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# TB MONITOR™

*The Monthly Report on TB Prevention, Control, and Treatment*

## INSIDE



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# New co-infection guidelines blast short-course, twice-weekly regimen

*Gold standard for isoniazid prophylaxis is nine months, not six*

New guidelines for treatment and prevention of TB in HIV-positive patients hold a stern reminder: What's convenient for programs isn't always what's best for the patient. Last month's official pronouncement on preventive therapy for HIV-positive patients comes as a disappointment to some program administrators, who had hoped for the go-ahead to provide the new short-course, two-month preventive regimen of pyrazinamide and rifampin (PZA/RIF) on a twice-weekly basis.

No way, the Centers for Disease Control and Prevention guidelines plainly state. Another unpleasant surprise is the reminder that when it comes to high-risk patients (including those with HIV), the duration of isoniazid prophylaxis isn't six months; it's nine months.

**"We wanted to make the point that recommendations for clinical decision making shouldn't be made on a cost-effectiveness basis."**

The recommendations reflect a conscious decision to drag people from the brink of wishful thinking and to clarify what the data do and don't support, says **Larry Geiter**, MPH, PhD, a consultant with Sequela Research Foundation in Rockville, MD. "We wanted to make the point that recommendations for clinical decision making shouldn't be made on a cost-effectiveness basis," says Geiter, an expert whose testimony is said to have swayed the roomful of national experts gathered to mull over the new guidelines.

"I can understand people's disappointment," says **Rick O'Brien**, MD, chief of the research and evaluation branch at the CDC's division of tuberculosis elimination. Purely from a programmatic perspective, he says, the less onerous recommendations "would have been great." The problem is that the data don't support such recommendations, he adds.

Reaction runs across the board. To some program administrators already hit with a new round of funding cuts **(see related story, p. 136)**, the guidelines offer powerful evidence that more study on short-course therapy is needed urgently.

"I think [rifampin and pyrazinamide] on a daily basis severely limit the advantages of short-course preventive therapy," says **David Ashkin**, MD,

medical director of Florida's TB control program. "We've had enormous amounts of difficulty getting people through preventive therapy."

Plus, preventive therapy only works if it's in the patient's stomach, Ashkin argues. Thus, what an intermittent course of PZA/RIF might lose in efficacy, it more than makes up for in adherence. "Even if RIF/PZA isn't as effective by, say, 3%, you more than offset that difference if you improve adherence by 30% to 40%," he says. Besides, "in the study that was already done, the data on twice-weekly looks as if it performed as well as daily," he adds.

Partly in the hope of gathering more evidence in support of twice-weekly PZA/RIF, Ashkin is considering a trial protocol of the twice-weekly regimen.

### *CDC discounts results of Haitian trial*

One of the investigators associated with the intermittent trial of PZA/RIF also expresses disappointment with the CDC guidelines and with the decision to discount the results of that trial, which was conducted in Haiti. "It's unfortunate," says **Jacqueline Coberly**, PhD, an assistant scientist at the department of international health at the school of hygiene and public health at Johns Hopkins University in Baltimore.

The CDC discounted the results of the Haitian trial for complicated reasons, says Geiter. Most importantly, the Haitian trial used as its standard for comparison a six-month course of self-administered isoniazid (INH). However, nine to 12 months of INH, not six months, is the gold standard for HIV-infected patients and should have been the standard for comparison in the trial, he adds.

True enough, says Coberly. "There's no question that nine months of INH is more efficacious than six," she says. "But when it comes to the probability of someone actually taking the nine months, we found only 55% of people actually finish; whereas 74% of people taking the [intermittent] PZA/RIF finish."

## Guidelines for patients co-infected with HIV, TB

New guidelines for treating and preventing tuberculosis among HIV-infected persons hold few surprises. The guidelines, issued by the Centers for Disease Control and Prevention in an Oct. 30 *Morbidity and Mortality Weekly Report* "Recommendation and Report" (volume 47) made the following points:

- All HIV-infected persons should be screened for TB. If infected, they should be treated to prevent the development of active disease.
- Either preventive or curative regimens must be evaluated carefully to prevent drug interactions with new therapies for HIV. In particular, rifampin should not be given in combination with protease inhibitors or with non-nucleoside reverse transcriptase inhibitors because it can seriously impair the effectiveness of these therapies.
- In such instances, the anti-TB drug rifabutin can be safely substituted for rifampin, allowing therapies for both TB and HIV to continue.
- Directly observed therapy should be provided.
- A new short-course regimen for preventing TB, consisting of daily therapy for two months with pyrazinamide and rifampin, now can be provided as an alternative to a yearlong course of isoniazid, the regimen previously prescribed for those co-infected with HIV and TB. ■

The trouble comes when the daily PZA/RIF and the intermittent are stacked against one another, says Geiter.

The Haitian trial and another in Zambia, the results of which haven't yet been published, compared two months of intermittent PZA/RIF to six months of INH, Geiter says. The Haitian trial put the level of protection for intermittent PZA/RIF at 60% and at 65% for six months of INH; that trial suggested intermittent PZA/RIF might — or might *not* — perform as well as six months of INH. Point estimates in the Zambian trial suggested the same, slightly ambiguous conclusions.

### *COMING IN FUTURE MONTHS*

- ■ A new test that offers a window onto latency
- ■ Latest studies about isolation
- ■ Report from American Public Health Association conference
- ■ Wrap-up from Infectious Disease Society of America conference
- ■ Whats new in managed care?

On the other hand, a third study comparing 12 months of daily INH to two months of daily PZA/RIF left no room for doubt, says Geiter. That trial found an 80% reduction from 12 months of INH; and an 84% reduction from two months of daily PZA/RIF, which suggests that two months of daily PZA/RIF might offer even better protection than 12 months of INH, he says.

"So we're saying that PZA/RIF on an intermittent basis is probably just as good as six months of INH but may actually be worse," he explains.

**To keep the debate interesting, at least one expert is blasting the CDC recommendation of daily PZA/RIF as misguidedly liberal rather than overly conservative.**

"Plus, we already know six months of INH isn't as good as 12." That, plus the way both the Haitian and Zambian trials seemed to tilt against the intermittent regimen of PZA/RIF, left intermittent PZA/RIF saddled with too many doubts, he says.

As the dust settles, other experts are taking a more philosophical stance, declaring intentions to cut their losses by ditching nine months of INH and substituting two months of daily PZA/RIF for both HIV-negative and HIV-positive patients. That regimen "has been shown to be state of the art, and I say people have no business using nine months of anything if they can use RIF/PZA," says **Lee Reichmann**, MD, MPH, director of the National Tuberculosis Center at New Jersey Medical School in Newark. "It's there; it works; I'll use it."

To keep the debate interesting, at least one expert is blasting the CDC recommendation of daily PZA/RIF as misguidedly liberal rather than overly conservative. "PZA plus rifampin? You tell my buddies at the CDC that I love them all, but that I said this is gonna be the biggest disaster they've ever given us," says **John Sbarbaro,** MD, professor of medicine at the University of Colorado Health Sciences Center in Denver. "It goes totally contrary to everything we know about PZA in the continuation phase," which, he adds, is practically the same as latency. "So why on earth add it? It merely adds hepatotoxicity. You're going to see a ton of hepatitis with this new regimen," he says. "This whole thing will set us back for 20 years."

One of Sbarbaro's colleagues and neighbors is more sanguine on the subject. "I don't think PZA is exactly dangerous," says **William J. Burman**, MD, infectious disease expert with the Denver TB control program. "But I do think there are some concerns about its tolerability. People may not want to put up with the side effects, which are fairly common, though seldom serious: the upset stomach, the itching after doses, the myalgia."

Back to that other line in the sand, nine months of INH vs. six months, Sbarbaro as well as experts on the more pragmatic side were more understanding. "Nine months of INH? That's just being conservative, but it makes sense," he says. "What's better? Eighty percent of the drugs for a few months, or 30% of the drugs for a year? It's counterintuitive, but the right answer is the second. That's because in preventive therapy, you're going after bugs that are dormant; and the longer you continue the therapy, the better the chance that the drugs will be there when the bugs wake up."

The nine-month rule also is important to emphasize because it helps explain why risk-benefit equations break down in the face of the higher risks for reactivation posed by HIV-positive patients, Geiter says. "Back in 1985, people began talking about a six-month regimen of IPT being more cost-effective. What kind of got lost over time is the fact that the individual patient would still benefit from taking another six months of treatment. And with HIV-positive patients, the overall risk for progressing to TB is so high that even on a cost-benefit basis, going from six to 12 months is still worthwhile."

### *Easier regimens won't sacrifice efficacy*

From the standpoint of what's doable, Geiter doesn't dispute appeals to practical arguments; he simply says it's important not to mix the nitty-gritty of real-life decision making with the practices dictated by the data.

Plus, programs can make regimens easier without sacrificing efficacy altogether, he adds. "If a public health program wanted to say, 'OK, we're going to give people PZA/RIF, but we'll only supervise them five times a week, or three times a week, and let them self-administer on the weekend. And then maybe [we'll] give them nine weeks of the drugs instead of eight weeks,' in practice that makes sense, even though it's not supported by clinical trial data," he says. "Or you could DOT [directly observed therapy] them five times a week and give them a drug holiday on

the weekend. There are all kinds of things you can do within reason to be creative."

In the same way, it's acceptable to aim for getting six months of INH into "your garden-variety, HIV-negative patient," Geiter says. "But what we've tended to lose sight of is that the data don't support that. What they actually show is that maximum benefit is achieved right about at nine months, and I think over the years we've lost sight of that fact."

With an HIV-negative patient, the risk of reactivation after six months is only about 10% to start with. Six months of INH cuts it by 65%, so adding another three months only buys an extra 3.5%, which isn't cost-effective in most cases, he says.

There's a practical reason to keep the bar high, he adds. If a program formally adopts a six-month course of INH as the ideal, it's hard to return to state legislatures after the fact and beg for more money for preventive care. On a smaller scale, he says, a primary care physician who thinks mistakenly that six months is the ideal probably will be happy with five months of treatment, and that would surely be a mistake.

Geiter sums it up this way: "If you're going to make these decisions on a cost-effective basis, you need to be clear that's what you're doing. I understand the pressure people are under. I'm just saying, don't mix clinical guidelines with cost considerations." ■

# Cuts aim to prevent Congressional axing

*Expert: Leftovers on the plate invite big trouble*

What drove the Centers for Disease Control and Prevention to trim $6 million in carry-over from money awarded to cooperative-agreement recipients was the fear that Congress might enact much bigger cuts of its own, says a CDC official.

There's supporting evidence that so many leftovers on TB controllers' plates might have had that effect, says **Patty Simone**, MD, chief of the field services branch of CDC's division of tuberculosis elimination.

"Federal immunization programs had the same thing happen to them," Simone says. "They had a huge increase in funding, and they also had a ton of carry-over. Congress looked at that and said, 'Forget it. We're going to cut your money.'"

That's why funding the CDC awarded to cooperative agreement recipients for fiscal year 1999 has been trimmed, just as the CDC warned would happen, by $6 million. With the news of next year's funding cuts finally in hand, TB controllers throughout the nation now are scrambling to assess how the cuts will affect local programs.

New money awarded to the CDC by Congress is "level," which is government-speak for "lower," and doesn't provide for cost-of-living increases many state and county programs are obligated to pay their employees. Therefore, the carry-over cuts have arrived at an especially unwelcome time, TB controllers say.

Past practice has dictated using carry-over funds to replace some of the "new" money that otherwise would have been awarded to a program. That practice, in turn, has meant more new money to go around, Simone says. "Of course, the states don't see it that way," she adds. "They just see it as money."

Typically, about half of all state programs wind up with some carry-over at the end of the year, she says. The reason is simple: Because TB rates have risen over the past decade, programs have had to play a fast game of catch-up, racing to build infrastructures to absorb the increase in Congressional largesse.

## *Carry-over increases pot of 'new money'*

Some states with carry-over were able to devise programs to spend the leftover money before the fiscal year ended. In other cases, the carryover simply was plowed back into the state's budget for the following year. The use of carryover had the effect of benefiting all programs because it made for a bigger pot of "new money," Simone adds.

To get rid of the telltale carry-over, which amounted to about $12 million in the last fiscal year, two strategies have been devised. First, states with large amounts of carryover have been told to "spend more efficiently," she says. The second strategy took the shape of this year's $6 million in cutbacks.

*(Continued on page 138)*

# Back to the future in a U-shaped curve?

*Controllers forced to cut programs, positions*

As state TB control programs got the bad news last month about funding cutbacks, there was plenty of predictable grumbling about "the U-shaped curve of concern."

"We've definitely taken a hit," says **David Ashkin**, MD, medical advisor to Florida's TB control program. "We were going to start trials on the new preventive therapy regimen [of rifampin and pyrazinamide]. Instead, we're having to cut positions and cut programs."

In Texas, the mood was equally somber. "It's not a great story to tell," says **Charles Wallace**, state TB controller. "The biggest impact from the cuts is that we'll have to scrap our whole community-based infrastructure; the whole thing is about to be erased." Wallace is referring to a painstakingly-assembled network of partnerships with community-based organizations that serve minorities and ethnic groups at high risk for TB. Those groups comprise people of color; ethnic minorities including Bosnians, Russians, and Ethiopians; and a large Mexican community.

"These are people who often don't speak the language yet and who need help linking up with a health department," he says. "A few weeks ago, we had to sit down with all these organizations and tell them that the funding is no longer there."

Officials at the National Tuberculosis Controllers' Association (NTCA) say they are trying to limit the depth of funding cuts. "We've tried to get across the concept of a floor, and the idea that there's a certain amount of funding you need to have to do surveillance and response even though the number of cases may be very small," says **Bruce Davidson**, MD, head of the NTCA. "Likewise, there need to be ceilings so that even if programs are very capable, there will be still be enough funding for other programs to carry out their high-priority activities."

Davidson also voices two other concerns. First, he says, programs that have done a good job reducing their caseloads shouldn't be punished by having money withdrawn. Second, programs that have been active in all categories, including case and contact work as well as preventive programs, shouldn't be penalized for their extra efforts.

"There's always been a floor," replies **Patty Simone**, MD, chief of the field services branch for the division of TB elimination at the Centers for Disease Control and Prevention. As for a ceiling, "We're certainly not going to give all the money to just one or two programs," she says. "We're trying to be fair, to base our decisions on need and not to penalize programs that have done a good job."

Several factors make the CDC's job tough, she adds. Even though TB controllers have asked for a simple formula — so many dollars per active case, for example — to ensure a fair distribution when funds are recompeted in fiscal year 2000, reality doesn't lend itself to a simple formula, Simone says.

Some states, for example, get additional support from city, county, or state governments. What's worse? she asks: penalizing programs that have worked hard to secure additional sources of local funding or penalizing those that haven't?

## *Congress may enact cutbacks*

The carryover problem, too, dates back to which programs asked for and received the biggest increases when caseloads first began to increase. Nearly half of all TB control programs have had some leftover funds every year since 1993, Simone says. The carryover has had the effect of benefiting practically all programs, but in the end, it may prove a Faustian bargain that provokes Congress to enact big cutbacks.

"I don't know what the other programs were doing, but we were certainly spending all our funds," says Ashkin. "You'd think right now, as cases are going down, we'd be shifting gears toward prevention. But now that disease is going down, the money is going down, too. We're close to many advances — new diagnostics, a new vaccine, now this new preventive therapy — and instead, we're on that slippery slope of the U-shaped curve of concern."

When it comes time to recompete the awards for fiscal year 2000, Simone says she's hoping to make a point with Congress by representing the funding needs according to a new scheme.

"Instead of asking for the moon, or asking simply for level funding, we need to explain [that] there always needs to be these two pots of money," she says. "The first is a stable amount that we'll always need for case activities. The second is for elimination, and [it] will need to be expanded as we move toward that goal."

Maybe Congress will understand. If so, it may be possible, program advocates hope, to avoid repeating history. ■

In an attempt to minimize the pain, the division of tuberculosis elimination has devised a formula of graduated cuts, Simone explains. Accordingly, programs that receive $500,000 or less in cooperative agreement funds will be "held harmless" and lose nothing. States in the next tier up will sustain cuts of 3% to 4%, while states in the tier above that have sustained cuts of 7% to 8%. New York City, "in a class of its own," will take an even larger cut.

### *A new formula to award funds*

On the plus side, financial awards will be recompeted two years ahead of time, by fiscal year 2000, and according to a new formula, Simone says. The new plan calls for dividing funds into two pots: one for top-priority activities, including case control and contact investigation, and the other for preventive therapy programs. Programs that have done a good job in reducing case totals and conducting contact investigations stand to receive less money from the first pot but more from the second, she says.

But even the new two-pot division can't guarantee a happy ending for everyone, Simone concedes. "There seem to be a lot of programs spending money on screening activities when they haven't done all they should have been doing on first-priority activities such as contact investigation. Often, there's a lot of political pressure on programs to do things like that. Until now, we've never held them accountable."

### *Success may lead to big cuts*

In addition, programs that used to have high caseloads but have experienced dramatic drops may have to take comparatively big hits when funds are recompeted, Simone says. One reason is that some of the big programs asked for — and received — big increases in 1993. Programs that underestimated their needs and asked for less simply didn't get as much because the CDC isn't allowed to award more than programs request.

When the awards are recompeted, programs that have been getting "more than their fair share" may find their funding trimmed substantially, Simone adds.

"But they've had the benefit of higher funding compared to some of the other programs. Now it's time for some of those other programs to get their fair share." ■

**ICAAC Highlights**

# Budget travelers at risk, Canadian study hints

*[Editor's note: The 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held Sept. 24-27 in San Diego, included several sessions related to tuberculosis. Here are some of the highlights.]*

In a study of tuberculosis skin-test conversions among travelers, Canadian researchers who've so far studied about 100 travelers have found a surprisingly high TB skin-test conversion rate: about 5%.

"Ten percent of Canadians leave and go overseas every year," says **Kevin Kain**, MD, FRCPC, director of the tropical disease unit at the University of Toronto. "Many of them are young, ranging from 18 to 25 years old, and they're taking off on low-budget tours. They hang out for three or four months, and then they come back. There are tons of opportunities in budget travel for these young people to get exposed to TB."

So far, Kain, (along with his colleague Doug MacPherson of McMaster University in Hamilton, Ontario) have administered two-step TB skin tests to about 100 clients who attend a "travel clinic" before embarking on a vacation. Those who return with skin-test conversions are offered isoniazid prophylaxis. "In that situation, it's a definite no-brainer," he adds.

Low-budget travel in particular may prove to be a risky proposition, Kain proposes. Certainly, prolonged jaunts to exotic ports of call offer more chances for exposure to TB than an encounter on an airline flight or other such instances of so-called "conveyance TB," he adds. "People get all excited about the dangers of contracting TB on an airplane flight, but the truth is that you go through a lot of grief for incremental improvements in peoples' health in such situations.

"In budget travel, though, there may actually be high-risk groups that could be identified. It might be possible to do a risk-benefit analysis: Are there certain destinations, a certain budget, a certain duration that makes including a Mantoux skin test worthwhile?" he asks. Most likely, the risks, if present, will prove to include a combination of such factors, he says.

For the record, Americans are not as prone as their neighbors to the North to strike out for the open road. In the United States, only 2% of the population travels abroad every year, Kain says. But even if only a small percentage of those travelers return with positive skin tests, it could mean a Mantoux test ranks at least on a par with a trusty guidebook and a sturdy pair of jeans. ▼

## Mice under stress reactivate with TB

An animal model showing how stress can reactivate latent tuberculosis in mice may help explain the shift from latency to reactivation in humans, says the scientist who developed it.

When mice with a steady-state TB infection were stressed by being placed in uncomfortably close quarters, the animals' bacterial counts rose markedly, says **Bruce Zwilling**, PhD, professor of microbiology at Ohio State University in Columbus. Next, after the mice were removed from the stressful environment, they were able to re-exert immunologic control over their disease, he adds.

**ICAAC Highlights**

In addition, Zwilling identified a shift in the kind of cytokines the mice were producing, from TH1 to TH2, which corresponded to the rise and fall in stress, as well as the rise and fall of bacterial loads. The two findings offer a clear analogy for what goes on in humans latently infected with TB who experience stress, he concludes.

"Conventional wisdom has always included the notion that stress is one risk factor for reactivation of TB, but it's been difficult to study that perception," he explains. "For one thing, there are too many confounding factors in peoples' lifestyles [to be able pinpoint a particular stress]."

For another, it's not possible for a study to isolate a period in humans where they are shifting from latency to reactivation because "people either have latent disease, or they have active disease," he says. "And they don't go to the doctor unless they have active disease."

In his study, Zwilling put mice into a "restraint model" (consisting of a 50 mm centrifuge tube) every night for two five-night sessions. Inside the tube, the mice could not turn around or back up. The animals were released from the tube during the daytime and weekends. During the restraint sessions, the animals' glucocorticoid levels rose and stayed elevated, returning to normal levels after the stress periods had ended.

Before the restraint sessions were initiated, Zwilling already had induced a steady-state TB infection in the animals. Colony counts in the animals showed that after four weeks of stress, the number of microorganisms began to rise. Eventually, the mice re-exerted immunologic control, and their colony counts began to subside until a steady-state infection was re-achieved.

To Zwilling, latently infected human beings placed under stress may react the same. "If you look at the literature from the pre-antibiotic era, people would get sick and then they'd get well again," says Zwilling. "They'd take 'rest cures.' Immunocompromise occurs during the stressful periods."

The link between stress and the immune system has been implicated in other illnesses as well. People with a common cold virus, or those who undergo a reactivation of a herpes virus, likewise self-report having been under high levels of stress.

Zwilling also documented shifts in the stressed animals' lymphocyte populations, which changed from TH1, which helps control TB, to TH2, which "permits" TB. The shift from "controlling" to "permissive" cytokines took place in both CD4 and CD8 cells, he notes. ▼

## Nebulizer implicated in day care outbreak

A nebulizer apparently served as a potent agent for transmitting tuberculosis in a day care facility, says **Sarmistha B. Hauger**, MD, director of pediatric infectious diseases at the Children's Hospital of Boston.

The nebulizer had been placed over the face of an infant who later was found to have endobronchial TB, Hauger says. The infant had been misdiagnosed with bronchospasm and was being treated with medication delivered through the nebulizer. "The baby had been coughing even without the treatment; but in general, children [with TB] are less infectious than adults since they don't have an especially forceful cough, and they tend not to harbor a lot of bacteria," says Hauger.

**ICAAC Highlights**

The nebulizer had the effect of provoking a more robust cough. Just as significant, perhaps, it generated an aerosol of droplets "in just the right

width particle to carry the bacteria," she says.

The infant was sick for four to five months before finally being diagnosed with TB. By that time, "he had both TB and pneumonia in his lungs, positive acid-fast bacilli stains, moderate to high amounts of bacteria in his tracheal aspirates, and also meningitis," she says. "This was a very severe case." The day care facility was a relatively confined space, and the infant had not been isolated from the other children.

As a result of the exposure, a cluster of children and adults was infected, and some developed active disease. Hauger was able to obtain an isolate from one of the children who developed disease; RFLP testing showed a match between that child and the index case.

In this instance, no one suspected TB because no risk factors were apparent. The facility served working- and middle-class families. The parents of the index case were middle class people who exhibited none of the stereotypical risk factors for TB. Eventually, she discovered that the infant probably was exposed during a brief encounter with an elderly friend of his grandparent, whose house the infant was visiting.

The take-home message is this: "For anyone with a prolonged respiratory illness, think TB," Hauger says. ■

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# Small budget, big output mark trial consortium

*Investigators want to tackle preventive therapies*

The Tuberculosis Trials Consortium (TBTC) certainly isn't short on ideas, enthusiasm, or projects. Compared with more lavishly funded consortia (the Clinical Program for Community Research in AIDS comes to mind), the TBTC could use more money; but even on a $4 million-a-year shoestring budget, it's a powerhouse, its proponents say.

"The level of enthusiasm is incredibly high," says **Rick O'Brien**, MD, chief of scientific activities at the division of tuberculosis elimination at the Centers for Disease Control and Prevention. "I've had people who've worked with similar operations tell me that this one [is] a real pleasure to work with."

"I think you could accurately say that we're suffering from growing pains," says **William J. Burman**, MD, infectious disease specialist at Denver Medical Health Center and an investigator for one of the division's 26 sites. "We've got interesting investigators, great topics, and interesting ideas for studies, but given the current budget, we have to make some tough choices."

Preventive therapy is one subject Burman and his colleagues especially would like to tackle. "There's some really exciting stuff out there," he says. "In animal models, rifapentine once weekly was highly effective as preventive therapy, even more effective than daily isoniazid for six to 12 months." That raises the tantalizing prospect of a preventive regimen that could be given just once a week for only three months for a total of only 12 doses, he adds.

Also on Burman's wish list is an anti-TB candidate now in Phase II studies at PathoGenesis Corp. in Seattle **(see article, p. 141)**. That drug, rifalazil, which has an extremely long half-life, produces exceptionally high concentrations in macrophages, studies have shown. Together, the two traits of therapy hold the promise of a much shorter course of therapy.

A third drug has proven to be useful against standard bacterial infections in Phase III trials and is showing substantial activity against TB, says Burman; the list goes on.

### *Where the patients are*

The trial network was established in 1993 for the specific purpose of testing a once-weekly regimen of rifapentine and isoniazid in the continuation phase of therapy for TB, formally designated U.S. Public Health Service (PHS) Study 22. Once the network was up and running, the decision was made to go ahead and formalize it, O'Brien adds.

As a CDC-funded entity, the TBTC holds a unique position in several ways. "It's the largest and perhaps the only consortium for which the CDC provides direct support for clinical trials," says O'Brien. One reason for that is historical: In 1960, the PHS tuberculosis division, with its long and distinguished history of conducting trials for TB drugs, was transferred to the CDC, he says.

The consortium is purely practical because the CDC has links with public health departments, "and that's where the patients are," says Burman. Consortia that lack that critical advantage sometimes have had to fold trials for lack of available subjects, O'Brien adds.

The division of tuberculosis elimination also has strong ties to the U.S. Veterans Administration, which maintains more than a dozen of the 26 sites and enrolls about a third of all trial subjects, he says. Plans call for expanding links to the National Institutes of Health and its tuberculosis research unit, a contract currently held by **Gerald Ellner**, MD, vice chair of the division of infectious diseases in the department of medicine and director of the TB research unit at Case Western Reserve University in Cleveland.

In the field of TB research, entities such as the tuberculosis research unit and the TBTC serve a critical need, Burman and O'Brien note. Whereas with other diseases, the pharmaceutical industry often is strongly motivated to conduct trials, that's not always the case with TB. "There's less financial incentive for large pharmaceutical firms to undertake drug development [for TB]," says Burman.

"There's a relative lack of profitability in drugs whose potential purchasers have little income. And when a drug acquires a TB indication, public health has been conditioned to ask whether we should restrict access to the drug in order to limit the development of resistance."

The TBTC may well have played a critical role in the recent decision by the Food and Drug Administration to grant approval to rifapentine, Burman says. With the exception of Study 22, only two other studies of the drug have been conducted. The first was a Chinese trial that used a form of the drug suspected of having low bioavailability. The drug's manufacturers conducted a second trial; but that study turned up an increased rate of relapse in the rifapentine arm. "So it's a fair question why the FDA approved the drug," he says.

He suggests two reasons. For one thing, a subsequent analysis of the manufacturer's trial found the rate of relapse was acceptable among subjects who'd shown a high rate of compliance. What helped tip the weight of evidence, he says, probably were data from the TBTC study. "I suspect it had an effect on the decision to license the drug."

Modeled after the structure of the highly regarded Clinical Program for Community Research in AIDS (even to the point of adopting its trial nomenclature), the TBTC now has formally adopted by-laws, a steering committee, and a scientific study committee. The trial network includes 26 principal investigators in the United States and Canada; other staff include nurse-clinicians and outreach workers at each of the 26 sites.

The consortium recently completed enrollment for Study 22, including two substudies, one of which aims to look at the pharmacokinetics of rifapentine. Plans also are under way to start more new studies in the next 12 months, O'Brien says.

Study 23 will evaluate the safety and efficacy of rifabutin short-course therapy for HIV-positive TB patients receiving HIV protease inhibitors. Study 24 will look at the efficacy of largely intermittent, short-course therapy for patients with isoniazid-resistant TB.

Study 25 will consist of a dose-escalation trial of rifapentine, with patients randomized to 600, 900, and 1,200 mg of once-weekly rifapentine plus isoniazid. The expectation is that the new drug will show good results in higher does by preventing the emergence of rifamycin resistance among HIV-positive patients. ■

# Newcomer drug company takes aim against TB

*Three promising new drugs in development*

PathoGenesis Corp., a pharmaceutical newcomer based in Seattle, has set its sites on a big target: respiratory illnesses, including tuberculosis, where a critical need exists for new and better drugs. So far, the company boasts an impressive track record with two promising TB candidate drugs in Phase II trials and a third candidate in development.

There's rifalazil, with a half-life of 48 hours, longer than that of any other rifamycin, and a strikingly high intracellular concentration. Such traits suggest that anti-TB regimens incorporating the drug might lend themselves to fewer doses, abbreviated treatment time, or both, TB experts say.

With rifalazil's long half-life, "It might be given once a week or even once every two weeks," says **Rick O'Brien**, MD, chief of the research and evaluation branch at the division of tuberculosis elimination at the Centers for Disease Control and Prevention. There is a potential problem, O'Brien adds: In Phase I trials, patients didn't tolerate dose equivalents extrapolated from animal studies as well as had been hoped, so doses have been scaled back for Phase II trials.

Enrollment was completed in July for those trials, which are being conducted in Brazil in

collaboration with the tuberculosis research unit of the National Institute of Allergy and Infectious Diseases. The contractor is Gerald Ellner of Case Western Reserve University in Cleveland, says **Maryellen Thielen**, a spokeswoman for PathoGenesis.

Also in Phase II trials is a second anti-TB drug candidate, tobramycin. Given in aerosolized form using a nebulizer, tobramycin offers the advantage of being delivered directly to the lungs instead of systemically, says Thielen. If the drug works as hoped — by quickly reducing bacterial loads in patients' sputum — it could prove useful as an adjunct to conventional therapy by reducing the time patients are infectious, she says.

Tobramycin already has been approved for the treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis patients, and it is being evaluated in Phase II trials for use against bronchiectasis, a severe form of chronic bronchitis. As an anti-TB agent, the drug has shown efficacy in all strains of TB against which it's been tested, including multidrug-resistant strains, says Thielen. It works as a ribosomal subunit inhibitor.

That leaves a third anti-TB drug, PA824, now in preclinical development. In test tube and animal studies, this third agent, a nitroimidazopyran compound, has proven as effective as

**PA824 has shown efficacy against nonreplicating organisms, suggesting it may be useful in treating latent TB as well as active disease.**

isoniazid against both drug-sensitive and multidrug-resistant strains of TB, she says.

Even better, PA824 has shown efficacy against nonreplicating latent organisms, suggesting it may prove useful in treating latent TB as well as active disease. PA824 appears to work by a novel mode of action, by inhibiting protein synthesis and the formation of cell wall ketomycolic acid, Thielen says.

PathoGenesis was founded in 1991 by Wilbur Gantz, former president of the pharmaceutical firm Baxter International, and it began research and development in 1993, she notes.

Remarkably, PathoGenesis moved its first drug, tobramycin, from research and development to market in just five years, she says. "For a small company like this one, it's essential to bring drugs to the market as quickly as possible. TB research takes longer than usual in part because the organism is especially slow-growing, but we've developed some assays to help us work more quickly."

The need for more anti-TB drugs makes research in this arena an attractive niche, she says, but it also raises the stakes.

"That there is a relative lack of competition makes it a nice place to be, but if we can't provide a significant benefit with a new therapy, there is no point to our work," Thielen explains. "As you know, current TB drugs are generic and low-cost, so that the cost to the system lies in hospitalization, directly observed therapy, and the like. If we can find a way to trim those costs, we can support the development of new drugs." ■

# Good prenatal package includes HIV, TB testing

*In Florida, practice leads to completed prophylaxis*

In Dade County, FL, women are offered both HIV and TB tests as routine parts of prenatal care, says **Joan Otten**, RN, director of the office of TB control at Jackson Memorial Hospital in Miami. "We probably test the majority of prenatal women for PPD, because it obviously has such an influence on the child," Otten says. "We've been offering HIV testing for at least two years, and PPD skin-testing much longer, probably as far back as four or five years."

The reason is found in Dade County's demographics, she adds. There, about half of the population is Hispanic or otherwise foreign-born with a substantial percentage arriving TB-infected, she says.

If a woman has a positive reaction to her skin test, and if active disease is ruled out, then preventive therapy is generally delayed until after the end of the first trimester "just to be safe," Otten says. If disease is present, treatment begins right away. In most cases, TB prophylaxis and treatment care are coordinated with prenatal care so women don't have to go to more than one place to get the care they need, she says.

A retrospective study of women offered HIV testing and TB skin testing at Jackson Memorial found that more than half of patients who were infected latently with TB completed preventive therapy.

In the study, researchers at the Miami School of Medicine and the Centers for Disease Control and Prevention looked at 218 women in prenatal care that had tested positive for HIV. Of the 208, 59 (28%) had a prior AIDS-defining condition; HIV status was unknown at the time of the first prenatal visit in 112 (54%) of the women.

A TB skin test was performed on 180 (87%) of the women. Of the 208, 135 (65%) had anergy testing performed as well. Of the 208, 81 women either tested positive to the TB skin test or were anergic. Of those 81, 48 (56%) started isoniazid prophylaxis. One patient developed hepatitis and stopped treatment; two others were found to have active disease, and they were treated accordingly.

By the time of delivery, "the majority of our OB patients have on record both an HIV and a PPD test," says Otten. "It just makes sense for us. It's such a convenient point of care." ■

# New TB guidelines dance the two-step

*Some physicians may balk at donning respirators*

Health care facilities are being urged to perform a risk analysis and to formulate a written TB infection control program based on those findings in newly published guidelines from The American College of Occupational and Environmental Medicine (ACOEM). **(For ordering information, see note at end of story.)**

Such a program might include any or all of the following action steps:

❑ two-step skin-testing of new hires;

❑ skin-testing every three to 12 months for employees who come into contact with TB patients;

❑ periodic training of health care workers to enhance awareness of TB risks;

❑ appropriate management of patients likely to have undiagnosed TB (emergency room patients, for example);

❑ implementation of engineering controls;

❑ respiratory protection, accompanied by respirator fit-testing and by training in the proper care and use of respirators.

Consensus about some of the guidelines followed only after considerable debate, explains **Lawrence W. Raymond**, MD, ScM, chief author of the guidelines and a member of ACOEM's lung disorders committee. Raymond also is director of the department of occupational and environmental medicine at the Carolinas Medical Center in Charlotte, NC.

One example was the recommendation for two-step testing. The lung disorders committee decided in its favor because of convincing evidence, Raymond says: "We found that many larger institutions in the state cut their so-called workplace conversion rate by a factor of 10 or more simply by going to the two-step. It's an example of one way institutions can save themselves a lot of anxiety, not to mention sparing employees from having to undergo an unnecessary course of prophylaxis."

In addition, Raymond anticipates that some physicians will bridle at the exhortation to don respirators and to be fit-tested for them. "But having seen my share of physicians and other health care workers suffering from TB, I think it's a good idea

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to play by the rules," he says. As for the recommendation to skin-test employees every three to 12 months, "every 12 months is probably going to be reasonable in most institutions caring for TB patients," he says.

The ACOEM guidelines are based on those promulgated by the Centers for Disease Control and Prevention and the National Institute of Occupational Safety and Health and on regulations proposed by the federal Occupational Safety and Health Administration. That's not to say they're redundant, Raymond says, since ACOEM is an international organization whose members may not have access to American guidelines and regulations. "We're a convenient funnel, as it were, for all sorts of job-related information," he says. Publishing the guidelines "is a good way to communicate awareness of TB in the workplace."

### *The premise that work affects health*

A society of 7,000 occupational and environmental physicians, ACOEM focuses on work-related health issues "ranging from something as simple as workplace falls to subjects as technically complex as dimethyl mercury poisoning to everything in between," Raymond says.

Environmental physicians are employed variously by multispecialty clinics, hospitals, industrial companies, and, in some instances, the government. The organization's founding father was Bernardino Ramazzini, a 17th century physician who believed that knowing what kind of work his patients performed was critical to understanding their illnesses.

When counseling health care workers with positive Mantoux skin tests who resist the offer of isoniazid prophylaxis, Raymond is reminded of a comment he once heard from TB expert John Sbarbaro. "In general, we say that if I convert my skin test today, the chances for reactivation over a lifetime are somewhere around 10%," he recalls Sbarbaro saying. But for health care workers, Raymond says, Sbarbaro pegs the odds much higher — at 30%.

"I always use that figure when I'm talking with someone who's [over age 35] and doesn't want to take the INH," Raymond says. "I ask them, 'Do you really want to take this chance of 30% that you'll reactivate?'"

*Guidelines are available from ACOEM, 55 W. Seegars Road, Arlington Heights, IL 60005. Web: http://www.acoem.org. Fax-on-demand: (800) 226-3626.* ■



## CE objectives

After reading this issue of *TB Monitor,* readers taking part in the continuing education program should be able to:

- List two points the new CDC guidelines make about preventive therapy for patients co-infected with TB and HIV.
- Explain what an animal model may show about the correlation between reactivation of TB and stress.
- Cite what percentage of Canadian travelers has converted their Mantoux skin test in a study.
- Explain what CDC TB experts fear might happen to funding from Congress if carryover is not reduced. ■