug. After review of recent reports, the agency now says that it appears increasingly likely that there may be an association between varenicline and neuropsychiatric symptoms. The FDA has asked Pfizer, the manufacturer of the drug, to elevate the prominence of these warnings on the package label, and the company along with the FDA is working on a Medication Guide for patients. The FDA is recommending that patients should tell their health-care providers about any history of psychiatric illness prior to starting varenicline. There is evidence that the drug may cause worsening of current psychiatric illness, and cause old psychiatric illness to reoccur. Moreover health-care professionals, patients, patients' families, and caregivers should be alert to monitor for changes in mood and behavior in patients treated with varenicline. The FDA warning also states that vivid, unusual, or strange dreams may occur while taking the drug and that patients may experience impairment of the ability to drive or operate heavy machinery. Varenicline was approved in May 2006 under the trade name Chantix by Pfizer Pharmaceuticals to ease withdrawal symptoms associated with smoking cessation.

Weight-loss Surgery Answer for Type 2 Diabetics?

Could surgery be the answer for type 2 diabetes? In a new study from Australia, 60 patients with type 2 diabetes and a BMI of 30-40 were randomized to adjustable gastric banding surgery or conventional therapy. Conventional therapy focused on weight loss by lifestyle changes. The main outcome measure was remission of type 2 diabetes and secondary measures included weight and components of the metabolic syndrome. Remission of type 2 diabetes was achieved by 22 patients in the surgical group (73%) vs 4 patients in the conventional therapy group (13%). Relative risk for remission in the surgical group was 5.5 (95% CI, 2.2-14.0). Surgical patients lost more weight, mean (SD) 20.7% (8.6%) vs 1.7% (5.2%) for the nonsurgical group at two years (P <.001). There were no serious complications in either group. The average weight loss to achieve remission of type 2 diabetes was 10%, which was achieved in 86% of the surgical patients and only 1% of the medical therapy patients. The authors conclude that for patients with type 2 diabetes, surgical therapy was more likely to achieve remission through greater weight loss. These results should be confirmed through larger, more diverse population and have long-term efficacy assessed (*JAMA* 2008;299:316-323). An accompanying editorial suggests that gastrointestinal tract surgery may offer a new goal in diabetes management—remission rather than just treatment. The editorialists also suggest that the cost and risks of such surgery must be balanced

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: iris.young@ahcmedia.com.

with the costs and risks of long-term diabetes management (*JAMA* 2008; 299:341-343).

Vytorin Needs More Study

Vytorin has been in the news recently after Merck/Schering-Plough released the preliminary results of the Effect of Combined Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) study. Vytorin is a combination of the statin simvastatin (Zocor) and ezetimibe (Zetia), a medication that blocks cholesterol absorption through the gut. The combination drug is better at lowering LDL than either drug alone, and it was hoped that this would translate to improved cardiovascular outcomes. ENHANCE randomized 720 patients with heterozygous familial hypercholesterolemia to treatment with either simvastatin 80 mg daily or Vytorin (simvastatin 80 mg plus ezetimibe 10 mg). Mean LDL cholesterol levels at baseline were 320 mg/dl. Simvastatin alone lowered LDL by 41% while Vytorin lowered LDL by 58%. The primary endpoint was change in mean carotid intima media thickness after two years of treatment. There was no difference in this primary endpoint or in the incidence of any adverse effects between the two treatment arms. ENHANCE was widely reported as a failure for Vytorin, and there were even reports that Vytorin increased the rate of plaque production, which was not the case. The study has been criticized because of its small size, atypical patient population, and primary outcome (carotid intimal media thickness) which is not a clinical outcome. The American College of Cardiology issued a statement on January 15 suggesting that "major clinical decisions not be made on the basis of the ENHANCE study alone." The FDA issued a statement on January 25 stating that it will conduct a review of Merck and Schering-Plough's trial once the final results of the study are available. Data from the ENHANCE study is due to be presented at the American College of Cardiology meeting in March.

Virus Resistant to Tamiflu Causing Concern

A small percentage of the influenza A virus causing illness worldwide this winter is resistant to oseltamivir (Tamiflu), according to the World Health Organization. Tamiflu-resistant forms have been found in European countries, Canada, and the US. Generally mutations of this sort attenuate the virus, making it less infectious; however this is not found be the case with the resistant strain of A/N1H1 known as A(H1N1 H274Y). The highest rate of resistance was found in Norway with 75% of isolated viruses showing resistance. The rate of resistance in the US was 3.8%. There are currently no plans to change recommendations for use of Tamiflu; however, WHO officials are "troubled by the discovery" according to the *New York Times*.

Choice of Antivirals for Flu

In other flu-related news, the CDC reports that primary care physicians frequently used inappropriate flu drugs during last year's flu season. A survey published in *MMWR* found that of 730 respondents, 54% prescribed anti-viral agents and of those, one quarter prescribed amantadine or rimantadine. These drugs are no longer recommended because of a high rate of viral resistance (MMWR 1/25/08:57(03); 61-65). Finally, the FDA has approved a real-time test for influenza A and B and RSV. The test, called ProFlu+ Assay produces results within about three hours, and has a 98% sensitivity, and 83% specificity. The assay is marketed by Prodesse Inc.

FDA Actions:

The FDA has strengthened its warning on the contraceptive patch Ortho Evra regarding the risk of venous thromboembolism. The warning is based on a study conducted by the Boston Collaborative Drug Surveillance Program that showed that the patch was associated with a higher risk of venous thromboembolism than oral contraceptive pills.

The FDA has taken the strongest stance yet against the use of over-the-counter cough and cold products for children younger than two years of age. On January 17 the agency issued a Public Health Advisory for parents and caregivers recommending that the products should not be used to treat infants and children because of reports of serious adverse events including death, convulsions, rapid heart rates, and decreased levels of consciousness. The agency continues to review use of these medications on children aged two to 11.

The FDA has warned seven pharmacy operations that produce "bio-identical hormone replacement therapy" that claims of their products' effectiveness may be false and misleading because they are not supported by medical evidence. These products are frequently compounded by large pharmacy operations and contain estrogen, progesterone, and estriol. Claims range from reduced risk of stroke, cancer, and lower rates of Alzheimer's disease associated with products. Compounded drugs are not reviewed by the FDA for safety and effectiveness however misleading claims violate federal laws. The FDA considers the term "bio-identical" a marketing term which implies benefit for which there's no medical or scientific basis. Compounding pharmacy that do not address these violations are subject to further enforcement according to the FDA press release. ■