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New ATS/CDC guidelines will insist on nine months of preventive therapy

Controllers ask that six-month regimen remain an acceptable option

By next fall, new recommendations for preventive therapy — make that "treatment of latent TB infection" as the preferred phrasing now goes — are expected to state firmly that nine months of isoniazid prophylaxis are preferable to six. What's not yet certain is whether the six-month regimen will be relegated to a humble footnote or manage to hang on to some of its former status by making the list of acceptable options.

The new recommendations are the product of joint deliberations between the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC).

At a meeting in Atlanta last month of the Advisory Council for Elimination of Tuberculosis (ACET), the reaction to the news — first announced at the ATS conference in Chicago in February — consisted mostly of grumbling and dismay.

'Six months is already a hard sell for someone who isn't feeling sick.'

Are the new recommendations a ploy to force programs to swallow the new two-month, short-course regimen of rifampin and pyrazinamide, side effects and all? How are programs already having a tough time getting six months of isoniazid into their patients supposed to convince them to take nine? In a year of level funding, where will the extra money come from?

Nancy Dunlap, MD, PhD, medical director of Alabama's TB control program, drew appreciative laughter from the ACET audience when she proposed innocently: "Why don't we just make nine months the footnote, and put six months back into the table?"

ATS and CDC point men for the new guidelines argue that what looks like a new and harder line is really just a reality check; plus, they say, one way or another, six months will still be available as an option.

"This statement really makes it clearer where the bar has been all along," says **Larry Geiter**, PhD, MPH, a consultant for Sequela Research Foundation in Rockville, MD, and the researcher who had been given the job of corralling existing evidence on preventive therapy for HIV-positive patients. "This will also give people the chance to go back to

their legislators and cite this statement as a clear, unambiguous point for advocacy."

As for the two-month course of preventive therapy, Geiter says he and the other guideline authors, far from wanting to push RIF/PZA onto programs, share their peers' reservations about the new regimen. "We have concerns about toxicity, and we honestly don't know what will happen when we give this to thousands of people," Geiter says.

Nine months for all, for clarity's sake

The decision to settle on nine months as an optimum duration of prophylaxis for both HIV-negative and -positive patients was intended partly to dispel potential confusion, adds **David Cohn**, MD, associate director of Denver Public Health, and the person given the job of reviewing data for HIV-positive patients.

The data clearly argue that nine months is better than six among HIV-negative patients, Cohn explains. Among the immune-compromised, however, no study has ever directly compared the efficacy of 12 months to that of six; hence the decision was made to split the difference for the sake of clarity.

But from a programmatic point of view, the troubles with urging nine months onto programs are manifold, says **Eric Brenner**, MD, medical epidemiologist at the state of South Carolina's Department of Public Health. "Six months is already a hard sell for someone who isn't feeling sick," says Brenner (who took the floor at the ATS conference in Chicago to make his points). "The longer you tell someone they have to take pills, the harder the sell." Drop-off rates, already a problem at six months, can be expected to increase with nine, he adds. So may toxicity, at least to some small extent.

Finally, it stands to reason that a regimen that's 50% longer will demand half again as much in the way of resources, whether that amounts to clinic visits, telephone calls, or direct observation of therapy.

The guidelines will run simultaneously in the CDC's *Morbidity and Mortality Weekly Report* as well as the ATS's *Journal of Respiratory and Critical Care Medicine*.

The recommendations also will take a new look at targeted screening for latent TB infection, says Cohn. They will urge programs to screen only high-risk populations, and not to screen frivolously, but rather to test only with the intention to treat.

Along with nine months of INH, the table of acceptable options for preventive therapy also was expected to include nine months of treatment on a twice-weekly basis (with directly observed preventive therapy); the new two-month, short-course regimen of rifampin/pyrazinamide; and rifampin daily for four months. ■

Ouch! Feds take knife to cooperative programs

Smaller pots, competition influence decisions

Even before federal dollars are re-awarded to TB control programs in mid-November for fiscal year 2000, one thing is clear: Some programs are going to be hurt.

"We don't like this either," says **Patricia Simone**, MD, chief of the Field Services Branch of the Division of Tuberculosis Elimination at the Centers for Disease Control and Prevention (CDC). "It's no fun to have level funding."

The combination of fewer federal dollars overall, coupled with heavy competition for a relatively small amount of money set aside for targeted screening, has anxiety levels simmering in many TB control programs.

"I guess what scares us a little bit is that the money people get will depend to some extent on the number of cases programs have counted in the last year," says **Carol Pozsik**, RN, MPH,

COMING IN FUTURE MONTHS

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- Two new CDC studies on contact investigations
- Combination drugs: Wallflowers at the dance
- Public relations tackles TB
- DOT takes knocks in South Africa

director of South Carolina's Division of TB Control, and the president of the National Tuberculosis Controllers Association (NTCA). "In my heart, I know that those of us who've done a good job bringing our numbers down won't be penalized for it — and that's what they tell us. But we have to be very careful to back up how we've spent the money they've given us."

A silver lining called the IOM report?

The silver lining, if one is out there, may be found inside a contractual agreement the CDC recently signed, requesting a formal review of TB programs from the National Academy of Science's Institute of Medicine (IOM) **(see related article, p. 40**). If all goes well, observers say, the IOM review could help leverage more money for TB programs from federal and state sources.

The recently published IOM review of sexually transmitted diseases, for example, had the effect of doing just that. By riveting press and public attention, the IOM report diverted a welcome flood of dollars into STD programs across the nation.

For now, trimmed-back federal funding for TB programs has been split into two categories, or "pots," says Simone. For carrying out core activities, between $86 million and $91 million will be awarded; for activities geared toward elimination (including targeted screening programs), between $5 million and $10 million will be doled out.

Exactly how much money ultimately will wind up in each pot isn't yet set in stone, says **Paul Poppe**, associate director for management and operations for the CDC's Division of TB Elimination (DTBE).

"Fiscally, [the two activities] aren't easily divisible," he explains. "We're not sure how much states are spending on the two kinds of activities, because in practice, they're often integrated."

The DTBE estimates that about 10% of federal dollars go to targeted testing, says Simone. Though some TB controllers have groused that separating the two pots doesn't reflect real-life needs of programs, there was a reason for doing so, adds Simone: to make sure there would be enough money given out for core activities.

The nation's three TB model centers will be put on short rations along with everyone else, adds Poppe. Implicit in the DTBE's recent announcement that "between two to three awards" will be handed out to model centers means just what it seems to say, he adds: One of the three model centers may not make the cut, and as a result may be shut down.

Competition for money in the second pot will be keen, with programs ranked according to merit in three areas. "It's important that applicants do a good job of clearly diagnosing their need for TB programs," Poppe says. "They also need to do a good job of documenting their progress toward objectives."

If programs can't show progress toward meeting national goals, they at least need to demonstrate progress toward meeting their own goals, and to give some indication of when they'll be meeting national goals, he adds.

"We don't want [targeted screening] programs out there reinventing the wheel," adds Simone. "We especially want to cut back on unnecessary testing. We're telling people not to test low-risk groups; and not to test groups unless you think you can get them to complete preventive therapy."

Programs also should have an outbreak response in place, according to Poppe and Simone.

"That's especially critical in low-incidence areas," Poppe says. "People need to think about what they would do if they suddenly had a half dozen new cases reported. Could they shift some of their own resources around?"

Smaller caseloads may equal less funding

As for money in the first pot — the one designated for core activities — no one will be left out in the cold, say DTBE officials. At the same time, it's clear that some programs will emerge more equal than others; and that those that have seen big drops in caseloads may see commensurate drops in funding.

"Our intent is not to devastate one program for the sake of others," Poppe says. "On the other hand, we've made it clear there will likely be some redistribution of money."

Applications will be rated according to two processes, Poppe says. Applications for money for core activities will be graded on what amounts to a pass/fail system known as a Technical Acceptability Review, or TAR.

"I suspect everyone will pass, and everyone will get some funds, because all areas should

IOM review to eye nation's TB programs

Report could bring TB into sharper focus

The Division of Tuberculosis Elimination (DTBE) at the Centers for Disease Control and Prevention (CDC) has commissioned a report from the Institute of Medicine on TB-related issues and programs in the United States.

The Institute of Medicine, a component of the National Academy of Science, was chartered in 1970 to examine policy matters related to public health. It is expected that the report will be ready for release in about a year, and will coincide with World TB Day, March 24, 2000.

The intent behind asking the IOM to prepare a report is straightforward, says **Larry Geiter**, MPH, PhD, a consultant with Sequela Research Foundation in Rockville, MD, and the staff officer for the IOM responsible for the study. "It's a way to obtain an independent, scientific review of TB programs and policies in the U.S.," he says.

Attracting more funding

At the same time, publication of an IOM report also has been known to focus legislators' attention, and to attract more funding, he concedes. "The risk in commissioning [such a report] is that TB could be deemed not to be of much importance — though I doubt that would happen," Geiter says.

"On the other hand, it could also have the impact of mobilizing forces and focusing attention on TB," he adds.

In late 1996, the IOM released a groundbreaking report on sexually transmitted diseases. That study, *The Hidden Epidemic: Confronting Sexually Transmitted Diseases* (Thomas Eng and William Butler, eds; the Committee on Prevention and Control of Sexually Transmitted Diseases of the Institute of Medicine; 1996), called for "a bold national initiative to reduce the enormous health burden of STDs." It noted that five of 10 of the most common diseases reported to the CDC were STDs, but that "no effective national system exists to combat them, and called for increased funding from the private and public sectors."

IOM to issue recommendations

The IOM study commissioned by the DTBE is expected to review and issue recommendations on issues including regional variations in the United States concerning TB morbidity, research needs; the impact of foreign-born people on morbidity rates; multidrug-resistant TB; America's role in international TB control; and the campaign to eliminate TB in the United States.

A 14-member committee will conduct the study. Membership is designed so that the committee is divided into roughly equal parts, including those with much, some, and no expertise in TB-related issues, says Geiter.

The committee held its initial meeting March 9. It will hold a workshop, with presentation from invited speakers, in Washington, DC, June 7-8. It is also scheduled to meet in closed sessions for three days in August in Woods Hole, MS; for two days in November in Irvine, CA; and during February 2000 in Washington, DC.

The report review process will take place in February and March 2000; and the targeted release date is March 24, 2000. ■

have the ability to conduct basic core activities," Poppe says.

For the competitive part of the application, an objective review panel will assign scores and rankings based on specific criteria. Members of the panel won't necessarily be insiders familiar with TB control programs, Poppe adds, "so in theory it'll be a truly objective review."

Big cities that have separate funding will be allowed to keep their separate funding status and won't become just one more city competing for state money, notes **Walter Paige**, executive director of the NTCA. "We queried states where there was separate funding for big cities, and universally the response was that they all wanted to continue with the present arrangement," he says. ■

RIF/PZA tryouts yield mostly good reviews

To quell GI complaints, some adjust PZA

Among the small numbers who've had time to try it out, the new regimen for short-course treatment of latent TB infection — two months of rifampin / pyrazinamide (RIF / PZA) — is drawing positive reviews from physicians and patients alike, albeit with some reservations.

Across Florida, about 30 HIV-positive patients have tried the two-month regimen, says **David Ashkin**, MD, the state's TB control officer. "Over 80% have completed [the program], and with a minimal amount of toxicity," Ashkin says. "Of course we don't have enough data to say anything yet about efficacy. But to my knowledge, no one's dropped out because of side effects."

Among small samples of patients who've tried the new regimen in Massachusetts and Georgia, physicians report some side effects, which shouldn't surprise anyone, experts say. "We expect side effects will be more frequent [than with six months of isoniazid], but there are ways to deal with that," says **Rick O'Brien**, MD, chief of the Research and Evaluation Branch of the Division of Tuberculosis Elimination at the Centers for Disease Control and Prevention. "One way is to use the lower end of the recommended dose of pyrazinamide."

Adjusting the dose did the trick in Atlanta, where providers decided RIF / PZA might be one

RIF/PZA goes to jail, but not for long enough

Delays, early releases hinder completion

One thing researchers in Atlanta knew about the city's TB community was that many patients had no regular health care provider. At best, many of them resorted to the emergency room of the public hospital when they got sick.

Researchers also found that 60% of the city's TB patients had spent some time in jail. Putting two and two together, **Naomi Bock**, MD, MS, a Georgia Department of Health medical epidemiologist, concluded that jail might be a good place to find people latently infected with TB, and provide them with preventive therapy.

Bock already knew from work she'd done at the city jail that numbers wouldn't be a problem; during an average month, the jail held about 100 inmates with positive skin tests who were candidates for preventive therapy. But since inmates in that system only stay an average of 100 days, there was a problem with time.

A trial of six months of isoniazid ended on a discouraging note, when only two of 100 released inmates showed up to continue their INH — despite generous incentives including hot breakfasts and $20 payments. But once the CDC approved the new two-month short-course regimen for HIV-negative patients, Bock decided to give the new treatment a try.

"Basically, all the [eligible] inmates were very interested," says Bock. "No one refused, which surprised me." By last September, Bock had recruited 131 eligible inmates whose records promised they'd be staying put for at least 100 days. In 56 instances, the records turned out to be wrong; plus, another 24 of the 131 had a history of previous INH treatment. That left Bock with 41 eligible inmates.

The first 10 who started treatment all suffered stomachaches, Bock says, but none wanted to quit; so she adjusted their PZA dosage downward, and the stomachaches resolved. Successive pools of subjects had their PZA adjusted downward, too.

Four subjects experienced itching, leading Bock to take them off the meds. ("If they'd been my patients in the real world, I'd probably have treated them through it; but in jail, I didn't want to take any chances," she notes.)

Then, to her frustration, another 17 inmates were released ahead of schedule. Of those, Bock was gratified when two actually showed up at the county health department to get more pills. Other challenges along the way have included delays in getting test results and X-rays back. What Bock terms "friendly persistence" has gone a long way to resolving most of these snags.

So far, eight of 41 inmates who started RIF / PZA have finished; the rest are in the midst of treatment, and Bock plans to keep enrolling inmates until she's reached at least 100. "So we've lost close to a third," she adds. "But when they're there, they're happy to do it." ■

way to get preventive therapy into a group of people whose most reliable source for health care turned out to be the city jail.

Jail inmates were surprisingly enthusiastic about trying out a two-month preventive regimen, says **Naomi Bock**, MD, MS, medical epidemiologist and clinical consultant for the Georgia Department of Health; and assistant professor in the department of medicine at Emory University in Atlanta. When they came down with stomachaches, she found that adjusting the dose of PZA downward fixed the problem. Completion rates so far aren't as good as Bock had hoped, but not for reasons related to tolerability. **(See related article, p. 41.)**

Just letting patients know what they're getting into — lots of pills, and maybe an upset stomach — will probably help them stay committed to the two-month regimen, contends O'Brien.

But in Massachusetts, **Ed Nardell**, MD, chief of pulmonary medicine at Cambridge Hospital and TB control officer for the Massachusetts Public Health Department, says patient education may be more complicated than such advice suggests.

A handful of patients in Massachusetts who tried short-course preventive therapy completed at rates that weren't quite as good as rates for a bigger group, which chose six months of INH, says Nardell. (Of 15 Massachusetts patients who tried RIF/PZA, eight finished, and seven quit, for a completion rate of 53%; among the INH group, of 52 patients, 30 finished, and 22 didn't, for a completion rate of 57%.)

The Massachusetts patients were all HIV-negative, as far as anyone knows, which invites comparison to the study of RIF/PZA by the CDC, which found that HIV-negative patients do not appear to tolerate the new regimen as well as their HIV-positive counterparts.

Perhaps HIV-positive patients are generally a more motivated bunch, Nardell surmises. "When you offer [regular HIV-negative patients] the choice, even though you warn them about possible side effects, what they really hear is the part about 'two months,'" he says. That may explain why at the first sign of discomfort, this group seems quick to fall by the wayside. (A patient survey suggested as much, with dropouts reporting only minor complaints.)

Still, Nardell plans to continue to keep offering his patients the choice. "It's nice to be able to forget about age 35 – because of course you only have to worry about that with isoniazid," he says. "That opens lots of doors." ■

Big cities credit drops to HIV drugs, DOT

Centers with lots of foreign-born to plateau?

Across the nation, many big cities saw their TB caseloads continue to fall last year. Some cities with larger proportions of cases among the foreign-born saw less impressive declines than their counterparts with more cases of the "homegrown" variety, an informal survey of big cities conducted by *TB Monitor* found.

New York City saw its cases fall by about 10% last year, says **Paula Fujiwara**, MD, the city's TB controller. Better treatment for HIV-infected patients has diminished the number of TB cases among the co-infected, she adds. "But the percentage of cases among the foreign-born is higher than ever, with not as much TB related to HIV. The face of TB is changing."

In Los Angeles, the drop was a more modest 3.6% — from 1,347 in 1997 to 1,299 in 1998. Though blessed with relatively small numbers of patients co-infected with HIV and TB, the city has a big pool of foreign-born residents latently infected with TB, thousands of whom receive preventive therapy at community-based organizations.

"We pay 10 places to screen foreign-born, and boy, can they yield the numbers," says **Gayle Gutierrez**, RN, MPH, lead nurse manager for the city's TB and HIV programs. "We find that even people who are scared of the health department will still go to their culturally sensitive neighborhood clinics — and that's been great."

In San Francisco, cases were down 14.5%. "That's the biggest drop we've ever recorded," says **Masai Kawamura**, MD, who heads the city's TB control division. "But I think we've probably hit rock bottom, and will plateau after this." Like its bigger neighbor to the south, San Francisco has many foreign-born residents, Kawamura adds. "Unless we build a high wall around the city, don't let any planes fly in, and put every foreign-born person with a positive skin test on isoniazid — well, I predict we'll continue to have TB in San Francisco," she says. "We could come down some more — but it'll take resources."

Houston likewise saw a drop, from 623 cases in 1997 to 462 cases in 1998, says **Kathy Penrose**, RN, MPH, program services coordinator for TB control. "We always thought we'd get this drop," says

Penrose. "We just didn't think we'd get it all at once." A variety of factors helped bring it about, Penrose adds, including having 89% of all patients on directly observed therapy (DOT); starting initial contact investigations promptly within three to seven days; and the fact that TB controllers have finally completed a massive project that delivered 1,000 doses a week of preventive therapy to Houston's tuberculin-reactive school children.

Big gains for Chicago

In Chicago, TB controller **William Paul**, MD, also cited a broad mix of reasons to account for his city's impressive drop in cases — from 599 in 1997 to 470 in 1998. "We don't have a dramatic story to tell like New York City, with massive infusions of funds overnight," says Paul. Instead, it's been a long, steady haul for the Windy City, starting in 1993, when Chicago instituted DOT as the standard of care in its public health clinics.

The year afterward, Cook County Hospital also implemented DOT. Paul also credits a county program that provides special services to homeless TB patients. By providing temporary housing during treatment, the program result has helped boost completion rates among the city's homeless to 95%, he adds.

A drop in TB among patients co-infected with HIV also has helped, Paul says. Cooperation and training sessions with HIV / AIDS programs have meant lots of little changes that have a big impact — for example, the city's public health clinic staff are now capable of doing HIV testing themselves, so TB patients don't get sent somewhere else for HIV testing.

Other cities reporting drops in last year's TB caseloads include Atlanta, Miami, Detroit, and Baltimore. ■

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Editor: **Alice Alexander**, (404) 371-8067
Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@medec.com).
Managing Editor: **Coles McKagen**, (404) 262-5420, (coles.mckagen@medec.com).
Production Editor: **Terri McIntosh**.

Editorial Questions
For questions or comments, call **Alice Alexander** at (404) 371-8067.

Smear-negative study questions assumptions

May account for big chunk of transmission

In a recent study of case clusters in San Francisco, at least 17% of smear-negative TB patients were shown to be infectious, despite the widespread assumption that such patients are much less infectious (or not infectious at all) compared to their smear-positive counterparts, says **Marcel Behr**, MD, assistant professor in the divisions of infectious diseases and microbiology at McGill University Health Sciences Center in Montreal.

Because Behr was purposefully conservative in how he categorized and made use of available data, it's possible that as many as a third of the smear-negative patients were infectious, he adds.

"This simply means you shouldn't use a [negative] smear as a brain-dead tool," Behr adds. "It's a century-old test that can detect 10,000 bacteria; and we have a disease that can be caused by 10 bacteria. So it would be very naive to think this should be the sole test used as a screen for infectivity."

When Behr compared RFLP (restriction fragment length polymorphism) results with smear cultures to analyze 71 case clusters in San Francisco, he found 15 of the clusters consisted entirely of smear-negative patients. Of course, he adds, it's not inconceivable that a smear-positive patient started the chain of infection and

then disappeared; but it's not likely that such an event took place 15 out of 71 times.

Preliminary results from a study of contact investigations at the CDC appear to bolster Behr's conclusions.

"A significant proportion" of both household contacts and non-household contacts appears to have been infected by smear-negative cases, says **Mary Reichler**, MD, medical epidemiologist in the Division of Tuberculosis Elimination at the CDC.

Some take-home messages

Practically speaking, Behr says, his study suggests health care providers should exercise caution — not always allowing smear-negative patients to roam the halls of the hospital at will, for example, or watching to make sure patients with three negative smears are responding promptly to whatever their provider is using to treat them.

"A second issue is whether you can use a smear as a guide for when someone can start going out in public," Behr adds. That question was not something the study attempted to address, he adds.

Traditionally, assumptions about the infectiousness of smear-negative patients have been shaped by conventional epidemiology, says Behr — a fact that explains some of the fallacies that trouble the issue.

"In the past, the way to assess how infectious people were was to look at their contacts," Behr explains. "We'd compare the tuberculin skin testing reactivity rates of the contacts of smear-positive people, smear-negative people, and what we called a 'control' group," he says. But there were several difficulties inherent in this approach, he adds.

For one thing, contacts' reactivity isn't always a reliable gauge of an index case's infectiousness, Behr says. That's because a person's contacts tend to mirror the person himself, he explains: "We hang around with people who are like us."

Second, reactivity in a contact doesn't tell anything about prior reactor status, and there often is no record of previous tuberculin skin testing status for comparison.

What's more, the farther the contact investigation extends, the more reactors the investigator may find. Yet the wider the net is cast, the less likely there is a connection between index case and contact. (One-third of the time, in fact, there is no epidemiological connection, merely coincidence, Behr found.)

The upshot isn't to say that show-leather epidemiology is wrong, adds Behr; "but it does have limits. What it told us was that smear-negatives weren't too worrisome, and that led us to stop looking. But if you don't look, you don't find. It becomes a self-fulfilling prophecy." ■