HRSA CARE ACTION

AUGUST 2009

Transmission

Symptoms

Testing

Treatment

TUBERCULOSIS + HIV = A COMPLEX CALCULUS

Tuberculosis (TB) continues to be a serious public health threat for people living with HIV/AIDS (PLWHA), especially for those with severely compromised immune systems. Unfortunately, the people disproportionately at risk for TB are the very people most at risk for HIV: people who are poor, underserved, uninsured, or minority—those whom Ryan White HIV/AIDS Program providers treat. To improve health outcomes and deliver comprehensive care, providers must—in addition to everything else they do—serve as TB diagnosticians.

Although TB incidence has decreased over the years, its decline has leveled off. From 1993 to 2000, the average annual percentage decline was 7.3 percent; between 2000 and 2007, it dropped to 3.8 percent annually.[1] If rates of decline remain sluggish, goals to eliminate TB will not be met for a century. Moreover, increases in multidrug resistant (MDR–TB) and extensively drug-resistant TB (XDR–TB) have been reported to the Health Resources and Services Administration and the Centers for Disease Control and Prevention (CDC).

TUBERCULOSIS TRANSMISSION and SYMPTOMS

TB is an airborne pulmonary disease. TB bacteria spread into the air when a person with untreated TB coughs, sneezes, spits, sings, laughs, shouts, or even speaks; people become infected by inhaling those bacteria. HIV infection significantly increases the risk of contracting TB, as do frequency and duration of exposure and density of infectious

DID YOU KNOW?

TB rates are more than 22 times greater among Asians, almost 8 times greater among Hispanics, and more than 8 times greater among African-Americans than among Whites.[2]

TB rates are almost 10 times higher among foreign-born persons than among those born in the United States.[2]

TB prevalence is higher among HIV-positive drug users, homeless and incarcerated persons, and heavy drinkers.[3,4]

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DIRECTOR'S LETTER

Although decreasing TB incidence rates might suggest a reduced threat from TB, we know that populations that are hardest hit by TB are also at highest risk for HIV, including minorities, injection drug users, and incarcerated and homeless persons—groups increasingly under our care.

Getting many of these groups into care and keeping them there can be challenging. But coinfection often leads to quicker disease progression and poorer treatment outcomes for both diseases, so prevention and early detection must be our top priorities. That way, we can increase our chances of catching TB before it becomes active, when it becomes more difficult to treat—and to survive. We must work to incorporate TB testing and treatment into patient care—and ensure better retention in care—by encouraging stronger patient-provider relations, improved linkages with health departments, directly observed therapy, and efficient and effective tracking systems for reading TB tests. After all, it is possible to prevent our patients from becoming ill with TB, but only with our continued dedication to providing targeted care to our consumers.

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HRSA CARE Action

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Photographs
Cover: stock image; page 3, a child in central Asia; page 6, a client receives a blood test, Brooklyn, NY; insert, blood work at a laboratory in Detroit, MI. Photographs except for cover: © See Change.

Additional copies are available from the HRSA Information Center, 888.ASK.HRSA, and may be downloaded at www.hab.hrsa.gov.

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droplets in the air. In areas with poor ventilation, TB bacteria can remain in the air for several hours, but sunlight and ultraviolet light can kill them.

Common symptoms of pulmonary TB include sudden weight loss, shortness of breath, cough, night sweats, fatigue, and fever. Pulmonary TB can be easily mistaken for bacterial pneumonia.[5,6]

LATENT and ACTIVE TB INFECTION

Latent TB infection (LTBI) occurs when a person is infected with tuberculosis but does not have active TB disease (i.e., they are not infectious in this stage). Infants, young children, injection drug users, diabetics, people with a recent TB infection, older adults, immunocompromised persons, and people inappropriately treated for TB are more likely to develop active TB disease. HIV dramatically increases the risk for reactivation of LTBI, from 10 percent over a lifetime to 10 percent per year.

In active TB (called *primary disease*), tubercle bacilli overpower the immune system, which attempts to seal off and kill infected cells by forming masses of inflamed tissue that surround infected cells (i.e., *granulomas*). TB bacilli start to multiply in the lungs and, sometimes, other parts of the body, leaving scarring and cavities filled with dead cells and infectious bacteria.

Although TB is an AIDS-defining opportunistic infection, it can occur at any CD4 cell count. TB progresses more rapidly in PLWHA, and HIV disease progression is accelerated by TB coinfection.[7–9]

TB TESTING

Proper diagnosis of LTBI versus active TB is crucial, because LTBI can rapidly progress to TB disease, particularly in PLWHA. LTBI can be diagnosed by tuberculin skin test (TST; also called PPD [purified protein derivative], the protein used in the skin test) or, less commonly, by using interferon-gamma release assay (IGRA) blood tests. TST results need to be read by a health care provider 2 to 3 days after the test is placed. (See insert, Table 1, for more on LTBI testing.)

Since 1989, the CDC has recommended HIV testing for all TB patients, and TB testing has been recommended for all PLWHA for more than

a decade.[10] Shockingly, a recent study reported that only 54 percent of newly diagnosed HIV patients in the United States received a TST.[11] And in 2005, only 69 percent (7,689 of 11,193) of TB patients had ever been tested for HIV; among TB patients with known HIV status, 13 percent (1,034) were HIV positive.[12]

The 2008 *U.S. Guidelines for Prevention and Treatment of Opportunistic Infections* recommend LTBI testing upon HIV diagnosis and retesting for people whose CD4 nadir reaches <200 cells/μL (but testing should take place after patients begin antiretroviral therapy [ART] and their CD4 cell count increases to ≥200 cells/μL). Annual testing is recommended for PLWHA at risk for TB (e.g., people who have been in close contact with infectious TB patients, have been incarcerated, or live in homeless shelters or other congregate settings; injection and noninjection drug users; children; and people with other sociodemographic risk factors for TB; see insert, Figure 1).[13,14]

HRSA's *HIV/AIDS Bureau's Core Clinical Performance Measures for Adults and Adolescents* sets forth performance measurement recommendations for TB testing for PLWHA. The goal of performance measures is to improve the quality of care—including TB screening. Because the issue of TB reflects an important aspect of care that affects HIV-related morbidity and mortality and highlights treatment decisions that affect a sizeable population, Ryan White HIV/AIDS Program grantees are encouraged to track the number of clients who have received documented testing for LTBI since HIV diagnosis. Grantees are also encouraged to track the number of PLWHA who do not have a history of positive TB tests or a previous documented positive TST or IGRA. In doing so, grantees will be able to improve quality management and early TB detection and will be able to monitor their findings for areas of improvement.

Increasing testing among PLWHA is critical, because TB diagnosis can be complicated in people who are HIV positive. Chest x-rays may be normal or atypical, and unusual manifestations of TB, including disseminated and extrapulmonary TB (i.e., infection of the kidney, lymph nodes, pleura, spine, brain, and genitourinary tract, among other parts of the body), are far more common among PLWHA—particularly women—than among people who are HIV negative.[15-18] In addition, immunosuppression increases the risk for extrapulmonary TB, although it can occur at any CD4 cell count. PLWHA with extrapulmonary TB are at high risk for disseminated TB, which can progress rapidly and can cause high fevers and sepsis syndrome.

Testing, diagnosis, and treatment recommendations do not differ for HIV-positive pregnant women. TB that goes untreated until late pregnancy can cause complications, such as premature birth, low birthweight and, rarely, congenital TB.

TB PREVENTION: BCG

Although it does not always prevent TB, the Bacille Calmette-Guérin (BCG) vaccine is given to infants and young children in many countries where the disease is prevalent. The BCG vaccine is rarely used in the United States because it does not offer complete protection against TB and may interfere with tuberculin skin test (TST) reactivity. BCG recipients may have a positive TST either from the vaccine itself or because they have been infected with TB. Interferon-gamma blood tests (such as QuantiFERON-TB Gold [QFT; Callistis Inc., Valencia, CA] or T-SPOT.TB [Oxford Immunotec, Oxfordshire, UK] are not affected by prior BCG vaccination; some evidence suggests that T-SPOT.TB is more sensitive than QFT for detecting TB.

Sources:
Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med*. 2008;149:177-84.
Chee CB, Gan SH, Khinmar KW, et al. Comparison of sensitivities of two commercial gamma interferon release assays for pulmonary tuberculosis. *J Clin Microbiol*. 2008;46:1935-40.

TREATING TB

Gerry Drewyer, a registered nurse at the Tarrant County (Texas) Health Department, tells a story illustrating the importance of medication adherence:

Before we started directly observed therapy [DOT, in which patients are observed taking each dose of their medications] *in the mid-1980s, TB patients were seen once a month. One person didn't take his TB meds as directed and developed drug-resistant TB. Thirteen other people were infected; two members of his family died from it. It cost more than a million dollars.*

"With TB there is such a limited number of good drugs, it is critical that people take their medicine," Drewyer adds. Patient-centered DOT programs help ensure treatment adherence and completion, both of which are crucial to avoid drug resistance.

LTBI treatment consists of 9 months of daily or twice-weekly isoniazid (INH) doses plus pyridoxine to decrease the risk of peripheral neuropathy, or 4 months of rifampin (RIF) or rifabutin (after assessing potential drug-drug interactions for HIV-positive patients; see Resources).[21,23,24] People with active TB require approximately 6 months of treatment with multiple drugs.

CDC treatment guidelines recommend drug susceptibility testing to see whether first-line TB drugs will work (i.e., INH, rifampin [RIF], ethambutol [EMB], and pyrazinamide [PZA]). Retesting is recommended if cultures become positive at any point during treatment or remain positive after 3 months of TB treatment.[25] The same drugs are used to treat TB in PLWHA (Table 2).

Side effects of first-line TB medications include rash, optic toxicity, gastrointestinal symptoms, fever, and hepatotoxicity.

PLWHA are five times more likely than their HIV-negative counterparts to die during TB treatment or to be diagnosed with TB at death.[25,26] ART during TB treatment is associated with improved TB- and HIV-related outcomes, but the best time to start ART in treatment-naïve HIV-positive TB patients is unclear.[26] Ongoing studies are addressing this issue.

Treating TB disease in PLWHA involves multiple considerations (Table 3). Treating both diseases at once may lower the risk of TB and HIV-related mortality, but interactions among antiretroviral agents and TB treatment, side effects, and high pill burden make doing so difficult. (For more information, see *Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis*, at www.cdc.gov/tb/tb_hiv_drugs/default.htm.)

People who initiate ART at low CD4 cell counts are at risk for immune reconstitution inflammatory syndrome (IRIS), which occurs when known or previously unrecognized TB disease flares up.[27] Symptoms include fever, weight loss, swollen lymph nodes, difficulty breathing, fluid buildup in the lungs and chest cavity, small tissue masses in the lungs, and the development or growth of central nervous system lesions. It is often difficult to distinguish between IRIS and TB treatment failure, because symptoms are similar.

Checking whether second-line drugs will work is indicated when HIV-positive people have been exposed to MDR–TB, are from areas where MDR– or XDR–TB is prevalent, or have TB disease that is resistant to first-line drugs. Second-line drug susceptibility testing is also recommended for HIV-positive TB patients who have been treated for TB in the past (especially within 2 years) and for people who remain TB culture positive after 3 months of treatment. Expert consultation is recommended for treatment of MDR– and XDR–TB, regardless of HIV status.

MULTIDRUG-RESISTANT TB and EXTENSIVELY DRUG-RESISTANT TB

MDR–TB is resistant to at least two drugs—INH and RIF. Globally, the World Health Organization estimates that each year, 490,000 cases of MDR–TB occur and more than 100,000 people die from the disease.[28] According to HRSA officials, "The ability of [TB] to develop resistance to treatments and to travel easily across borders makes worldwide TB control efforts critical . . . while the total number of MDR and XDR TB cases is small, their impact on the U.S. TB control programs can be significant in terms of human capital and financial resources."[29]

MDR–TB is treatable with second-line drugs, but they are more toxic than first-line drugs, and 2 years of treatment are required, versus 6 months for drug-sensitive TB.

HIV coinfection worsens treatment outcomes for people with MDR–TB. Successful programs report that TB susceptibility testing, ART, patient-centered adherence and peer support programs, DOT, and completion of TB treatment are associated with improved outcomes.[30,31]

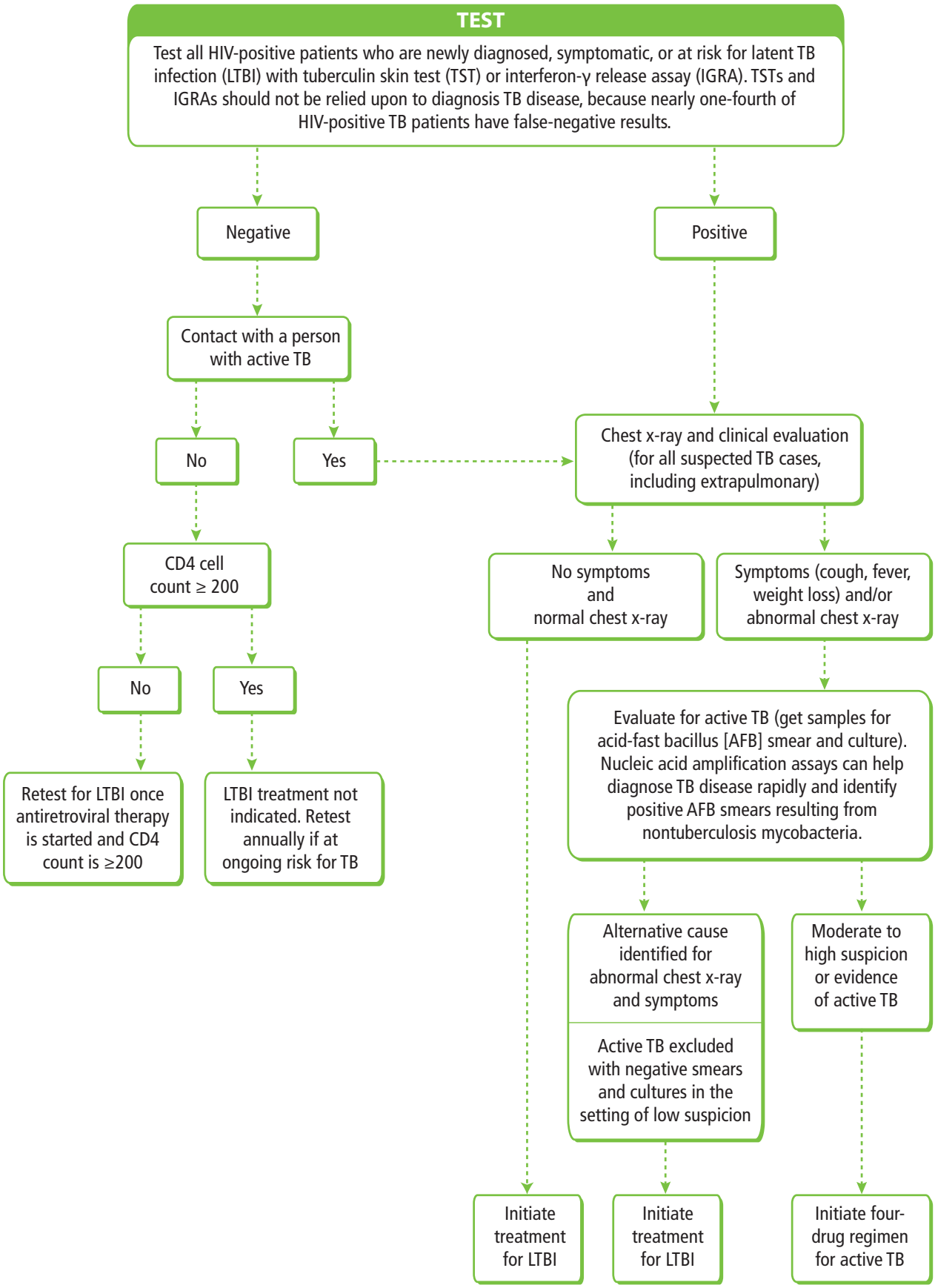
Failure to diagnose and properly treat MDR–TB has led to the development of XDR–TB, which is resistant to at least two first-line drugs (INH and RIF), any fluroquino-

TABLE 1. LTBI TESTING[19-22*]

Type of Test	Testing Method and Turnaround	Advantages	Disadvantages	Cost
Tuberculin Skin Test (TST); also called PPD	▸ Purified tuberculin protein derivative is injected under the skin of the forearm by a trained medical provider. ▸ Must be read by a trained health care provider 48 to 72 hours after the test is placed	▸ Generally very safe ▸ Does not require a laboratory ▸ Inexpensive ▸ FDA approved	▸ Less specific than QuantiFERON-TB Gold.TB and T-Spot.TB ▸ Less sensitive in immuosuppressed people (including PLWHA) ▸ Requires training and standardized procedures to place and read TST ▸ Results are contingent upon the patient's return to have the test read 48 to 72 hours after it was placed ▸ False positive and false negative results may occur ▸ May be reactive in people who have been vaccinated with Bacille Calmette-Guérin (BCG)	$20–$26
QuantiFERON-TB Gold (interferon-gamma release assay)	Blood test; 24- to 48-hour turnaround (longer if batched)	▸ More specific than TST testing; prior BCG vaccination does not affect accuracy ▸ FDA approved	▸ Possibility of false-negative or indeterminate results in people with advanced immunosuppression ▸ Laboratory required	$221–$297
T-SPOT.TB (interferon-gamma release assay)	Blood test; 24- to 48-hour turnaround (longer if batched)	▸ More specific than TST testing; prior BCG vaccination does not affect accuracy ▸ May be more sensitive than TST and QuantiFERON-TB Gold ▸ Inadequate data on performance in people <17 years old, pregnant women, and people with hemophilia ▸ FDA approved	▸ Possibility of false-negative or indeterminate results in people with advanced immunosuppression ▸ Laboratory required	$221–$297

*Marks, SM. Division of Tuberculosis Elimination and Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention. Personal communication. December 29, 2008.

FIGURE 1. TB DIAGNOSIS in HIV-POSITIVE PATIENTS



Source: National Institutes of Health, CDC, Infectious Diseases Society of America (IDSA). *Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents.* 2008. Available at: www.cdc.gov/mmwr/pdf/rr/rr5804.pdf. Accessed June 18, 2009.

TABLE 2. TB TREATMENT for HIV-POSITIVE PATIENTS[13]

Type of TB	Initial Treatment	Subsequent Treatment
Drug-susceptible TB	2 months of INH, RIF or rifabutin, PZA, and EMB*	▸ Followed by 4 months of INH, RIF, or rifabutin ▸ If cavitary lung disease is present and culture is positive after 2 months, extend INH and RIF for 3 months.
Extrapulmonary TB	2 months of INH, RIF, PZA, and EMB	▸ Followed by 4 to 7 months of INH and RIF ▸ If central nervous system or bone and joint TB are present, extend treatment to 9 to 12 months.

Note: Some studies support prolonging TB treatment for 9 months in PLWHA to reduce the risk of relapse.
INH = isoniazid; RIF rifampicin; PZA = pyrazinamide; EMB = ethambutol.
*If drug susceptibility testing confirms that there is no resistance to INH, RIF, and PZA, EMB can be discontinued.

TABLE 3. TB and HIV TREATMENT STRATEGY for ART-NAÏVE PATIENTS[13]

CD4 Count	Recommended Strategy
CD4 < 100 cells/μL	Some experts recommend delaying ART initiation for 2 weeks so that TB drug toxicity can be identified and managed and the risk of immune reconstitution inflammatory syndrome can be reduced.
CD4 = 100 to 200 cells/μL	Some experts recommend waiting to initiate ART until after 8 weeks (2 months) of treatment for TB disease.
CD4 = 200 to 350 cells/μL	Same treatment strategy recommended for CD4 = 100 to 200 cells μL.
CD4 > 350 cells/μL	Start ART after 8 to 24 weeks or after end of TB treatment.

Note: ART = antiretroviral therapy.

lone, and one or more injectable second-line drugs (i.e., amikacin, kanamycin, and capreomycin). Worldwide, an estimated 40,000 cases of XDR–TB occur each year.[28] In June 2008, WHO reported XDR–TB cases in 49 countries, including the United States (four cases in 2006, two in 2007).[2]

XDR–TB is difficult to treat because options are limited. Identifying appropriate regimens with drug susceptibility testing, psychosocial support, prompt management of side effects and—in some cases—lung resection has improved treatment outcomes in HIV-negative people.[32-34]

XDR–TB-related mortality rates are high, and disease progression is rapid among PLWHA, underscoring the need for prompt HIV and TB diagnosis; TB culture and drug susceptibility testing; infection control in hospitals, clinics, prisons, and other congregate settings; and ART.

TB/HIV PROGRAMS

Incorporating Testing and Treatment

"TB never went away in the Bronx, where we have recent immigrants, homeless people in shelters, and people who intermittently access care—a perfect mix of elements that make our population at high risk for TB. The Bronx was the epicenter of the TB outbreak in New York in the early 1990s; patients and providers remember," explains Robert S. Biel, clinical director at Montefiore Medical Center's CICERO Program in Bronx, New York. Fortunately, Montefiore, like many Ryan White HIV/AIDS Program clinics, has successfully incorporated TB testing and treatment into patient care.

Successful programs have in common (1) a patient-centered focus and (2) simple systems to alert providers about annual TB testing. For example, multiple reminders help prompt busy clinic staff to remember annual TB testing for each patient.

Successful TB/HIV programs have in common a patient-centered focus and systems to alert providers about annual TB testing.

At the Montefiore Medical Center, a flag was added to nursing assessments to direct nurses to a form for tracking TSTs. In addition, doctors check the schedule each week and list patients who are due for TB testing or did not return for their most recent TST read. The strategy is paying off: According to Judith Schrager, administrative nurse manager, Montefiore sees "less than 10 cases of TB per year, and only one or two cases are MDR-TB."

Some clinics have fully integrated TB testing, care, and treatment. "Our HIV-positive patients get tested for TB each year. The doctor also works in the HIV clinic so patients get all their care in one place," says Drewyer.

Clinics have used several strategies to encourage patients to return for TST readings. One is to strengthen the patient-provider relationship. "Nurses are encouraged to develop relationships with our patients because it increases return rates," says Schrager. Drewyer agrees: "We treat our patients as we would treat our mothers." Clinics call patients and provide them with subway fare to encourage them to come back for TST readings. At Montefiore, the wait for TST readings has been minimized; patients are seen within 5 minutes of their arrival.

Adherence is also crucial for successful TB treatment. DOT has been an effective strategy. Drewyer says, "We train our staff to be community health aides. They go to schools, shelters, and people's jobs to deliver medication for latent and active TB. One hundred percent of our TB patients are observed, taking 100 percent of their medication. [DOT] programs help people get healthy, allowing them to earn a living, and to be with their families."

Helping patients understand the need for testing and what a positive TST means is also necessary. At Montefiore, the New York Department of Health oversees TB treatment for latent and active TB. TB patients receive a palm card listing their CD4 cell count and viral load along with their TST and TB treatment history. Nurses explain TST results and the TB disease process. They stress "the importance of staying on HIV treatment and other medications, maintaining regular clinic visits, being aware of any TB exposure or symptoms, and seeking health care for pulmonary issues after finishing TB treatment. Patients also receive written information about TB care," says Schrager.

Collaborating With Partners

Partnerships with public health authorities are the cornerstone of establishing and maintaining successful TB control programs. The TB epidemic in New York City illustrates this point. In 1992, the city's TB epidemic peaked at 3,800 cases.[35] The epidemic was driven by several factors, primarily high rates of HIV, poverty, and homelessness along with drastic city, State, and Federal funding cuts, which left the city with an underfunded and poorly coordinated TB control program. At the time, DOT reached less than 2 percent of TB patients, and cure rates ranged from under 15 percent to only 50 percent.[36]

As a result of collaboration between city and State health departments, Medicaid, the Ryan White HIV/AIDS Program, and an influx of funding, the epidemic was stemmed, allowing New York City Health Commissioner Margaret Hamburg and colleagues to institute an innovative, aggressive response to get it under control. Outreach workers delivered TB medications to patients, thereby increasing treatment completion rates from 50 percent in 1989 to 90 percent in 1994.

At the same time, infection control procedures and isolation facilities[37] reduced TB infections in hospitals, shelters, and correctional facilities. By 2007, New York City reported just 914 TB cases—the lowest rate since reporting began in 1897—and fewer than 10 cases of

MDR–TB.[38] The city's Bureau of Tuberculosis Control continues to offer a range of services to medical providers, hospitals, community-based organizations, shelters, and social service agencies working together to treat TB.

Effective partnerships, however, do not always have to be so far reaching. Sometimes success can be found by reaching out to an organization right down the road. In Tarrant County, Drewyer worked out a deal with a local homeless shelter. The shelter received money for each person who got a chest x-ray, additional funds for each diagnosed TB case, and even more money for each treated TB case. The shelter used the funds to purchase HEPA filters and ultraviolet lights to kill TB bacteria. Drewyer says, "We weren't finding people [with TB] until they wound up in the emergency room. Our TB incidence was 77 percent higher in shelters than the rest of the community until we began our program. We developed a questionnaire about housing status, TB testing history, and TB signs and symptoms. For homeless people, we gave them a photo identification that was scanned at shelters. We identified 42 cases in the first year."

Continued Challenges

Despite these measures, some patients fall through the cracks. Montefiore's return rate is about 60 percent. "Our homeless and drug-using patients are at risk: They are more susceptible to TB and less likely to get messages, less likely to follow up, and less likely to stay in care. HIV patients who are not here legally get scared if they are TST positive, because we report cases to the New York Department of Health," says Schrager. Recognizing the barriers to health care for immigrants in New York, Alan D. Aviles, president of the New York City Health and Hospitals Corporation, and Guillermo Linares, immigrant affairs commissioner, launched a campaign in 2006 to assure immigrants that their immigration status is not listed or shared with government authorities.

CONCLUSION

Because TB is a serious and common comorbidity among PLWHA, many Ryan White HIV/AIDS Program providers have developed programs to promptly detect, prevent, and treat TB. Much more work remains to be done to increase education among consumers—and providers—about TB's continued threat. Strong patient-provider relationships, along with the development of efficient tracking systems for ensuring that patients return to have their TSTs read and the incorporation of DOT and other adherence strategies can ensure that TB rates continue to fall and early detection continues to rise.

TB is curable; results from ongoing studies will shed more light on optimal treatment for people coinfected with HIV and TB. Improved TB diagnostics are in development. Those innovations, combined with heightened awareness among frontline providers, will help decrease TB-related morbidity and mortality among PLWHA in the future.

ONLINE RESOURCES

HRSA AIDS Education and Training Center TB Resources
www.aidsetc.org/aidsetc?page=homesearch&post=1&SearchEntry=TB

TB Guidelines and Recommendations
www.cdcnpin.org/scripts/tb/cdc.asp
www.cdc.gov/tb/pubs/mmwr/Maj_guide/List_date.htm
www.nyc.gov/html/doh/downloads/pdf/tb/tb-protocol.pdf

TB Education and Training Resources
www.findtbresources.org/scripts/index.cfm

Treatment of Tuberculosis
www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf

Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV Infected Children
http://aidsinfo.nih.gov/contentfiles/Pediatric_OI.pdf

Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis, Centers for Disease Control and Prevention,
www.cdc.gov/tb/tb_hiv_drugs/default.htm

TB Program Evaluation Handbook
www.cdc.gov/tb/Program_Evaluation/TBEvaluationHandbook_tagged.pdf

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