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TBeat

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Directly Observed Therapy
A Short History and Overview

Tuberculosis is a disease that has been impacting the health of individuals, communities and nations throughout history. Long recognized as an infectious disease, early therapy was isolation and palliative care. With the advent of medications that could cure patients, management of the disease moved to include the goal of successful completion of drug therapy. This required patient cooperation; typically one third of patients on their own fail to follow their physician's advice and do not correctly follow or finish therapy. This has serious implications with TB disease where the well-being of the patient and public health interest overlap—lack of a cure means continued infectiousness and risk of exposure to others.

While inadequate treatment of tuberculosis has many causes (the most common two being improper or delayed diagnosis of disease and non-adherence to a prescribed drug regimen); the consequences are far-reaching and can include:

- Risk of transmission to others continues or increases
- Patient's risk of death increases greatly
- Risk of relapse increases
- Risk of acquired drug resistance increases
- Increased cost to eventually complete a "cure"

While research continues to seek improved diagnostic tools and new antituberculous medications, other efforts have centered on the role of patient adherence to enhance treatment outcomes. The most widely accepted single method to date is patient **D**irectly **O**bserved **T**herapy (DOT).

Brief History

Fox in a study in 1958 in Madras, India found supervised administration of therapy increased the cure rate of TB-infected patients. His daily drug regimen of injectable streptomycin and an oral dose of pyrazinamide was manageable even in a developing country. In the 1960s he developed intermittent regimens that further enhanced patient adherence to the supervised treatments.[1]

In the 1950-60s in Hong Kong, Moodie noted ambulatory care clinics with direct supervision of TB medications resulted in a 70% completion rate. He found that the clinics were successful because they were convenient for the patient NOT the staff![1,2]

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In the 1960s, Chile experimented with "tratamiento supervisado" through their National Health Service. TB patients were treated in a public health clinic under direct supervision; they were also given food, social services and could even meet with a psychologist. The system worked very well on a regional level. With the acceptance of a short intermittent course of isoniazid and rifampin to treat new cases of tuberculosis, in 1984 the Chilean government implemented directly observed therapy short course (DOTS) throughout their country.[3]

The problems associated with patient nonadherence to therapy was not isolated to under-developed countries. In the 1960s, Stradling and Poole in London had doubts about the efficacy of self medication for their TB patients. The need for daily injections reduced their completion rate to 51%; they argued for intermittent therapy. When that became possible, they included the direct supervision of medications and their outcomes improved.[1]

Early TB treatment protocols in the United States focused on identifying factors in patients that would predict their behavior and favorable treatment outcomes. In 1968, Sbarbaro at National Jewish Hospital in Denver started supervised direct treatment for "uncooperative patients;" it quickly expanded to 75% of his TB patients, many who were "unreliable patients that self-administrated their treatment incorrectly or inadequately." At that point, Sbarbaro embraced supervised treatment for all his patients and began a long campaign to try to change the accepted US standard of self-administration to directly observed therapy (DOT) of TB medications.[1]

Despite encouraging results from DOT in some health departments in the US (Mississippi state; Baltimore; Tarrant County, Texas), many were reluctant to embrace the practice because they felt it imposed on the patient (except in extreme cases of public health threat) or the cost to implement the policy was prohibitive. It wasn't until the early 1990s when tuberculosis re-emerged with the HIV epidemic as a serious public health threat that the focus turned to ways to counter the spread of TB and stop drug resistance. New York City led the way with TB cases and implementation of DOT—in the space of two years they went from 137 people on DOT to 1282 and their TB rate declined for the first time in 15 years.[1]

In 1993, the Advisory Council for the Elimination of Tuberculosis (ACET) added DOT to the federal policy of standard of care for TB treatment. It stipulated that any localities that had less than a 90% treatment completion rate must incorporate universal DOT. The Center for Disease Control (CDC) further strengthened DOT as a standard of care by including it in their cooperative agreement applications from state and local health departments.

Pros and Cons of Directly Observed Therapy

After the 1993 ACET and CDC mandate, Directly Observed Therapy (DOT) for tuberculosis quickly became the recommended standard of care in the US. Opponents have countered with the imposition the strategy has on the civil liberties of the patient and the stigma

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Pros and Cons of Directly Observed Therapy *continued from page 2*

is brings. Adoption of a universal DOT policy would and does negate this criticism. All TB patients have their medications administered by DOT; this is viewed as a positive policy not a punitive measure.

A more valid objection has been the cost to implement and deliver DOT. A study in 1997 by Burman, et al compared the cost and effectiveness of DOT and self-administered therapy (SAT). The direct costs of initial therapy with DOT and SAT were close ($1,206 vs. $1,221 per patient, respectively). When you included patient time costs, then DOT was higher. But, when the costs of relapse and failure were factored in, then DOT was less costly than SAT irrespective of outpatient or inpatient costs. [4]

Several studies in the US have looked at the success of DOT in improving the completion rate versus an array of other drug administration strategies. A 1998 paper by Bayer, et al looked at TB cases from 1990-1994 in US cities that had more than 100 TB cases per year. Their general conclusions were universal DOT did improve completion rates when it was carefully implemented in departments that had low completion rates to start with, but departments that already had good rates – DOT did not significantly increase their completion rates. [5]

A report in the MMWR, dated 3/23/2001, found the treatment success (bacteriologic cure and treatment completion) with DOTS was 88% for new TB patients, 60% for retreated TB patients and 97% for prisoners in the Orel region of Russia. No data was given as to what the cure rate was prior to the new policy, but the authors did conclude that DOTS would be a useful tool to help control the re-emergence and spread of TB in Russia. [6]

Jasmer, et al in 2004 compared treatment outcomes among all culture-positive patients treated for active pulmonary TB in San Francisco County, California. Patients treated by DOT had a higher cure rate than the SAT patients (97.8% vs. 88.6%) and decreased TB-related morbidity (0% vs. 5.5%). They also concluded that 44% of the SAT had risk factors for non-adherence and were assigned to the wrong group. The authors recommended DOT from the start of therapy for all at-risk patients. [7] Other authors argue that selective DOT is problematic because predicting adherence in patients is too complex and the resulting errors lead to relapses, treatment failures, acquired drug resistance and transmission to others. [8]

While most studies have shown TB cure rate improvements with DOT, some have not and this has stirred a debate in the interna-tional forum. Three carefully controlled, randomized clinical trials of DOT were done in Pakistan, Thailand and South Africa. These studies showed little or no improvement in the TB cure rate for DOT as compared to SAT at home. [11] But these studies did not include any corrective responses to non-adherence such as enablers or incentives which are associated with high rates of successful treatment completions in the US. [8]

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DOT in the US and the Heartland Region

All data comes from the CDC's 2005 Surveillance Report found at http://www.cdc.gov/tb/surv/default.htm.

Table 1 **Tuberculosis Cases and Case Rates per 100,100 Population: Heartland National TB Region, 2005 and 2004**

	Cases		Case Rates		Rank According to State		Population Estimates
State	2005	2004	2005	2004	2005	2004	July 1, 2005
United States	**14,097**	**14,515**	**4.8**	**4.9**	**-**	**-**	**296,410,404**
Arizona	281	272	4.7	4.7	14	14	5,939,292
Illinois	596	568	4.7	4.5	16	18	12,763,371
Iowa	55	47	1.9	1.6	40	42	2,966,334
Kansas	60	62	2.2	2.3	34	33	2,744,687
Minnesota	199	199	3.9	3.9	23	25	5,132,799
Missouri	108	127	1.9	2.2	39	36	5,800,310
Nebraska	35	39	2	2.2	38	34	1,758,787
New Mexico	39	42	2	2.2	37	35	1,928,384
North Dakota	6	4	0.9	0.6	48	50	636,677
Oklahoma	144	178	4.1	5.1	22	12	3,547,884
South Dakota	16	11	2.1	1.4	36	45	775,933
Texas	1,535	1,683	6.7	7.5	4	3	22,859,968
Wisconsin	78	95	1.4	1.7	43	40	5,536,201
Total for Region	**3152**	**3327**	**-**	**-**	**-**	**-**	**72,390,627**

Table 2 **Percentages of TB cases by Initial Drug Regimen, Use of Directly Observed Therapy (DOT), and Completion of Therapy (COT): United States: 1993 compared to 2003** (updated March 29, 2006)

	Initial Drug Regimen[1,2]				Directly Observed Therapy[3]		Therapy ≤1 year indicated[4]	
Year	IR	IRZ	IRZ,E/S	IRZE	DOT Only	Both DOT and SAT	COT ≤1 year	COT
1993	13	31.2	40.9	40.4	21.7	14.4	64.1	87.5
2003	1.4	8.1	81.5	81.4	56.6	28.4	81.5	92.2

[1]Includes persons alive at diagnosis.
[2]I=Isoniazid, R=Rifampin, Z=Pyrazinamide, E=Ethambutol, S=Streptomycin. Excludes cases with no information on initial drug regimen; 1% received no initial drug therapy, less than 1% were started on one drug, and approximately 9% had an initial multidrug regimen other than IR, IRZ, or IRZ,E/S.
[3] Includes persons alive at diagnosis with initial drug regimen of one or more drugs prescribed.
[4] Includes persons alive at diagnosis with initial drug regimen of one or more drugs prescribed who did not die during therapy. Excludes person with initial isolate resistant to rifampin and pediatric (aged <15) cases with meningeal, bone or joint, or miliary disease.

The VISION of the Heartland is to provide *excellence*, *expertise*, and *innovation* in training, medical consultation, and product development to reduce the impact of tuberculosis in our region.

DOT in the US and the Heartland Region *continued from page 4*

Table 3 **Tuberculosis Cases and Percentages by Directly Observed Therapy (DOT): Heartland National TB Center Reporting Areas 2003[1]**

State	Total cases	Cases with Initial Drug Regimen Prescribed[2]	Cases with Information on Directly Observed Therapy		Percentage of Cases by Directly Observed Therapy[3]	
			#	%	DOT Only	Both DOT and SAT[4]
United States	**14,840**	**14,382**	**14,155**	**98**	**57**	**28**
Arizona	295	283	263	92.9	79.5	8.7
Illinois	632	608	607	99.8	54.2	21.1
Iowa	40	38	38	100	65.8	28.9
Kansas	75	70	69	98.6	92.8	4.3
Minnesota	214	212	210	99.1	82.4	11.4
Missouri	130	123	122	99.2	42.6	43.4
Nebraska	28	27	27	100	59.3	3.7
New Mexico	49	47	47	100	80.9	17
North Dakota	6	5	5	100	60	0
Oklahoma	163	155	155	100	99.4	0
South Dakota	20	19	19	100	73.7	5.3
Texas	1580	1524	1439	94.4	69.6	26.5
Wisconsin	66	63	63	100	36.5	33.3
Total for Region	**3298**	**3174**	**3064**	**96.5**	**-**	**-**

[1]Most recent year for which data are available.
[2]Includes persons alive at diagnosis with initial drug regimen of one or more drugs prescribed.
[3] Percentage for United States based on 52 reporting areas (50 states, New York City, and the District of Columbia). Percentages shown only for reporting areas with information reported for ≥75% of cases.
[4] Self Administered Therapy

Components of Directly Observed Therapy

Directly Observed therapy (DOT) for tuberculosis is the delivery of every scheduled dose of TB medication by a health care worker. The health care worker directly administers the patient's ingestion or injection of the TB medication. The CDC recommends that all patients should be considered for DOT because it is difficult to reliably predict which patients will be adherent. There are groups of patients for who DOT typically is **required:**[10,11]

- Persistently positive test results
- History of criminal incarceration
- History of previous TB disease
- History of refusal of medical care
- Physiological resistance to one or more TB drugs
- Homelessness
- HIV co-infection
- History of non-adherence to drug therapies
- Psychiatric disorder
- Drug abuse or misuse
- Cognitive dysfunction

And then there are patients for who DOT is **highly recommended:**[10,11]

- Congregate living scenarios
- Elderly with cognitive impairment
- High risk contacts living in household
- Patients who seem to have difficulty in understanding their TB diagnosis
- Children and adolescents
- Recently immigrated individuals
- Patients receiving intermittent therapy

Often, barriers exist that can impact a patient's ability to be adherent to the recommended regimen even with DOT. Often overlooked is the need for social support in facilitating access and adherence; some barriers can be minimized through the use of incentives (small rewards that encourage or motivate) or enablers (free transportation, reminder calls, social services, food to minimize medication side effects). Additionally, every effort should be made to accommodate DOT to the patient's schedule.

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Components of Directly Observed Therapy *continued from page 5*

More and more TB programs are using DOT to administer treatment for latent TB infections (LTBI). That is because this group has low completion rates; completing treatment for LTBI can reduce the risk of TB disease by 90%. It is recommended that if program resources are low, DOT for TB disease has priority over LTBI DOT. [10,11]

World Wide Use

In the early 1990s, the World Health organization embraced directly observed therapy and added the component of a shortened course (DOTS)—isoniazid, rifampin, pyrazinamide and ethambutol for 2 months followed by isoniazid and rifampin for 4 months. Countries that have applied the strategy have seen remarkable results: [12]

- Peru saw an 8% drop in TB transmissions and successful treatment of 91% of TB cases
- China averted 30,000 TB deaths per year and has cure rates among new cases of 96%
- Cure rates of up to 95% even in poorest countries
- 8 out of 10 patients treated in DOTS programs in 1997 were reported successfully treated compared with less than 4 out of 10 in non-DOTS programs

There are five components of DOTS as described by the World Health Organization (WHO). They are:

- Political commitment and resources to control tuberculosis – this component must be the strongest link in the chain
- Diagnosis of cases based on sputum microscopy – accurate diagnosis is first step in early detection of active TB infection
- Standardized treatment with short course chemotherapy and directly observed treatment during at least the initial phase of treatment
- Regular drug supply to ensure uninterrupted treatment of patients
- Monitoring programs using standard recording and reporting system that includes reports of treatment outcomes – also acts as an early warning for emerging disease trends (MDR or XDR)

In 1998, to combat the emergence of multidrug resistant TB (MDR-TB), the WHO and several of its partner organizations came up with a modified DOTS program - DOTS-Plus. It works as a supplement to the standard DOTS program already in place. It ensures that 2nd line TB drugs are stored and dispensed at specialized health centers with appropriate facilities and well trained staff. The staff must adhere tightly to the WHO recommendations in order to minimize the risk of creating drug resistance to the 2nd line drugs.

Footnotes

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Continued on page 7

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[9]Garner, P. and Volmink, J. "Directly Observed Treatment for Tuberculosis." British Journal of Medicine, October 11, 2003, volume 327, p. 823-824.

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[11] Centers for Disease Control and Prevention, Division of Tuberculosis Elimination. "Patient Adherence to Tuberculosis Treatment; Self-Study Module, 1999." p. 40-41.

[12] Joint Effort to Eradicate Tuberculosis: An Initiative in India by Sandoz Business Unit. "TB & DOTS" 2004. http://www.ourjeet.com/general1/tb_dots.asp

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Introducing—Heartland Training Schedule for 2007

Heartland National TB Center has developed its training schedule for 2007. With the publication of the new *CDC Contact Investigation* guidelines in 2005, many health departments have begun updating their policies based on the new recommendations. Heartland has put together an interactive, skill-building course that highlights the changes and teaches the new recommendations as well as interviewing and cultural competency. There are several trainings scheduled around the Heartland region; public health workers who are directly involved in TB contact investigations or setting policy for such investigations are encouraged to attend one of Heartland's Contact Investigation courses.

Additionally, Heartland will hold three TB Intensive courses in 2007. Summer and winter classes are scheduled for the University of Texas at Tyler Health Center. A new course is being offered in the fall in Chicago. The training is designed for the advanced medical practitioner who deals with TB patients on a regular basis. The class utilizes leading TB experts in such areas as pediatrics, radiology, HIV and TB co-infections, laboratory diagnosis including new methodologies, and TB treatment choices and patient monitoring.

A complete listing of all Heartland trainings offered for 2007 can be found on Page 9. Proposed topics are subject to change; please check the Heartland website for up-to-date offerings and to register on-line. Priority is given to Heartland regional partners; classes have enrollment caps so early registration is recommended.

Heartland 2007 Training Calendar is located on page 9

TB*it*

Briefs from the CDC's MMWR, March 22, 2007

Trends in Tuberculosis Incidence – United States, 2006

A CDC analysis of national tuberculosis (TB) surveillance data shows slowing progress in the efforts to eliminate TB in the U.S. In 2006, the national TB rate fell to an all-time low of 4.6 cases per 100,000 people, with a total of 13,767 active cases. However, the decline in the TB rate in 2006 (3.2 percent) was one of the smallest in more than a decade. TB continues to disproportionately affect minorities and foreign-born individuals. Compared with whites, Asians were 21 times more likely to have TB in 2006, and blacks and Hispanics were approximately 8 times more likely. Foreign-born individuals accounted for more than half of all TB cases and had a rate nearly 10 times higher than U.S.-born individuals (21.9 vs. 2.3 cases per 100,000). Among TB cases with a reported HIV test result, 12.4 percent were infected with HIV, a major risk for TB disease. However, almost a third of TB cases did not have a documented HIV test result, underscoring the need for increased HIV testing and improved reporting to ensure that all patients with TB are routinely screened for HIV. The proportion of TB cases that were multi-drug resistant (MDR) remained stable from 2004 to 2005, and accounted for 1.2 percent of cases for which these data are available. Drug-resistant cases are more costly and difficult to treat, and can be fatal. The authors note multiple steps will be needed to accelerate progress and guard against a resurgence of TB in the U.S.

For the complete article, go to http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5611a2.htm

Extensively Drug-Resistant Tuberculosis – United States, 1993-2003

Analysis finds 49 documented cases of extensively drug-resistant (XDR) tuberculosis (TB) in the United States between 1993 to 2006. While the risk of XDR-TB remains relatively low in the U.S., cases have been widely dispersed geographically and pose a continued risk to efforts to treat and control TB. XDR TB is resistant to at least the first-line anti-TB drugs isoniazid and rifampin, as well as any fluoroquinolone and at least one of three second-line injectable TB drugs. CDC researchers compared XDR TB cases during two periods: 1993-99 and 2000-06. As a proportion of MDR TB cases, XDR TB remained stable at roughly 3 percent during the two time periods analyzed. The composition of cases shifted, with the proportion of XDR TB cases that were foreign-born increasing from 39 percent to 76 percent, reflecting the disproportionate impact of TB on this population. Additionally, while HIV status was unknown for many cases, the proportion of XDR TB cases that were HIV-infected declined from 73 percent to 20 percent, likely reflecting improved HIV and TB treatment. Because drug-susceptibility results are incomplete, these data underestimate U.S. XDR TB cases. Recognizing the ease with which XDR TB can spread, the authors stress the need for renewed vigilance in resistance testing, reporting, treatment, contact investigation, and expanded outbreak detection and response capacity.

For the complete article, go to http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5611a3.htm

Upcoming Trainings

Heartland National TB Center—2007 dates

Date	Course	Location
April 25-26	Contact Investigation	St. Paul, Minnesota
May 17-18	Contact Investigation	Norman, Oklahoma
May 21-23	Contact Investigation	Chicago, Illinois
June 5-8	TB Intensive	Tyler, Texas
July 17-19	Contact Investigation	San Antonio, Texas
August 29-31	Responding to a TB Event	Wichita, Kansas
September 11-13	Contact Investigation	Arizona
September 25-27	TB Intensive	Chicago, Illinois
September 26-27	TB Update (Midwest TB Controllers)	Chicago, Illinois
October	TB Update (4-Corners TB Controllers)	Colorado
November 6-9	Hospital Infection Control	San Antonio, Texas
December 4-7	TB Intensive	Tyler, Texas

Please go to http://www.heartlandntbc.org/training.asp#regional for contact and registration information for each course. Proposed topics are subject to change; check website for the latest updates.

Case Presentation

Failure to Convert: Non Adherence to Treatment

Case History:

A 67 year old Hispanic male was diagnosed with drug susceptible pulmonary tuberculosis in September 2005. He presented with a three week history of night sweats, weight loss, nausea, shortness of breath and a productive cough. A chest x-ray (CXR) showed extensive bilateral cavitary disease. He was Hepatitis C positive with elevated baseline liver enzymes; HIV testing was negative. Sputum smears were AFB positive with greater than 10 organisms per high powered field. The patient's weight at diagnosis was 96 lbs.

The patient's past history included heroin addiction (stopped in 1997), cigarette and alcohol use. He was hospitalized in 1983 with a bullet wound which resulted in a nephrectomy and a colostomy. The colostomy was reanastomosed at a later date.

On September 30, 2005, the patient was started on standard four drug therapy with isoniazid (INH) 300 mg, rifampin (RIF) 600 mg, pyrazinamide (PZA) 1500 mg and ethambutol (EMB) 1200 mg with Vitamin B6 50 mg. He continued on daily directly observed therapy (DOT) until October 16, 2005 when the EMB was dropped after his isolate was reported to be susceptible to all first line drugs and the remaining three drugs were changed to twice weekly by DOT. After 2 months of therapy (December 16, 2005), the PZA was discontinued. The patient was felt to be compliant with his medication and tolerated the drug regimen. He improved clinically with resolution of his fever, sweats and chills. His appetite and energy improved. His cough decreased and he gained 14 pounds.

His sputum smears converted to negative in late January 2006. He had two negative cultures but his sputum specimen of February 27th (after 4 ½ months of treatment) grew *Mycobacterium tuberculosis.* Later a susceptibility study showed the isolate to be sensitive to all drugs. A CXR March 23, 2006 revealed continuing cavitary changes in the right upper lobe although smaller in size than on radiographs at the time of diagnosis. A CT scan noted cavitation in the upper lobes—right greater than left with the largest cavity in the right upper lobe measuring 3.2 cm. Scatter nodules were seen throughout the bilateral lobes, lingual and right middle lobe. Although the patient had a good clinical response to anti-tuberculous therapy, he showed a limited radiographic response and bacteriologically he remained positive. He was considered a treatment failure and sent to the Texas Center for Infectious Disease (TCID).

AT TCID, the patient was continued on INH and RIF; EMB (800 mg) was restarted along with Amikacin (600 mg twice weekly injection) and Levofloxacin (750 mg daily) along with Vitamin B6 50 mg daily. This fortified drug regimen was continued until he had 3 negative 6-week cultures. With the repeat negative cultures, Amikacin, Levofloxacin and EMB were dropped and the INH and RIF were changed to twice weekly The patient admitted to the nursing staff that he had not actually taken the RIF during the time DOT was provided in the community. He noted that he would "cheek" the pill and spit it out later.

In June of 2006, the patient was discharged to DOT. He has since successfully completed DOT.

Teaching Points:

- Directly Observed Therapy (DOT) is when a healthcare worker watches the patient swallow each dose of the prescribed anti-tuberculosis drugs. It should be considered for all patients because there is no reliable method to predict patient adherence to therapy.
- In addition to ensuring compliance, an important component of DOT is ongoing assessment for drug related toxicity and education. Patient education about the medications prescribed for TB and their side effects should be clearly communicated to the patient. They should have a good understanding of what to expect; it is preferable to have them verbalize to you what side effects they should look for. At follow-up visits, open-ended questions should be used to assess for side effects. A question such as the following may give important information about the patient's recognition of a common side effect of rifampin as well as an indication of drug ingestion, i.e. "Are your sweat, tears and urine orange?" If the patient is on RIF, a negative answer might indicate they are not taking their medication.
- The health care provider should carefully evaluate the patient to determine if they have swallowed the dose. Asking the patient to drink a liquid beverage or to talk with the health care provider for

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Case Presentation, Teaching Points *continued from page 10*

several minutes following the DOT dose may help to avoid "surreptitious non-compliance." With some patients it is necessary to inspect the oral cavity including along the cheeks after a DOT dose. Adults and children as young as 9 years have been reported to exhibit cheeking and other behaviors to circumvent a DOT dose being ingested. It is helpful to ensure that the patient does not subsequently vomit or induce vomiting.

- If concerns about DOT exist, extra caution is needed to detect unusual ways a patient might avoid taking a DOT dose.
- DOT insures patient adherence which serves to prevent relapses and drug resistance.
- The duration of therapy is the actual number of doses a patient receives, NOT the length of therapy. Accurate record-keeping and continued assessment of the patient will allow interventions/changes, if needed, to occur quickly and insures adherence so therapy can be successfully completed.
- If DOT is not possible, then it is recommended to use pills that are a combination of drugs so the patient cannot decline a single drug. The 2 most common "pill" combinations can be given in multiples to achieve the proper dosage:
    - *Rifimate* = Isoniazid (INH) 150 mg + Rifampin (RIF) 300 mg
    - *Rifater* = INH 50 mg + RIF 120 mg + pyrazinamide (PZA) 300 mg
- **The failure to convert sputum cultures (positive to negative**) after 2 months of appropriate, monitored therapy is considered a delayed response. Failure to convert cultures to negative after four months of therapy is defined as treatment failure. Patients who have a delayed response should be carefully assessed. The following is recommended:
    1. Obtain repeat drug susceptibilities on the patient's last positive isolate; this checks for acquired drug resistance. Commonly, the initial culture isolate from the patient is tested against all the first line anti-tuberculosis drugs to insure that the isolate is not drug resistant; if it shows resistance to more or more drugs then the drug regimen is changed.
    2. Obtain an accurate DOT history and re-evaluate for any evidence of non-compliance. Our patient likely experienced treatment failure because after a good initial response, he no longer wanted to take medication. Inadequate or incorrect medication can cause treatment failure and can lead to acquired drug resistance.
    3. Obtain drug serum levels. Adequate blood levels of anti-tuberculosis drugs are necessary. Low serum drug levels can be associated with a delayed, response, treatment failure, relapse, or acquired drug resistance.
- Serum drug levels check to see if therapeutic levels of the anti-tuberculosis drugs are present in the patient's blood. Blood is usually collected 2 hours after ingestion of the drug. Low serum levels can be a result of impaired absorption or accelerated metabolism of TB drugs. For INH and RIF, it is possible to increase the dose of the given drug to reach therapeutic levels taking caution to carefully assess for side effects. The therapeutic levels of the common TB drugs levels are shown below:

Therapeutic Levels for Some Common Anti-Tuberculosis Medications

Medication	Number of Hours Following Dose	Dose	Therapeutic Level
Isoniazid	2 hours (if the sample was drawn at 2 hours post dose, and the concentration is within 1 ug/mL of the daily range or within 3 ug/mL of the 2x weekly range, no dosage change is needed)	Daily 2x weekly	3-6 mcg/mL 9-15 mcg/mL
Rifampin	2 hours	600 mg	8-24 mcg/mL
Ethambutol	2-3 hours	15-25 mg/kg (daily) 50 mg/kg (2x weekly)	2-6 mcg/mL 8-12 ug/mL

From: Schlossberg, D, editor. Tuberculosis and Nontuberculous Mycobacterial Infections, fifth edition. McGraw-Hill, Medical Publishing Division. 2006. p. 87.

Note: Patients that have stomach or small intestine resections; malabsorption syndromes; chronic or recurring diarrhea should have their serum drug levels monitored periodically and closely to insure adequate treatment of their TB.

References *on page 12*

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References

Centers for Disease Control and Prevention, Division of Tuberculosis Elimination. "Treatment of LTBI: Maximizing Adherence, updated May 2005: Fact Sheet." http://www.cdc.gov/tb/pubs/tbfactsheets/LTBIadherence.htm

Centers for Disease Control and Prevention, Division of Tuberculosis Elimination. "Patient Adherence to Tuberculosis Treatment; Self-Study Module, 1999." p.40-41.

Khan, A. E. and Kimerling, M. E. "Chemotherapy of Tuberculosis" in Tuberculosis and Nontuberculous Mycobacterial Infections, fifth edition. Schlossberg, D, editor. McGraw-Hill, Medical Publishing Division. 2006. p. 77-90.

Related Links

The Centers for Disease Control and Prevention (CDC) Division of Tuberculosis Elimination (DTBE) will be updating the URLs (webpage addresses) on the DTBE website (http://www.cdc.gov/tb). Specifically, "NCHSTP" will be removed, and long, cumbersome URLs will be shortened. DTBE plans to make the transition on April 18, 2007.

Example for Questions and Answers About TB webpage
Old URL: http://www.cdc.gov/nchstp/tb/faqs/ New URL: http://www.cdc.gov/tb/faqs/

What about all the materials that advertise the old URLs?

Not to worry. Redirects — webpage that directs users to another webpage — to the new URLs (webpages) will be posted on old webpage URLs. DTBE will monitor usage of the old webpage URLs and, as usage decreases, the specific webpage redirects will be replaced with a general redirect to the DTBE homepage. Once usage drops to zero, the redirect will be removed from the DTBE website.

New bookmark: Division of TB Elimination, CDC

Regional News

TB Training and Patient Educational Resources

1. ***Forging Partnerships to Eliminate Tuberculosis: A Guide and Toolkit*** has been posted on the CDC Division of Tuberculosis Elimination website and is available on the homepage (www.cdc.gov/tb) or directly at http://www.cdc.gov/tb/pubs/forge/default.htm. The print version should be available within the next few months.

2. ***TB Notes Newsletter—****download at http://www.cdc.gov/tb/notes/TBN_1_07/tbn107.pdf* No. 1, 2007 (PDF - 201K)

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In the Works

Heartland has developed several TB training materials. In addition to the algorithms below, other products have been updated and are now located on the Heartland website in PDF format available for printing or downloading.

NEW—available by email request only (send requests to natalie.hamilton@uthct.edu):

TB at a Glance

This is a spiral bound pocket guide for clinicians that provides basic information on the diagnosis, treatment and management of latent tuberculosis infection and tuberculosis disease.

TB Core Reference Set for Clinicians (CD-ROM)

This CD-ROM provides an array of documents and resources with the latest information on tuberculosis. These resources will assist the clinician in making the appropriate diagnosis and treatment plan for adults and children based on guidelines from the Center for Disease Control and Preventions (CDC), American Academy of Pediatrics, American Thoracic Society, Francis J. Curry National TB Center and Infectious Diseases Society of America.

Client/Patient Management Algorithms and Short Clinical Guides

- Assessing and Managing the Risk of Liver Disease in the Treatment of LTBI (PDF ~ 266 KB)
- Characteristics of Second-Line Drugs for MTB (PDF ~ 44 KB)
- Evaluation of Pregnant Patient at Risk for TB (PDF ~ 250 KB)
- Management of the TB Patient at Risk of Hepatotoxicity (PDF ~ 269 KB)
- MDR TB Care Plan (PDF ~ 48 KB)
- Revised Tuberculosis Treatment Guidelines-2003 (Poster) (PDF ~ 51 KB)
- Tuberculosis Adverse Drug Events (PDF ~ 54 KB)
- Tuberculosis Medication Drug and Food Interactions (PDF ~ 50 KB)
- Tuberculosis Treatment Guidelines-2003 (PDF ~ 110 KB)

QuantiFERON®-TB Gold Webinar Presentations

- CDC Guidelines for Use of QuantiFERON®-TB Gold Test (PDF ~ 80 KB)
- QuantiFERON®-TB Gold Test: A 100 Year Update for the Diagnosis of Tuberculosis Infection (PDF ~ 182 KB)
- QuantiFERON®-TB Gold: Practical Applications (PDF ~ 190 KB)

We are always striving to improve our products and provide innovative, useful training tools for our partners. To that end, please send comments, questions or suggestions for future products to:

Anne Williamson, Director of Education and Training
anne.williamson@uthct.edu
210-531-4590

Please check out the other RTMCCs product lines. They can be found at:

- Francis J. Curry National TB Center, products
- New Jersey Medical School Global TB Institute, products

The MISSION of Heartland National TB Center is to build capacity with our partners. We will share expertise in the treatment and prevention of tuberculosis by: developing and implementing cutting-edge trainings, delivering expert medical consultation, providing technical assistance, and designing innovative educational and consultative products.