



TB IN AIDS PATIENTS

by Charles Peloquin, Pharm.D.

The incidence of tuberculosis has been, distressingly, on the rise in recent years, and this surge poses a particular threat to AIDS patients.

Patients with AIDS face a triple whammy when it comes to tuberculosis. First, immunosuppression increases their susceptibility to developing an active tuberculosis infection, and makes them even more dependent on pharmacologic control than patients with relatively normal immune systems.

Second, the increased incidence of multidrug-resistant strains of the tuberculosis bacterium means that infections often do not respond to first-line drugs.

Tuberculosis treatment today must proceed with great care, avoiding regimens that are not only powerless to eradicate the infection but may even exacerbate its drug-resistant state.

Third, recent findings made at National Jewish have shown that at least some AIDS patients have a reduced capacity to absorb certain orally-administered drugs through their gastrointestinal tracts. This means that AIDS patients who receive standard doses of anti-tuberculosis drugs may achieve suboptimal or useless serum concentrations of these agents.

Drug Malabsorption in AIDS Patients

Through the middle of last year, my associates and I had reviewed serum concentrations of antituberculosis drugs in multiple specimens drawn from 32 AIDS patients. We tested one to seven drugs in each patient; a median of 75% of the tested drugs produced below-normal serum concentrations and were apparently malabsorbed in each patient. Our study included 10 tuberculosis drugs, including the first-line drugs isoniazid, rifampin, and ethambutol, and seven second-line agents.

This observation did not come as a complete surprise because other evidence suggests that AIDS patients also have difficulties absorbing other drugs and certain vitamins. The way by which AIDS leads to this gastrointestinal malfunction is not clear.

Because we have only recently observed this phenomenon of malabsorption of tuberculosis drugs in AIDS patients, it is not yet clear how widespread the problem is or whether specific characteristics of AIDS can be used to identify patients who are most at risk. For example, there may be a correlation between the severity of a patient's immunosuppression and

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UPDATE

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the degree of malabsorption. Preliminary findings suggest that such a correlation exists. We are in the process of doing additional studies to more definitively address this and related issues.

In the meantime, the message for physicians is that an AIDS patient with tuberculosis who does not respond to treatment may not be absorbing the drugs properly, so that serum concentrations of the drugs may be inadequate. If an AIDS patient with tuberculosis appears unresponsive to a treatment regimen, assuming that the regimen was properly designed to take into account the possibility of infection with a multidrug-resistant strain of tuberculosis, the next step would be to consider directly measuring the serum concentrations of the drugs that the patient is taking.

Preliminary findings suggest there may be a correlation between the severity of an AIDS patient's immunosuppression and the degree of drug malabsorption.

For the time being, measurement of drug serum concentrations in unresponsive AIDS patients must be considered an option, not a standard of care. We cannot yet say whether malabsorption occurs in 5% or 50% of patients. If the frequency is 5%, assaying serum drug concentrations in most patients will not be reasonable in an era of cost

containment. If the frequency is 50%, however, then routine serum assays for administered drugs is probably a reasonable expense.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) involves the measurement of serum concentrations and adjusting the dose based on that information. Originally, antimycobacterial drug TDM was performed using bioassays in which serum specimens from patients were introduced onto growth plates inoculated with a test strain of bacteria or mycobacteria. Serum concentrations of a drug were identified by the specimen's ability to inhibit growth of the test culture. However, this method was slow, and was only able to screen patients who were given one drug at a time.

Today, TDM has been vastly improved by two modern laboratory techniques: high performance liquid chromatography and gas chromatography. Both methods allow us to measure drug concentrations in a serum specimen that contains several different drugs, and to get the results within a matter of hours.

Most oral antituberculosis drugs reach their peak serum concentrations 1-3 hours after being swallowed; two hours after ingestion is therefore a good compromise, a time when most drugs are near their maximum serum concentration in most patients.

Based on this, a patient undergoing TDM would ideally report to the laboratory two hours after dosing to have a serum specimen taken. However, it is possible that an individual patient may absorb a normal amount of orally delivered drug, but do it more slowly than average. For this reason, a better determination of drug absorption would involve drawing two serum specimens, for example at two and six hours, or two and 10 hours. The more specimens collected, the better the analysis for an individual patient. Of course, the number of specimens drawn and tested must be balanced against the expense of each assay and the inconvenience of specimen collection.

What if a serum specimen cannot be drawn at two hours? Right now, that might present a problem, but my colleagues and I are collecting data that will eventually eliminate the need for a two hours specimen. We are recording serum concentrations from many patients at varying times after treatment for all of the standard antituberculosis drugs. Eventually, using a technique known as population modeling, we will be able to plot a curve for each drug that represents a pharmacokinetic model of that drug's mean serum concentration in patients at all times after administration. When these computerized models become available, a single specimen could be drawn at any time after dosing and still provide useful information. Two or more specimens would allow for a better description of a drug's pharmacokinetic behavior in each patient.

Once TDM is performed on a patient, the serum drug concentrations are assessed using the standard peak (two hour) concentrations, which ideally exceed the minimum inhibitory concentrations for that patients' *Mycobacterium tuberculosis* isolate. If a patient's drug concentration is significantly below the standard, and delayed absorption is ruled out, the physician has three options: use a higher dose, use a different route of delivery, or use a different drug.

For most patients, increasing the oral dose they receive would be the most reasonable initial strategy. Close monitoring of the patient is then essential to determine whether higher doses result in higher serum concentrations, and also to see whether the patient can safely tolerate a higher-than-normal dose.

Changing the route of drug delivery from oral to injected is another possibility; however, not many of the antituberculosis drugs can be given this way. Injected delivery is less convenient, and generally is 10-50 fold more expensive than oral treatment.

Drug Selection

The third option, changing the drugs that the patient receives, must be done with great care by someone who is experienced in tuberculosis treatment. Additional drug resistance may emerge if a single new drug is added to a failing regimen. Because very few drugs are effective against tuberculosis, a mistake made in treating such a patient can easily lead to a difficult situation.

Drug selection, and the exact combination of drugs used, is of particular importance when one or more second-tier antituberculosis drugs must be used. These agents have only marginal activity against tuberculosis, and they cause significant toxicities, so they must be selected and combined very carefully.

The increasing prevalence of multidrug-resistant tuberculosis means that a cautious and methodical approach to drug selection must begin as soon as a patient is presumptively diagnosed with the disease.

A patient is first suspected of having tuberculosis by characteristic symptoms such

as weight loss, cough, night sweats, and fever. Importantly, AIDS patients may not present with these characteristic symptoms. As many as 70% of AIDS patients, depending on the degree of immunosuppression, may present with extrapulmonary tuberculosis. The next diagnostic steps include a skin test, which determines whether the patient's immune system has been primed to recognize *M. tuberculosis*, and a chest x-ray. Finally, a sputum smear is examined microscopically to look for mycobacteria.

A patient who is positive by these criteria may be a candidate for empiric antituberculosis treatment until more definitive information is obtained by culturing a sputum specimen, a process that takes at least 2-3 weeks. If the patient is also positive for the human immunodeficiency virus, then empiric therapy is indicated. HIV-positive patients have been known to die while awaiting tuberculosis culture results. The

Centers for Disease Control recommends an initial regimen of at least four drugs: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. Empiric therapy may also be employed if the patient is HIV-negative. If the patient is being retreated, an option is to place the patient in respiratory isolation and await susceptibility test results. This approach precludes the risk that the infecting strain will become resistant to additional drugs in a regimen that is structured incorrectly.

The purpose of culturing is two fold. It confirms that the infection is tuberculosis and not

HIV-positive patients have been known to die while awaiting tuberculosis culture results.

The Mycobacteriology Laboratory at National Jewish serves as a major national center for evaluating how well new drugs work against tuberculosis. The Pharmacokinetics Laboratory can then determine just how much of each drug is needed to treat the patient's specific strain of tuberculosis. It has the most complete array of tests in the world to reveal how much of the tuberculosis medications have reached a patient's bloodstream. This is the only lab in the US that determines serum concentrations for **all** TB drugs using HPLC and GC methods.

Dr. Peloquin is a consultant to the FDA and to the CDC for TB drug related issues. For lab information call 800-423-8891 x 1427 (Dr. Peloquin) or x 1925 (Dr. MacPhee).

another mycobacterium, and it allows for drug-susceptibility testing, the results of which will identify the drugs that are best suited to treating the patient's infection.

Selecting the drugs that make up a patient's empiric regimen will depend on whether the patient was previously treated for tuberculosis and what drugs had been used. If a patient who is failing therapy has already been treated with a particular drug, especially for weeks or months, it is likely the drug wasn't effective then and won't be effective now. Each time a patient is treated for tuberculosis the chance of a successful outcome diminishes.

At National Jewish, we prepare a "drug-o'-gram" for each patient who is starting antituberculosis treatment. This chart is a diary of each antituberculosis drug taken by a patient, and is a key step in the battle against an infection caused by a multidrug-resistant strain.

The first-line antituberculosis drugs are, of course, the best agents to use initially if the patient has no history of failed treatment with these agents. Isoniazid and rifampin are the most important drugs based on their relatively high potency and favorable side-effect profile. Pyrazinamide, ethambutol, and streptomycin are used with isoniazid and rifampin to shorten the duration of treatment or prevent the emergence of drug resistance. The first four of these drugs are administered orally; streptomycin is given by intramuscular or intravenous¹ injection.

If second-line drugs must be used, the general strategy is to mix and match these agents based on their perceived potency and toxicity. We try to distribute the toxicity profiles across a range of organ systems, rather than using two or more drugs that produce similar side effects.

Another principle is to use a mix of injected and oral drugs. This way, if the initial regimen fails, the patient is not left with a combination made up entirely of injected drugs.

¹ Intravenous injection of streptomycin in 100 ml of dextrose 5% water or normal saline over 30 minutes has been shown to be safe and effective, but has not yet been approved by the FDA.

National Jewish Center for Immunology and Respiratory Medicine Proposed "Normal Range" for Antimycobacterial Drugs

Drug	Usual Dose	Proposed 2 hr range (µg/ml)
Aminosalicylate (PAS) ^a	4000 mg	40-70
Ciprofloxacin	750-1000 mg	4-6
Clofazimine	100-200 mg	0.5-2
Cycloserine	250-500 mg	20-35
Ethambutol	15-25 mg/Kg	2-6
Ethionamide	250-500 mg	1-5
Isoniazid	300-450 mg	3-5
Ofloxacin	600-1000 mg	8-12
Pyrazinamide	1000-2000 mg	20-60
Rifampin	600-750 mg	8-24
Capreomycin and the Aminoglycosides (amikacin, kanamycin, streptomycin)		<u>C_{max}</u> ^b
(conventional ^c)	15 mg/Kg	35-45 or
(high dose ^d)	25 mg/Kg	65-80

^a Range applies to immediate release tablets. Range for PASER granules (Jacobus Pharmaceuticals, Princeton, NJ) is being established.

^b Back-calculated maximum concentration at the end of an intravenous infusion or 1 hour after an intramuscular injection, using 1 compartment model and ≥ 2 carefully timed post dose concentrations.

^c Conventional dose given 5 times weekly

^d High dose given 3 times weekly under experimental protocol

Adapted from Peloquin CA: Therapeutic drug monitoring: principles and applications in mycobacterial infections. Drug Therapy 22:31, 1992; with permission.

Treatment must also be tailored to the patient's lifestyle. Cycloserine, for example, tends to cause confusion and lethargy, and so would not be a good first choice for a patient who can continue to work. However, if the patient will be home convalescing this drug may be a good option.

A patient's initial, empiric regimen may require modification after a few weeks when the drug susceptibility results are available. But the value of susceptibility test results must also be assessed critically, particularly if the patient

underwent a previous round of tuberculosis treatment. The patient may harbor a subpopulation of drug-resistant *M. tuberculosis* that was not detected when the sputum specimen was originally tested.

If susceptibility testing shows that the patient's infection is resistant to a drug the patient is taking, a one-for-one drug substitution may be possible if the results are back within 2-3 weeks. However, if the results don't come back for 2-3 months, and the patient appears to be failing treatment, then it is inappropriate to add a single new drug to a failing regimen. In these cases the best approach is to add at least two new drugs, while withdrawing the agent that tests show is ineffective. In this situation it is vital to have a physician experienced in treating multidrug-resistant tuberculosis assist in selecting the patient's new drug regimen.

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