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FDA mulls Quantiferon petition for licensure

Phase 3 trial data to play big role

The makers of Quantiferon-TB were scheduled to ask the U.S. Food and Drug Administration (FDA) for a license to market their new diagnostic test for latent TB in this country on Oct. 12.

The FDA was expected to base much of its answer to that request on data scheduled for publication in the Oct. 10 issue of the *Journal of the American Medical Association* (*JAMA*). The *JAMA* article was to have laid out the findings from a Phase 3 trial of Quantiferon in the United States in which Quantiferon was compared with the tuberculin skin test (TST).

Cellestis Ltd., the Australian firm that makes Quantiferon, has asked the FDA to approve the product for exactly the same indications as the TST, says **Jim Rothel**, PhD, chief scientific officer for Cellestis.

The new test offers substantial logistical advantages over the TST, because it consists of only one step, not two, and because results are far less subject to subjective interpretation, says Rothel. Quantiferon uses an enzyme immunoassay to measure the amount of gamma-interferon, a cytokine produced by individuals whose immune systems have been primed to react to tuberculin.

Superior logistics notwithstanding, the FDA's task will be to decide whether the test gives more accurate results than the much-maligned TST. To do that, the Phase 3 trials used people with no known history of TB exposure to gauge specificity and persons with culture-confirmed TB to assess sensitivity, says Rothel.

But to compare the two tests' ability to detect latent TB infection, the only standard available is the TST. Clearly, the two tests don't always agree. (Analysis of early data from the trials suggested they disagreed 70% to 90% of the time.) But given the well-known fallibility of the TST, is that good news or not?

"It's exactly what we'd hoped for — our test didn't always agree with the TST," says Rothel. Whether the

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FDA agrees with his interpretation is, he concedes, the big question.

In tests in cattle, results suggest the difference is due to Quantiferon's superior performance, he adds. Bovigam, also made by Cellestis, is used to detect latent TB in cattle by reacting to a cytokine produced by the animals. In side-by-side comparisons with the bovine equivalent of the TST, Bovigam disagreed with the skin test about 20% of the time. In those tests, it was easier to interpret the discrepancy, because cultures from the cattle provided a ready reality check. In the animal trials, Bovigam was clearly the winner, giving more accurate readings.

But Bovigam is testing for a different cytokine than Quantiferon, so it's not accurate to say results from the Bovigam trials apply equally to Quantiferon, says **Gerald Mazurek**, MD, an epidemiologist at the Center for Disease Control and Prevention's Division of TB Elimination who has overseen the Phase 3 trials.

Still, Quantiferon's performance has looked promising in two other respects. Although it sometimes does react positively in people who have received a bacille Calmette-Guèrin (BCG) vaccination in the past, it appears to be flummoxed by BCG less often than TST, says Rothel.

When it comes to nontuberculous mycobacterial infections, such as *Mycobacterium avium*, Quantiferon seems a much cannier instrument, with early data showing it reacted to atypicals only one-third as often as TST. **(See related story in *TB Monitor,* October 2000, p. 97.)**

Both tests sometimes fall short when it comes to spotting TB in active cases, concedes Rothel. In the case of Quantiferon, that's because levels of gamma-interferon plummet with onset of active disease and often don't rebound until as late as a year later, he says. The fact that all patients in the Phase 3 trials had already begun treatment probably threw off Rothel's test further, he says; the test would have performed better in pretreatment subjects, he adds.

In Australia, Quantiferon is already licensed for use and is being used in place of the TST in two hospitals in Perth, Rothel says. "But I won't lie to you," he adds. "Most people here have been waiting before they switch to see the results of the Phase 3 trials in the U.S."

Even if the FDA gives full approval at the licensure hearing, Rothel says he doesn't expect an overnight revolution in the way clinicians assess latent TB. "First we'll have to dispel a certain amount of myth and folklore, I expect," he says. ■

Funding shortage imperils promising quinolone trials

$20M to $30M needed

Trials for the most promising new candidate on the horizon for shortening TB treatment may never get off the ground unless a funding source can be found, says **William J. Burman**, MD, infectious disease specialist at the Denver Medical Health Center and chairman of the Core Science Group at the TB Trials Consortium (TBTC).

Exciting trial data from India suggest that adding a fluoroquinolone to both the induction and continuation phase would pack so much punch that both the frequency and the duration of treatment could be scaled back substantially. The problem is that the cost of the trials is expected to run between $20 million and $30 million, says Burman.

Despite that obstacle, researchers are plowing ahead on several fronts. That includes work on possible designs for a trial involving one of the drugs; negotiations with Bayer Pharmaceuticals, which holds the license to make the drugs; and tests of early bacteriocidal activity (EBA) to help researchers decide which quinolone to use.

Looking to AIDS for a model

As for funding, Burman says it's wrong for TB control programs to have to fight over the same meager pie as TB researchers. The best solution would be to give the Tuberculosis Trials Consortium its own line item in the budget, a perk the AIDS research community has long enjoyed. "You don't see Ryan White [treatment] money having to compete with AIDS research money," he points out. "That's the way it ought to be for TB, too."

Debate on appropriations for domestic TB spending for 2002, set to start last month, was postponed by terrorist attacks.

Finances notwithstanding, other prospects for the trials look good. **Giorgio Roscigno**, former chief of the New York-based Global Alliance for TB Drug Development, is negotiating with Bayer Pharmaceuticals.

Bayer also dispatched envoys to a recent National Institutes of Health meeting on new TB drug development. "They mostly sat back and listened, but they weren't actively discouraging, which we took as a good sign," Burman reports.

Last month, TBTC researchers met with other TB experts at the Centers for Disease Control and Prevention to explain various possible trial designs. One permutation on the table would substitute a quinolone for ethambutol, or perhaps isoniazid, in the initial phase of treatment, says Burman. "Ethambutol does nothing, for all we can tell, so from an efficacy standpoint there would be essentially zero risks," Burman says. "Isoniazid also does relatively little in the context of four-drug therapy."

Next, the idea would be to take a look at efficacy by measuring culture-conversion rates at two months, says Burman. Data from recent trials of quinolones conducted in Chennai, India, grabbed researchers' attention, indicating that adding one of the drugs may increase conversion rates by 10% or more.

To everyone's considerable frustration, the Chennai trials failed to include a control arm. Still, if the TBTC can replicate anything near the Indian researchers' results, the impact could be profound.

Once-weekly dosing a possibility

TBTC researchers also like the idea of adding a quinolone to the continuation phase, where they might team it with long-acting rifapentine (RPT), says Burman. Doing that might reduce frequency of dosing to once weekly — as in Study 22 — but more effectively, because many experts have decided that a quinolone is probably going to prove a stronger partner for RPT than isoniazid, the agent teamed with it in Study 22.

Work also is under way to help researchers decide which quinolone to use. Toxicity concerns are mild, Burman adds, because the drugs already have been used extensively as second-line agents in treatment of multidrug-resistant TB, as well as in some AIDS trials. To weigh the efficacy of the various quinolones, the consortium is about to start tests of EBA by assaying subsequent sputum samples to assess kill power early in treatment.

Candidates to be vetted in the EBA studies may include levofloxacin (which is backed by the most clinical experience and toxicity data), moxifloxacin (which performed strongest in recent work in animals), and gatifloxacin (fewer data exist for this drug, Burman says).

To help cut costs and expedite enrollment, the TBTC will probably collaborate on the trials with

the National Institute of Health's TB Research Unit, says Burman. The collaboration would be a first, but it's not a done deal. One potential problem is that the TB Research Unit's mandate, on paper at least, directs it to look for surrogate markers, not to conduct trials.

That brings Burman back to why the TBTC deserves its own funding source. It's the only agency in the country equipped to conduct TB trials, he points out. The reason is simple: Trial sites all have close ties to public health TB clinics — so close that in some instances, the trial site is the TB clinic. That means ready access to TB patients. "That's been a good move," Burman adds. "It's what has let us be a successful TB research organization." ■

Domestic TB funds probably still secure

Impact of terrorist attacks on the budget

Last month's terrorist strikes could actually help prospects for domestic TB funding, as well as other good causes with strong bipartisan support, say policy experts at the American Lung Association (ALA) in Washington, DC.

The $40 billion Congress swiftly approved last month in emergency funding will "almost surely" come from the once-sacrosanct Social Security Trust Fund surplus, says an ALA policy analyst who asks not to be named. "Once the piggy bank is broken," the analyst adds, Congress may be less reluctant to tap into the trust fund money for other causes, including TB control.

Debate on next year's budget for domestic TB spending had been set to start the week of Sept. 10. As this newsletter went to press, debate had been postponed by last month's events for at least a week, and perhaps longer.

Budget serves to set tone

The domestic TB bill, called the Omnibus TB Control Act, seeks an increase of $200 million for domestic TB control programs and asks for $240 million for TB research at the National Institutes of Health. In his proposed budget, President Bush had indicated he would seek flat funding for the Centers for Disease Control and Prevention; at that time, ALA experts remained hopeful, pointing out that the proposed presidential budget served only to set a tone, not to establish policy.

As last month drew to a close, the fate of funding for international TB control was looking bleaker. Well before the terrorist attacks, the full House had approved only $90 million for international TB control. An additional $20 million was added as part of $100 million approved by the House for the Global AIDS Fund. (Supplemental funds along with money from a separate bill were expected to raise the total for the Global Fund to about $300 million.)

A comparable Senate bill for international TB spending that was before an appropriations committee would have awarded even less than the House version — only $70 million for international TB control programs and $50 million for the Global AIDS Fund.

The STOP-TB Now Act, the companion bill for international TB spending, had sought $200 million for 2002 international TB control activities. The Global AIDS Fund, according to World Health Organization experts, was seeking at least $1 billion in contributions from the United States. ■

Good listening skills yield more information

Course uses actors to hone technique

The skill of "active listening" lies at the heart of a good patient interview," says **Rajita Bhavaraju**, MPH, health educator at the New Jersey Medical School's TB Model Center in Newark. Bhavaraju addressed this subject in a class called "Effective TB Interviewing and Contact Investigation," held in October at the center.

Cultivating active listening means, first of all, not approaching an interview too intently focused on an agenda.

"That's probably the most common mistake we see in novice interviewers," says Bhavaraju. "They go through the interview almost like a checklist." That approach often results in interviewers missing important cues from the patient — perhaps about barriers to compliance.

"If the patient keeps coming back to the subject of child care, for example, the interviewer has to be able to recognize that those needs could be a barrier to adherence," she adds. "Interviewers need to be able to adjust."

Along with a patient approach, interviewers need to avoid certain kinds of behaviors to keep the information flowing. Avoid close-ended questions requiring only a "yes" or "no" answer, Bhavaraju says. For example, asking a patient, "Do you live with anyone?" will probably elicit less information than "Tell me about the people you live with."

Such an approach also pays off by establishing rapport, Bhavaraju adds. Rapport between interviewer and patient is crucial because "in many cases, the same people who conduct the initial interview will be managing the case," she points out. "It's often a long-term relationship." Plus, a patient who trusts an interviewer is more likely to provide important information.

Generic 'foreign-born' patient added

That doesn't mean the patient does all the talking, Bhavaraju says. Interviewers have to get across certain concepts, such as the importance of adherence. In those instances, it's important "not to talk over the patient's head," she says.

The workshop uses a variety of interactive teaching techniques, including the use of so-called "standardized patients" — actors assigned to play a patient with a particular history. It's a technique often employed by medical schools, Bhavaraju says.

"We have an interviewer go through an entire interview with an actor," she says. "We ask actors to react to the interviewer's style." The actors are trained to adjust their reactions as well, Bhavaraju says, easing up "if someone is obviously struggling, and in other cases, really challenging people."

Though the primary aim is to build a good interviewing style, the course addresses cultural competency and different kinds of contact investigation. For the first year, this month's class includes an actor who plays a generic foreign-born patient (from the country of "Slowamba"), complete with whatever accent the actor wants to try out, as well as strong beliefs about the supposed protective value of the bacille Calmette-Guerin vaccine.

Each year's class is a bit different from those of previous years, says Bhavaraju. Invariably, participants have a wide range of experience, too. "We have some people with a few weeks' experience; others have been at this for more than 20 years." Those with more experience often make important contributions to the class, she adds.

The class is offered once or twice a year, Bhavaraju says. For those unable to attend, the course materials, along with instruction about how to use them, are offered to TB control divisions.

For more information, contact Bhavaraju at the TB Model Center at (973) 972-3270. ■

Drug facility funding needs a booster shot

Money will run out at year's end

The Global Drug Facility will run out of money by the end of this year, says **Ian Smith**, MD, spokesman for the World Health Organization's STOP-TB division. The drug facility is designed to ensure a steady supply of drugs in countries where TB is endemic. Without that steady supply, even relatively strong TB control programs in developing countries can be rendered dysfunctional, because interruptions in drug supply engender patient relapse and drug resistance.

Canada, with a pledge of US $10 million, is the only country to have given any money at all. The drug facility has concluded agreements with 12 countries to provide anti-TB drugs for the next three years, says Smith. Another five countries are in the midst of negotiating their own agreements.

A country Smith says he can't name yet has promised to step into the breach and provide emergency funding for the next three years if other donations fail to materialize.

Waiting on global health fund

One hold-up is that some potential donors — the United States among them — are waiting to see whether the Global AIDS Fund (also intended to help victims of TB and malaria) will be able to direct some of its contributions to the drug facility, says Smith. Congress is expected to approve about $300 million for the Global AIDS Fund, an amount far below the $1 billion the WHO says is needed from America.

No matter where the money comes from, more

must be found if the drug facility is to keep on functioning. "If we're going to get anywhere with this thing, we need a huge amount more money," says Smith.

Putting money into the drug facility is a great buy, at $10 for a full year's worth of drugs, adds **Joanne Carter**, legislative director for Results International, a grass-roots advocacy organization based in Washington, DC.

Only one person in four has access to the drug regimen recommended by the WHO for TB treatment. Lack of access to drugs has been one of the major constraints to countries seeking to expand their TB treatment programs. ■

WHO launches campaign against drug resistance

Attitudes must change, experts say

A new international campaign intended to slow the global rise of drug resistance takes aim at the complacent attitude many people have adopted about the use of antibiotics.

"One big message is that antibiotics are not without risk," says **Rosamund Williams**, MD, who is coordinating activities for the new campaign, launched last month by the World Health Organization (WHO). "The other big message is that we must work harder at preventing infections in the first place."

The campaign highlights the rise of resistance not just to TB drugs, but to drugs across the entire spectrum, says Williams. In societies where drugs are misused, underused, or overused, high resistance rates tend to develop to many classes of drugs, not just one, she adds.

Overall, resistance to TB drugs accounts for only a small portion of all kinds of drug resistance. "If you stack TB drug resistance against, say, hospital-acquired infections, you find other resistant infections are far more common," she points out. In a society with lots of drug resistance, virtually every patient with gonorrhea might well have a drug-resistant strain, while drug-resistant TB might be confined to just 8% to 9% of the population in a certain region or area.

But that's not really a meaningful comparison, Williams notes. "That's because drug-resistant TB is a much longer-term problem, and one patient with drug-resistant TB can transmit infection to many others," she says.

On the plus side, drug-resistant TB has a built-in opportunity other resistant diseases usually lack, Williams says. With TB, there exists a formal structure — namely, the public health clinic — to allow patients to receive treatment and to allow the enactment of measures to decrease inappropriate drug use. "That's not the case with many of the other, so-called 'trivial' infections," she adds.

Making sure everyone is better-informed

Strategies proposed by the new campaign target all segments of society, says Williams. Better-informed patients will cease to pressure physicians to give them antibiotics they don't need. Better-informed physicians will prescribe only drugs that are needed. Hospital managers can implement procedures to monitor the effectiveness of drugs that are used. Health ministers can make sure the most critical drugs are available.

The initiative's patient-specific recommendations include the following:

- Educate patients on the appropriate use of drugs.
- Educate patients on how to prevent infection.
- Educate patents on how to prevent transmission of infection.
- Encourage patients to take measures for symptom relief when drugs are not appropriate.

For prescribers and dispensers, specific recommendations include:

- Educate prescribers and other dispensers of drugs about the right use of drugs and the dangers of resistance.
- Encourage appropriate infection control, such as immunization.
- Teach the accurate diagnosis and management of common infections.
- Educate patients on proper drug use and on the importance of adherence.
- Alert prescribers to factors that may exert undue influence, such as advertisements and incentives.

The new campaign also targets the use of drugs by the livestock and poultry industries to promote growth and treat sickness. The use of drugs as growth-promoters should be curtailed and gradually phased out, recommendations say. At present, half of all antibiotics produced are used in the livestock industry. Drug-resistant microbes in animals can infect humans as well. ■

Good ALA or bad ALA: What's the difference?

History, rates, and physician involvement cited

At a meeting of TB folks not so long ago, somebody mentioned the subject of the American Lung Association (ALA). "My chapter never does anything for us," was one comment. "Oh? Ours is really helpful," someone else replied.

What accounts for the difference? According to **Diane Maple**, media representative for the ALA in Washington, DC, local epidemiology and resources both play a big part.

TB-related activism or lack thereof "is definitely a function of local TB rates and of whether we have the staff to do it," she says. "Where there's a big TB problem, most lung associations have at least one staff person part-time [working on TB]." But each lung association must raise its own money, she adds. "With two or three staff members in an office trying to do everything, devoting a whole position to just TB would be a real luxury."

Lee Reichman, MD, former president of the ALA and executive directive of the Model TB Center at the New Jersey Medical School in Newark, agrees — but won't let the ALA off the hook altogether. "This is something that's always bothered me," he says. "I've been very disappointed that in some places, the ALA hasn't always fulfilled its mandate to be a leader in TB control."

That doesn't mean TB experts should sit around grousing, Reichman adds. "The ALA is volunteer-driven," he points out. "Get on the board. Get some influence. A lot of doctors don't have the patience to do this, but you've got to get out there and build that grass-roots support."

Maple agrees: "If there's someone working on TB, get to know them."

Two lung associations in two cities, both working hard to fight TB, show two different ways TB activism works.

Hooking up communities in Chicago

Chicago's ALA chapter founded the highly effective Metro Chicago TB Coalition. Since its inception two years ago, the coalition has picked up 40 to 50 partner organizations, held workshops for homeless shelters, planned strategies with HIV clinics, and staged fundraisers.

At the TB coalition's last quarterly meeting, so many people showed up that some had to be turned away.

Local TB controllers say much of the credit belongs to a tireless woman named **Judith Beison**, a community outreach coordinator. Hired a year ago to work half-time on TB (she devotes the rest of her time to asthma), Beison brings an energetic, straightforward approach to the process of coalition-building.

"I get out and talk to people," she says. "I think it's important to help communities connect. If there's a better way to do it, someone's going to have to tell me what it is." Although Beison came to her new job knowing next to nothing about TB, she says her co-workers have been a big help, supplying her with videos and workbooks. "It's been a steep learning curve for me," she concedes.

Southside Symposium made connections

Last October, she launched the first of an ambitious series of planning initiatives, staging the Southside Symposium, which brought together TB providers from that part of the city. The principal aim of the symposium was to get people connected, she adds. "If someone has TB, we wanted to make sure that all their caregivers were talking, and to expedite referrals, and to make sure the public and private sectors are collaborating," she says. What sounds like a simple goal proceeded to play out in a carefully planned step-wise process.

Between 75 and 80 people showed up, including nurses, physicians, community leaders, public health types, and social workers, she says. After some education in TB basics, the crowd split up into five groups; then the groups talked about how better to engage communities in their area, Beison says. The next step was the formation of a Southside planning group. The planning group gave birth to collaborative agreements on how best to manage TB patients.

Last spring, the lung association staged a second planning symposium, this time on the city's west side. Last month, Beison was busily preparing for this month's Northside Symposium, when she wasn't talking with shelter operators, HIV clinics, politicians, and people on the subway. "I talk to everyone I can," she says cheerfully. "They're like, 'Do you mean to say I can still get that disease? Just standing next to someone?'"

ALA Milestones

1904: National Association for the Study and Prevention of Tuberculosis is formed. First nationwide, voluntary health organization aimed at conquering a specific disease.

1907: First Christmas Seals are printed and sold to raise money for a cash-strapped TB sanitorium on the Brandywine River in Delaware.

1929: National Association supports research into how to improve X-ray machines and techniques.

1930-1940: National Association teams with public health system to conduct mass screenings using tuberculin skin tests and chest X-rays.

1948: National Association launches fellowships program at universities, producing many leading pulmonologists.

1958: National Association adds asthma, emphysema, and other lung diseases to its portfolio.

1960: First anti-tobacco campaign begins.

1963: "Clean Air Committees" established.

1973: Name changed to American Lung Association.

1984: "The Asthma Handbook" issued.

1993: ALA, under President Lee Reichman's direction, successfully campaigns to double federal appropriations for TB project grants, from $15.3 million to $34.4 million, and makes $39.3 million in emergency grants.

In San Diego, it's a different story. There, the ALA affiliate is a strong player in TB with a long history of involvement. "Here, the environment is right," says **Ross Porter**, communications director of San Diego's ALA chapter. "With our rates, it's imperative that we focus on TB. But along with that, we have historic roots."

In 1907, the local lung association worked hard to raise money to build a TB sanatorium, Porter says. But the municipality mounted a not-in-my-backyard opposition, forcing the issue all the way to the state supreme court; ultimately, pro-sanatorium forces won the day.

In the 1960s, a physician named Kenneth Moser, MD, became active in the lung association. His daughter, Katherine (now the TB controller for San Diego county), stepped into her father's shoes and now sits on the ALA board. "Kathy is a volunteer leader and a real policy driver here at the ALA," says Porter. "We include her in anything that has to do with TB."

For the past 10 years, the San Diego ALA has held a binational TB conference on World TB Day, occasionally generating much publicity and featuring big-gun speakers. Last year, the association broke with precedent, focusing instead on new TB guidelines.

This year, the group's big project will be to revamp and strengthen its web site, Porter says. "We want to be a resource for physicians," he explains. "Kathy [Moser] wants to update our web site and keep it up to date. We're building a database of pulmonary doctors; soon, we plan to be a real source of news and updates."

With direction from a pediatric task force, the lung association also conducted school-based testing for a while. "We're no longer doing that, but we did raise school nurses' awareness," Porter says. "Plus, now the nurses know exactly who to call."

Porter has also begun to collaborate with a local member of Results International —- the grass-roots advocacy group that's adopted TB as a special cause —- in writing letters to the editor and otherwise trying his hand at political advocacy, he says.

These days, along with work on the TB web site, the chapter is exploring new ways to reach targeted communities. One of the most popular outreach tools is a colorfully decorated, forty-foot bus (powered by non-polluting compressed natural gas, of course). The Lung Express, as it's called, visits elementary schools and provides kid-friendly interactive learning, with exhibits on air pollution, asthma, and TB. "There's even a model of a lung you can walk through," says Porter. The exhibits were fashioned with the help of a science and technology museum in Portland, OR, he adds. ■

Overhaul gets under way for old control guidelines

Changes abound in the landscape

Work has started on a new set of guidelines to govern the elements of TB control. The previous document on that subject dates all the way back to 1991 — so far back that the document is essentially out of print.

The control guidelines are one of a TB "triad" of major documents that are either undergoing revision or else just emerging from the revision process.

The other two in the triad include recommendations on treatment and diagnosis. This year for the first time, a corollary set of guidelines on the prevention of latent TB infection — which might qualify as a fourth major set — was added.

Those charged with the revision will take a fresh look at case-finding, case-holding, contact investigation, and other basics of TB control, says **Zack Taylor**, field services branch chief at the Centers for Disease Control and Prevention's Division of TB Elimination in Atlanta. As they do so, they'll have to reframe these arenas in light of big changes in TB demographics and falling caseloads, he adds.

The team charged with the revision includes representatives from the American Thoracic Society, the CDC, and, for the first time, the Infectious Disease Society of America. Also contributing input will be the American Academy of Pediatrics and the National TB Controllers Association.

Last month, a committee met to hash out recommendations for a draft document. But don't hold your breath; the new guidelines on control aren't expected out until about this time next year. ■

Lots of entries vie for World TB Day theme

Usually decided by a small, insider group

TB professionals around the world have submitted ideas for a theme in 10 words or fewer, for this year's World TB Day, says **Jeanette Sanchez**, communications adviser for the World Health Organization's (WHO) STOP-TB group.

Traditionally, the theme for World TB Day gets decided by a handful of people at the WHO and the International Union Against Tuberculosis and Lung Disease. Making a contest out of the assignment was intended "to open it up to a wider audience, and maybe to get a different perspective and some fresh ideas," says Sanchez. The winner gets to attend a major World TB Day event at the WHO's expense and will report on the event (for later publication by STOP-TB).

In past years, themes often were centered around directly observed treatment short course (DOTS), the WHO-approved strategy for fighting TB. Plenty of contest entries this year have mentioned DOTS, too, Sanchez says, but others have taken new tacks, such as "soliciting support from various segments of society," she says. The deadline for contest entries was last month. ■

Research shows HIV resurgence in U.S.

Also, too many HIV infected people are tested late

HIV prevention efforts of the past two decades have scored two grades of "A," but there are even more "needs to improve" grades.

Researchers and public health officials speaking at the Centers for Disease Control and Prevention's 2nd National HIV Prevention Conference, held in Atlanta on Aug. 12-15, 2001, presented mixed news about the success of previous prevention efforts and hope for the future.

The latest CDC data show a leveling off of AIDS cases and deaths, and recent studies involving sexually transmitted diseases (STDs) among HIV-infected and at-risk individuals indicate the possibility of a future upswing in AIDS rates.

"Data continues to mount suggesting there is a true increase in risk behaviors," says **Helene Gayle**, MD, MPH, director of the National Center for HIV, STD and TB Prevention at the CDC.

"Several studies show HIV-infected men getting other STDs, which is evidence of risk behavior in a population that already has HIV," Gayle adds.

On the positive side, mother-to-child transmission has been reduced to levels that haven't been seen since the early years of the epidemic, a significant improvement from the peak rates of the early 1990s.

Also, there is increasing evidence that a majority of men who have sex with men (MSM) are continuing to use condoms consistently, some two decades into the epidemic, notes **Cynthia Gomez**, PhD, of the Center for AIDS Prevention Studies at the University of California - San Francisco.

However, young MSM are not reducing their sexual risk behaviors as consistently, Gomez says. "This is a generation that has not received the

intensive prevention message that the other men in their 40s have received, and it is not the same epidemic, so we can't repeat what we did in the 1980s and expect it to be effective."

The younger generation of MSM is a much faster-moving and -acting group, and they receive a great deal of information through advanced technology. This leads to risk behaviors associated with meeting other MSM through Internet web sites.

For example, the CDC has observed that some recent outbreaks of STDs has been associated with people using the Internet to "hook up" with sexual partners, says **Ron Valdiserri**, MD, MPH, deputy director of the National Center for HIV, STD and TB Prevention.

"The Internet is the 21st century version of anonymous sex, and it's equally important to use that venue to provide information and reinforce messages about safer sex," Valdiserri adds.

In other good news, injection drug users (IDUs) residing in New York City have had a substantial decline in HIV incidence rates in recent years. That success story is directly attributed to legislative and funding changes that have made syringe exchange programs readily available to IDUs in most of the city's boroughs.

"The HIV / AIDS epidemic among IDUs in New York City is one of the biggest local epidemics in the developed world, with over 50,000 cases of AIDS among IDUs, their partners, and their children, representing about 8% of all AIDS cases in the United States," says **Don Des Jarlais**, PhD, a investigator from Beth Israel Medical Center in New York City.

"That's more cases than has occurred in any European country," Des Jarlais says. "It got started in the 1970s with the introduction of HIV into the injection drug-using population, and the percentage of infected injectors went rapidly up to about 50% by 1983 and stayed at 50% through 1991."

Early prevention work included illicit needle-exchange programs, but the HIV incidence rate remained at a high rate: 4% to 5% of HIV-negative IDUs became infected each year, he says.

Then in 1992, the state legalized and funded needle-exchange programs. Prevention efforts, including voluntary HIV counseling and testing programs, began to show significant improvement in HIV rates.[1] About 40% to 50% of injectors used the exchange programs, resulting in a substantial decline in risk behaviors. This, in turn, has resulted in a dramatic decrease in HIV infection rates, Des Jarlais says.

"The percentage of IDUs infected has gone from 50% in 1990 to currently 20% of injectors who are infected," Des Jarlais says. "The new infection rate has declined from 4% to 5% per year in the 1980s to about 1% per year."

This data is based on a meta-analysis of 12 different studies with more than 6,000 person-years at risk. During the at-risk period, there were only 52 new HIV infections. The total percentage of IDUs infected is based on six studies with more than 11,000 participants.

STDs, risk behaviors still increasing

Despite these two areas of positive prevention news, the overall picture regarding new HIV infection rates is grim, according to the conference participants.

Other research presented in August showed a high HIV incidence among MSM ages 23-29 and resurgence of other sexually transmitted diseases, unprotected sex, and late HIV testing across various at-risk populations.

All of these factors indicate that prevention efforts are not reaching everyone who needs to hear the message, CDC officials say.

"Men who have sex with men continues to be the highest-risk group, and we're seeing troubling signs of resurgent epidemic among gay men, with increases in STDs and risk behaviors," Gayle says.

Worse, the declines in AIDS incidence and deaths are over until new treatment advances come to light, Valdiserri says.

"Very significant numbers of people are learning they have HIV very late in the course of their infections, and even those who report risk to their doctors are often not getting the prevention and testing and counseling they need," Valdiserri says.

"To make progress in reducing AIDS cases, as well as new HIV infections, it is essential to reach these individuals with earlier testing and better prevention and care, as well as prevention services tailored to meet their specific needs," he adds.

Several reports highlighted the problem of late HIV testing. For instance, the CDC reviewed behavior data from 12 states and local health departments participating in a supplemental HIV / AIDS surveillance project. The CDC found from 18,850 interviews that 40% of people diagnosed with AIDS from 1990 to 1999 first discovered they were infected with HIV within one year of the time they found out they had AIDS, says **Michael Campsmith**, a CDC investigator.

Late testing was common in all groups, regardless of age, ethnicity, gender, or HIV risk exposure category, Campsmith says.

"Given that without treatment AIDS typically develops 10 years after infection, this means that many of these patients had gone as long as a decade without appropriate medical support or prevention services," Campsmith adds.

The large cohort interview found that 40% of men and 41% of women were tested late. About 46% of black and Hispanic men tested late, compared with 32% of white men. Also, 42% of black women and 44% of Hispanic women reported late testing, compared to 36% of white women. When divided by risk category, researchers found that 39% of MSM, 40% of IDUs, and 51% of people who were exposed to HIV through heterosexual contact were tested late, Campsmith says.

In a similar CDC study presented at the prevention conference, late testing was found to be especially true for men, certain ethnic groups, and people over age 30.2

That study showed that 45% of men had been tested late compared with 31% of women, and that 53% of people age 45 or older tested late compared with 26% of those who were under age 30.

Kaiser weighs in on late testing

Late testing was also the subject of a recent study by the Kaiser Permanente National Consortium Chair, which was formed by Kaiser Permanente of Oakland, CA.

A large health care insurer, Kaiser provides health insurance to 12,000 HIV-infected people and used this database to determine best practices in HIV care.

"We identified all cases of HIV infection newly diagnosed in 1998 among Kaiser Permanente members who had been members for at least one year," explains **Leo Hurley**, MPH, a data analyst with Kaiser.

After identifying 434 HIV cases nationwide, investigators reviewed these patients' medical records for up to five years prior to diagnosis, looking for clinical events and patient characteristics that might have been expected to trigger an earlier test for HIV, Hurley says.

They found that nearly half of the cases had AIDS-defining CD4 cell counts at diagnosis, and these patients may have benefited from earlier detection.[3]

"We found that 44% of the cases had immunological AIDS at first diagnosis of HIV," Hurley says. "And 40% of the case had either risk factors or clinical signs of possible underlying HIV infection noted 12 or more months prior to diagnosis."

Also, according to chart notes, many of these

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cases had been identified as being at risk for HIV infection on one or more occasions, but not all of the people were subsequently tested for the virus. Some were tested and found negative, but others were offered HIV testing that they declined, and others were not offered testing, Hurley adds.

"Our third finding was that after diagnosis, it was determined that 80% of the cases belonged to the highest-risk category of male-to-male sex, and this was noted in the chart prior to diagnosis less than half of the time," Hurley says.

"The bottom line of the study is that even among persons with reasonable access to quality health care, HIV may go undetected for several years after infection," Hurley adds.

The study's seven diagnostic clinical events were oral infection, pneumonia, unexplained fever, herpes zoster, seborrheic dermatitis, night sweats, and unexplained weight loss.

The CDC prevention conference highlighted a few programs that have successfully reached at-risk populations with testing, counseling, and treatment referrals. These include a North Carolina outreach project that targets the homeless and a Maryland HIV testing van program that visits areas where HIV prevalence is higher.

HIV-positive and at-risk individuals also fall through health care system cracks with regard to condom use counseling, according to some studies presented at the CDC conference.

"People who are newly diagnosed with STDs may not know that they are at increased risk for transmitting HIV to partners," says **Thomas Lampinen**, PhD, an investigator from the University of Washington in Seattle.

A solution might be for HIV clinics to regularly include a drug and sexual risk assessment on an annual basis and use this information to enhance and supplement prevention counseling, Lampinen says.

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CE objectives

After reading each issue of *TB Monitor,* health care professionals will be able to:

- Identify clinical, ethical, legal, and social issues related to the care of TB patients.
- Summarize new information about TB prevention, control, and treatment.
- Explain developments in the regulatory arena and how they apply to TB control measures.
- Share acquired knowledge of new clinical and technological developments and advances with staff. ■