Treatment of Tube

American Thoracic Society, CDC, and Infectiou

Please note: *An erratum has been published for this article. To view the erratum, please click here.*

This Official Joint Statement of the American Thoracic Society, CDC, and the Infectious Diseases Society of America was a
2002. This report appeared in the *American Journal of Respiratory and Critical Care Medicine* (2003;167:603--62) and is be
America, and the *MMWR* readership.

Purpose

The recommendations in this document are intended to guide the treatment of tuberculosis in settings where mycobacterial c
available. In areas where these resources are not available, the recommendations provided by the World Health Organization
be followed.

What's New In This Document

- The responsibility for successful treatment is clearly assigned to the public health program or private provider, not t
- It is strongly recommended that the initial treatment strategy utilize patient-centered case management with an adhe
- Recommended treatment regimens are rated according to the strength of the evidence supporting their use. Where p
- Emphasis is placed on the importance of obtaining sputum cultures at the time of completion of the initial phase of t
- Extended treatment is recommended for patients with drug-susceptible pulmonary tuberculosis who have cavitation
  treatment is completed.
- The roles of rifabutin, rifapentine, and the fluoroquinolones are discussed and a regimen with rifapentine in a once-a
- Practical aspects of therapy, including drug administration, use of fixed-dose combination preparations, monitoring
- Treatment completion is defined by number of doses ingested, as well as the duration of treatment administration.
- Special treatment situations, including human immunodeficiency virus infection, tuberculosis in children, extrapuln
  and renal disease are discussed in detail.
- The management of tuberculosis caused by drug-resistant organisms is updated.
- These recommendations are compared with those of the WHO and the IUATLD and the DOTS strategy is describe
- The current status of research to improve treatment is reviewed.

Summary

Responsibility for Successful Treatment

The overall goals for treatment of tuberculosis are 1) to cure the individual patient, and 2) to minimize the transmission of *M*
benefits both for the individual patient and the community in which the patient resides. For this reason the prescribing physic
responsibility not only for prescribing an appropriate regimen but also for successful completion of therapy. Prescribing phys
However, given a clear understanding of roles and responsibilities, oversight of treatment may be shared between a public he

Organization and Supervision of Treatment

Treatment of patients with tuberculosis is most successful within a comprehensive framework that addresses both clinical an
be based on each patient's clinical and social circumstances (patient-centered care). Patients may be managed in the private s
responsible for ensuring that adequate, appropriate diagnostic and treatment services are available, and for monitoring the res
It is strongly recommended that patient-centered care be the initial management strategy, regardless of the source of supervis
therapy (DOT), in which patients are observed to ingest each dose of antituberculosis medications, to maximize the likelihoo
patient-centered approach to case management (enhanced DOT) have higher rates of treatment completion than less intensiv
that facilitate adherence to the drug regimen. Such measures may include, for example, social service support, treatment ince

coordination of tuberculosis services with those of other providers.

Recommended Treatment Regimens

The recommended treatment regimens are, in large part, based on evidence from clinical trials and are rated on the basis of a Diseases Society of America (IDSA). The rating system includes a letter (A, B, C, D, or E) that indicates the strength of the r supporting the recommendation (Table 1).

There are four recommended regimens for treating patients with tuberculosis caused by drug-susceptible organisms. Althoug specified circumstances, described subsequently. Each regimen has an initial phase of 2 months followed by a choice of seve together with the number of doses specified by the regimen are described in Table 2. The initial phases are denoted by a num number plus a letter designation (a, b, or c). Drug doses are shown in Tables 3, 4, and 5.

The general approach to treatment is summarized in Figure 1. Because of the relatively high proportion of adult patients with initial phase for the 6-month regimen to be maximally effective. Thus, in most circumstances, the treatment regimen for all a (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (Table 2, Regimens 1--3). If (when) drug susceptibility children whose visual acuity cannot be monitored, EMB is usually not recommended except when there is an increased likeli "adult-type" (upper lobe infiltration, cavity formation) tuberculosis. If PZA cannot be included in the initial phase of treatme consist of INH, RIF, and EMB given daily for 2 months (Regimen 4). Examples of circumstances in which PZA may be with initial phase of Regimen 4 until drug susceptibility is determined.

The initial phase may be given daily throughout (Regimens 1 and 4), daily for 2 weeks and then twice weekly for 6 weeks (R EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to IN suggests that EMB can be discontinued safely in less than 2 months (i.e., when susceptibility test results are known), but ther Although clinical trials have shown that the efficacy of streptomycin (SM) is approximately equal to that of EMB in the initi less useful. Thus, SM is not recommended as being interchangeable with EMB unless the organism is known to be susceptib

The continuation phase (Table 2) of treatment is given for either 4 or 7 months. The 4-month continuation phase should be u three groups: patients with cavitary pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture phase of treatment did not include PZA; and patients being treated with once weekly INH and rifapentine and whose sputum may be given daily (Regimens 1a and 4a), two times weekly by DOT (Regimens 1b, 2a, and 4b), or three times weekly by D noncavitary pulmonary tuberculosis (as determined by standard chest radiography), and negative sputum smears at completio once weekly for 4 months by DOT (Regimens 1c and 2b) (Figure 1). If the culture at completion of the initial phase of treatm months. All of the 6-month regimens, except the INH--rifapentine once weekly continuation phase for persons with HIV infe patients. The once-weekly continuation phase is contraindicated (Rating EI) in patients with HIV infection because of an una twice weekly treatment, either as part of the initial phase (Regimen 2) or continuation phase (Regimens 1b and 2a), is not rec receive either daily (initial phase) or three times weekly (continuation phase) treatment. Regimen 4 (and 4a/4b), a 9-month re

Deciding To Initiate Treatment

The decision to initiate combination antituberculosis chemotherapy should be based on epidemiologic information; clinical, p bacilli (AFB)--stained sputum (smears) (as well as other appropriately collected diagnostic specimens) and cultures for myco initial evaluation, but a negative PPD-tuberculin skin test does not exclude the diagnosis of active tuberculosis. However, a p tuberculosis, as well as latent tuberculosis infection in persons with stable abnormal chest radiographs consistent with inactiv If the suspicion of tuberculosis is high or the patient is seriously ill with a disorder, either pulmonary or extrapulmonary, that regimens should be initiated promptly, often before AFB smear results are known and usually before mycobacterial culture r diagnosis of tuberculosis. If the diagnosis is confirmed by isolation of *M. tuberculosis* or a positive nucleic acid amplificatio initial AFB smears and cultures are negative, a diagnosis other than tuberculosis should be considered and appropriate evalua (in this circumstance a reaction of 5 mm or greater induration is considered positive), empirical combination chemotherapy s therapy and no other diagnosis has been established, a diagnosis of culture-negative pulmonary tuberculosis can be made and of treatment, an adequate regimen for culture-negative pulmonary tuberculosis (Figure 2). If there is no clinical or radiograph tuberculosis considered.

If AFB smears are negative and suspicion for active tuberculosis is low, treatment can be deferred until the results of mycoba months) (Figure 2). In low-suspicion patients not initially being treated, if cultures are negative, the PPD-tuberculin skin test one of the three regimens recommended for the treatment of latent tuberculosis infection could be used. These include (*1*) IN PZA for a total of 2 months. Because of reports of an increased rate of hepatotoxicity with the RIF--PZA regimen, it should b monitored closely, and do not have contraindications to the use of this egimen.

Baseline and Follow-Up Evaluations

Patients suspected of having tuberculosis should have appropriate specimens collected for microscopic examination and myc obtained. Sputum induction with hypertonic saline may be necessary to obtain specimens and bronchoscopy (both performed produce sputum, depending on the clinical circumstances. Susceptibility testing for INH, RIF, and EMB should be performed susceptibility testing should be done only in reference laboratories and be limited to specimens from patients who have had p demonstrated resistance to rifampin or to other first-line drugs, or who have positive cultures after more than 3 months of tre

It is recommended that all patients with tuberculosis have counseling and testing for HIV infection, at least by the time treatr
be obtained. Patients with risk factors for hepatitis B or C viruses (e.g., injection drug use, foreign birth in Asia or Africa, HI
measurements of serum amino transferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), bilirubin, a
visual acuity and red-green color discrimination should be obtained when EMB is to be used.
During treatment of patients with pulmonary tuberculosis, a sputum specimen for microscopic examination and culture shou
on culture. More frequent AFB smears may be useful to assess the early response to treatment and to provide an indication o
evaluations will depend on the site involved. In addition, it is critical that patients have clinical evaluations at least monthly t
Generally, patients do not require follow-up after completion of therapy but should be instructed to seek care promptly if sig
Routine measurements of hepatic and renal function and platelet count are not necessary during treatment unless patients hav
infection, alcohol abuse). At each monthly visit patients taking EMB should be questioned regarding possible visual disturba
discrimination is recommended for patients taking doses that on a milligram per kilogram basis are greater than those listed i

Identification and Management of Patients at Increased Risk of Treatment Failure and Relapse

The presence of cavitation on the initial chest radiograph combined with having a positive sputum culture at the time the init
risk for adverse outcomes (treatment failure, usually defined by positive cultures after 4 months of treatment, or relapse, defi
this reason it is particularly important to conduct a microbiological evaluation 2 months after initiation of treatment (Figure 1
organisms who are started on standard four-drug therapy will have negative sputum cultures at this time. Patients with positi
For patients who have positive cultures after 2 months of treatment and have not been receiving DOT, the most common reas
include extensive cavitary disease at the time of diagnosis, drug resistance, malabsorption of drugs, laboratory error, and biol
In USPHS Study 22, nearly 21% of patients in the control arm of the study (a continuation phase of twice weekly INH and R
juncture relapsed. Patients who had only one of these factors (either cavitation or a positive 2-month culture) had relapse rate
is recommended that, for patients who have cavitation on the initial chest radiograph and whose 2-month culture is positive,
whether the drugs are given daily or intermittently) (Figure 1 and Table 2). The recommendation to lengthen the continuatio
treatment duration for patients with silicotuberculosis showing that extending treatment from 6 to 8 months greatly reduced t
which the once weekly INH--rifapentine continuation phase was extended to 7 months for patients at high risk of relapse. Th
trial in which the continuation phase was 4 months.
For patients who have either cavitation on the initial film or a positive culture after completing the initial phase of treatment
continuation phase should be made on an individual basis.

Completion of Treatment

A full course of therapy (completion of treatment) is determined more accurately by the total number of doses taken, not sole
below) should consist of at least 182 doses of INH and RIF, and 56 doses of PZA. Thus, 6 months is the minimum duration o
interruptions in drug administration. In some cases, either because of drug toxicity or nonadherence to the treatment regimen
the goal is to deliver the specified number of doses within a recommended maximum time. For example, for a 6-month daily
treatment is not completed within this period, the patient should be assessed to determine the appropriate action to take---con
may require more restrictive measures to be used to ensure completion.
Clinical experience suggests that patients being managed by DOT administered 5 days/week have a rate of successful therap
mean DOT given 5 days/week and the required number of doses adjusted accordingly. For example, for the 6-month "daily"
treatment given 5 days/week has been used in a number of clinical trials, including USPHS Study 22, but has not been evalua
might be given the medications to take without DOT on weekends.
Interruptions in treatment may have a significant effect on the duration of therapy. Reinstitution of treatment must take into a
duration of the interruption. In general, the earlier in treatment and the longer the duration of the interruption, the more serio

Practical Aspects of Patient Management During Treatment

The first-line antituberculosis medications should be administered together; split dosing should be avoided. Fixed-dose comb
the risk of acquired drug resistance and medication errors. Fixed-dose combinations may be used when DOT is given daily a
intermittent dosing. It should be noted that for patients weighing more than 90 kg the dose of PZA in the three-drug combina
formulations approved for use in the United States: INH and RIF (Rifamate®) and INH, RIF, and PZA (Rifater®).
Providers treating patients with tuberculosis must be especially vigilant for drug interactions. Given the frequency of comorb
medications, the effects of which may be altered by the antituberculosis medications, especially the rifamycins. These interac
Adverse effects, especially gastrointestinal upset, are relatively common in the first few weeks of antituberculosis therapy; h
minor side effects. Although ingestion with food delays or moderately decreases the absorption of antituberculosis drugs, the
nausea with the first-line drugs, dosing with meals or changing the hour of dosing is recommended. Administration with foo
Drug-induced hepatitis, the most serious common adverse effect, is defined as a serum AST level more than three times the u
normal in the absence of symptoms. If hepatitis occurs INH, RIF, and PZA, all potential causes of hepatic injury, should be s
should be performed and the patient questioned carefully regarding exposure to other possible hepatotoxins, especially alcoh
amikacin/kanamycin, capreomycin, or a fluoroquinolone (levofloxacin, moxifloxacin, or gatifloxacin), may be used until the
limit of normal and symptoms have significantly improved, the first-line medications should be restarted in sequential fashio

is essential in managing these patients.

Treatment in Special Situations

HIV infection

Recommendations for the treatment of tuberculosis in HIV-infected adults are, with a few exceptions, the same as those for I
(Regimens 1c and 2b) is contraindicated in HIV-infected patients because of an unacceptably high rate of relapse, frequently
rifampin resistance has also been noted among HIV-infected patients with advanced immunosuppression treated with twice v
<100/μl should receive daily or three times weekly treatment (Regimen 1/1a or Regimen 3/3a). DOT and other adherence-pr
Management of HIV-related tuberculosis is complex and requires expertise in the management of both HIV disease and tube
interact with antituberculosis medications, it is strongly encouraged that experts in the treatment of HIV-related tuberculosis
other antiinfective drugs. Rifampin can be used for the treatment of tuberculosis with certain combinations of antiretroviral a
rifampin and appears to be equally effective although the doses of rifabutin and antiretroviral agents may require adjustment
recommendations are likely to be modified.

On occasion, patients with HIV-related tuberculosis may experience a temporary exacerbation of symptoms, signs, or radiog
radiographic worsening (paradoxical reaction) occurs in HIV-infected patients with active tuberculosis and is thought to be t
and signs may include high fevers, lymphadenopathy, expanding central nervous system lesions, and worsening of chest radi
evaluation has excluded other etiologies, particularly tuberculosis treatment failure. Nonsteroidal antiinflammatory agents m
day for 1--2 weeks, then in gradually decreasing doses) may be used, although there are no data from controlled trials to supp

Children

Because of the high risk of disseminated tuberculosis in infants and children younger than 4 years of age, treatment should b
recommended for adults are also the regimens of choice for infants, children, and adolescents with tuberculosis, with the exc
in childhood-type tuberculosis there is less concern with the development of acquired drug resistance. However, children and
sputum production. In such situations an initial phase of four drugs should be given until susceptibility is proven. When clini
EMB can be used safely at a dose of 15--20 mg/kg per day, even in children too young for routine eye testing. Streptomycin,
Most studies of treatment in children have used 6 months of INH and RIF supplemented during the first 2 months with PZA.
rate of less than 2%. Most treatment studies of intermittent dosing in children have used daily drug administration for the firs
Because it is difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis, it is frequently necessary to rely o
to guide the choice of drugs for the child. In cases of suspected drug-resistant tuberculosis in a child or when a source case is
morning gastric aspiration, bronchoalveolar lavage, or biopsy.

In general, extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. Exceptions
support 6-month therapy; thus 9--12 months of treatment is recommended.

The optimal treatment of pulmonary tuberculosis in children and adolescents with HIV infection is unknown. The American
drugs, and the total duration of therapy should be at least 9 months, although there are no data to support this recommendatic

Extrapulmonary tuberculosis

The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease
increasing evidence suggests that 6- to 9-month regimens that include INH and RIF are effective. Thus, a 6-month course of
meninges, for which a 9- 12-month regimen is recommended. Prolongation of therapy also should be considered for patients
recommended for patients with tuberculous pericarditis and tuberculous meningitis.

Culture-negative pulmonary tuberculosis and radiographic evidence of prior pulmonary tuberculosis

Failure to isolate *M. tuberculosis* from persons suspected of having pulmonary tuberculosis on the basis of clinical features a
Alternative diagnoses should be considered carefully and further appropriate diagnostic studies undertaken in persons with a
A diagnosis of tuberculosis can be strongly inferred by the clinical and radiographic response to antituberculosis treatment. C
has been a response attributable to antituberculosis treatment. If either clinical or radiographic improvement is noted and no
regimens in this circumstance include one of the standard 6-month chemotherapy regimens or INH, RIF, PZA, and EMB for
infected patients with culture-negative pulmonary tuberculosis should be treated for a minimum of 6 months.

Persons with a positive tuberculin skin test who have radiographic evidence of prior tuberculosis (e.g., upper lobe fibronodul
subsequent development of tuberculosis. Unless previous radiographs are available showing that the abnormality is stable, it
assess the possibility of active tuberculosis being present. Also, if the patient has symptoms of tuberculosis related to an extr
been excluded (i.e., by negative cultures and a stable chest radiograph), the treatment regimens are those used for latent tube
for 2 months (for patients who are unlikely to complete a longer course and who can be monitored closely) (Figure 2).

Renal insufficiency and end-stage renal disease

Specific dosing guidelines for patients with renal insufficiency and end-stage renal disease are provided in Table 15. For pati
DOT and to avoid premature removal of drugs such as PZA and cycloserine. To avoid toxicity it is important to monitor seru
little information concerning the effects of peritoneal dialysis on clearance of antituberculosis drugs.

Liver disease

INH, RIF, and PZA all can cause hepatitis that may result in additional liver damage in patients with preexisting liver disease

be used if at all possible, even in the presence of preexisting liver disease. If serum AST is more than three times normal bef
several treatment options exist. One option is to treat with RIF, EMB, and PZA for 6 months, avoiding INH. A second optio
susceptibility are demonstrated, thereby avoiding PZA. For patients with severe liver disease a regimen with only one hepatc
agent, such as a fluoroquinolone, for the first 2 months; however, there are no data to support this recommendation.
In all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-
Pregnancy and breastfeeding
Because of the risk of tuberculosis to the fetus, treatment of tuberculosis in pregnant women should be initiated whenever th
of INH, RIF, and EMB. Although all of these drugs cross the placenta, they do not appear to have teratogenic effects. Strepto
(congenital deafness) and should not be used. Although detailed teratogenicity data are not available, PZA can probably be u
the International Union against Tuberculosis and Lung Disease (IUATLD). If PZA is not included in the initial treatment reg
Breastfeeding should not be discouraged for women being treated with the first-line antituberculosis agents because the smal
Conversely, drugs in breast milk should not be considered to serve as effective treatment for tuberculosis or for latent tuberc
all women taking INH who are either pregnant or breastfeeding. The amount of pyridoxine in multivitamins is variable but g
Management of Relapse, Treatment Failure, and Drug Resistance
Relapse refers to the circumstance in which a patient becomes and remains culture negative while receiving therapy but, at s
radiographic deterioration that is consistent with active tuberculosis. In the latter situation rigorous efforts should be made to
for drug resistance. Most relapses occur within the first 6--12 months after completion of therapy. In nearly all patients with
containing regimens using DOT, relapses occur with susceptible organisms. However, in patients who received self-administ
resistance is substantial. In addition, if initial drug susceptibility testing was not performed and the patient fails or relapses w
were resistant from the outset.
The selection of empirical treatment for patients with relapse should be based on the prior treatment scheme and severity of
were treated under DOT, initiation of the standard four-drug regimen is appropriate until the results of drug susceptibility tes
three additional agents to which the organisms are likely to be susceptible should be included.
For patients with relapse who did not receive DOT, who were not treated with a rifamycin-based regimen, or who are known
and to begin an expanded regimen with INH, RIF, and PZA plus an additional two or three agents based on the probability o
(levofloxacin, moxifloxacin, or gatifloxacin), an injectable agent such as SM (if not used previously and susceptibility to SM
drug.
Treatment failure is defined as continued or recurrently positive cultures during the course of antituberculosis therapy. After
90--95% of patients will have negative cultures and show clinical improvement. Thus, patients with positive cultures after 3
the delayed conversion. Patients whose sputum cultures remain positive after 4 months of treatment should be deemed treatm
Possible reasons for treatment failure in patients receiving appropriate regimens include nonadherence to the drug regimen (t
biological variation in response. If treatment failure occurs, early consultation with a specialty center is strongly advised. If f
regimen could be started or administration of an altered regimen could be deferred until results of drug susceptibility testing
positive, an empirical regimen should be started immediately and continued until susceptibility tests are available. For patien
laboratory for drug susceptibility testing to both first- and second-line agents.
A fundamental principle in managing patients with treatment failure is never to add a single drug to a failing regimen; so doi
drugs to which susceptibility could logically be inferred should be added to lessen the probability of further acquired resistan
SM (if not used previously and the patient is not from an area of the world having high rates of SM resistance), amikacin, ka
cycloserine, or ethionamide. Once drug-susceptibility test results are available, the regimen should be adjusted according to t
Patients having tuberculosis caused by strains of *M. tuberculosis* resistant to at least INH and RIF (multidrug-resistant [MDR
be referred to or consultation obtained from specialized treatment centers as identified by the local or state health department
patients with MDR strains, they are also at increased risk for treatment failure and additional resistance and should be manag
Definitive randomized or controlled studies have not been performed to establish optimum regimens for treating patients wit
on expert opinion, guided by a set of general principles specified in Section 9, Management of Relapse, Treatment Failure, a
various patterns of drug-resistant tuberculosis (all are rated AIII).
The role of resectional surgery in the management of patients with extensive pulmonary MDR tuberculosis has not been esta
surgeons with experience in these situations and only after the patient has received several months of intensive chemotherapy
to prevent relapse.
Treatment of Tuberculosis in Low-Income Countries: Recommendations of the WHO and Guidelines from the IUAT
To place the current guidelines in an international context it is necessary to have an understanding of the approaches to treatm
American Thoracic Society/CDC/Infectious Diseases Society of America (ATS/CDC/IDSA) recommendations cannot be ass
tuberculosis and the resources with which to confront the disease to an important extent determine the approaches used. Give
incidence countries, it is also important for persons managing these cases to be familiar with the approaches used in the coun
The major international recommendations and guidelines for treating tuberculosis are those of the WHO and of the IUATLD
a distillation of IUATLD practice, validated in the field.

The WHO and IUATLD documents target, in general, countries in which mycobacterial culture, drug susceptibility testing, r
differences exist between these new ATS/CDC/IDSA recommendations, and the current tuberculosis treatment recommenda
built around a national case management strategy called "DOTS," the acronym for "directly observed therapy, short course,"
components of DOTS are 1) government commitment to sustained tuberculosis control activities, 2) case detection by sputur
standardized treatment regimen of 6--8 months for at least all confirmed sputum smear--positive cases, with DOT for at least
5) a standardized recording and reporting system that enables assessment of treatment results for each patient and of the tube
A number of other differences exist as well:

- The WHO and the IUATLD recommend diagnosis and classification of tuberculosis cases and assessment of respor
  recommended because of cost, limited applicability, and lack of facilities.
- Chest radiography is recommended by both the WHO and IUATLD only for patients with negative sputum smears
- Both 6- and 8-month treatment regimens are recommended by the WHO. The IUATLD recommends an 8-month re
  suspected of having or known to have HIV infection, ethambutol is substituted for thioacetazone
- The WHO and the IUATLD recommend a standardized 8-month regimen for patients who have relapsed, had interr
  considered "chronic" cases and are highly likely to have tuberculosis caused by MDR organisms. Susceptibility test
  the WHO, if testing and second-line drugs are available. The IUATLD recommendations do not address the issue.
- Neither baseline nor follow-up biochemical testing is recommended by the WHO and the IUATLD. It is recommen
  them promptly.

A Research Agenda for Tuberculosis Treatment

New antituberculosis drugs are needed for three main reasons: 1) to shorten or otherwise simplify treatment of tuberculosis c
3) to provide more efficient and effective treatment of latent tuberculosis infection. No truly novel compounds that are likely
further work to optimize the effectiveness of once-a-week rifapentine regimens using higher doses of the drug and using rifa
New categories of drugs that have shown promise for use in treating tuberculosis include the nitroimidazopyrans and the oxa
thought to be necessary for maintaining the latent state, might be useful for treatment of latent tuberculosis infection.
A number of other interventions that might lead to improved treatment outcome have been suggested, although none has und
administration of "protective" cytokines such as interferon-g and interleukin-2, and nutritional supplements, especially vitam
Research is also needed to identify factors that are predictive of a greater or lesser risk of relapse to determine optimal length
supervise treatment. In addition, identification of behavioral factors that identify patients at greater or lesser likelihood of bei

1. Introduction and Background

Since 1971 the American Thoracic Society (ATS) and CDC have regularly collaborated to develop joint guidelines for the di
intended to guide both public health programs and health care providers in all aspects of the clinical and public health manag
The most recent version of guidelines for the treatment of tuberculosis was published in 1994 (*2*).
The current document differs from its predecessor in a number of important areas that are summarized above. The process by
substantially from the previous versions. For the first time the Infectious Diseases Society of America (IDSA) has become a
prior statement committees but has not previously been a cosponsor of the document. Practice guidelines that serve to compl
representatives of the American Academy of Pediatrics (AAP), the (United States) National Tuberculosis Controllers Associ
the revision. By virtue of their different perspectives these committee members served to provide broader input and to help e
current guidelines are intended for areas in which mycobacterial cultures, drug susceptibility tests, radiographic facilities, an
For this revision of the recommendations essentially all clinical trials of antituberculosis treatment in the English language li
IDSA/USPHS rating scale (*4*).
This revision of the recommendations for treatment of tuberculosis presents a significant philosophic departure from previou
primarily on the provider or program initiating therapy rather than on the patient. It is well established that appropriate treatn
the risk of disability or death from tuberculosis, and nearly eliminates the possibility of relapse. For these reasons, antituberc
the treatment of, for example, hypertension or diabetes mellitus, wherein the benefits largely accrue to the patient. Provider r
of their care. All reasonable attempts should be made to accommodate the patient so that a successful outcome is achieved. H
nonadherent.
The recommendations in this statement are not applicable under all epidemiologic circumstances or across all levels of resou
of therapy described in this document apply regardless of conditions, the diagnostic approach, methods of patient supervisio
recommended, are quite different in high-incidence, low-income areas compared with low-incidence, high-income areas of t
document and those of the IUATLD and the WHO is found in Section 10,Treatment of Tuberculosis in Low-Income Countri
In the United States there has been a call for the elimination of tuberculosis, and a committee constituted by the Institute of M
had two main recommendations related to treatment of tuberculosis; first, that all U.S jurisdictions have health regulations th
treatment be administered in the context of patient-centered programs that are based on individual patient characteristics and
treatment services, as well as the drugs that are used, to treat patients effectively. This philosophy is the core of the DOTS st
Recommendations oof the WHO and the IUTLD), developed by the IUATLD and implemented globally by the WHO. Thus
high- and low-incidence countries, the fundamental concern, regardless of where treatment is given, is ensuring patient adhe

References

1. DuMelle FJ, Hopewell PC. The CDC and the American Lung Association/American Thoracic Society: an enduring events in TB control. TB Notes Newslett 2000;1:23--27.
2. American Thoracic Society, Centers for Disease Control and Prevention. Treatment of tuberculosis and tuberculosis http://www.thoracic.org/adobe/statements/tbchild1-16.pdf
3. Horsburgh CR Jr, Feldman S, Ridzon R. Practice guidelines for the treatment of tuberculosis. Clin Infect Dis 2000;
4. Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Purpose of q
5. Geiter LJ, editor. Ending neglect: the elimination of tuberculosis in the United States. Institute of Medicine, Commi Press; 2000. Available at http://www.nap.edu/catalog/9837.html.
6. World Health Organization. What is DOTS? A guide to understanding the WHO-recommended TB control strategy Organization; 1999. Available at http://www.who.int/gtb/dots.

2. Organization and Supervision of Treatment

Successful treatment of tuberculosis depends on more than the science of chemotherapy. To have the highest likelihood of su individual patient's circumstances. Optimal organization of treatment programs requires an effective network of primary and care facilities and community outreach programs, and between the private and public sectors of medical care. This section de likelihood of being successful.

As noted previously, antituberculosis chemotherapy is both a personal health measure intended to cure the sick patient and a Typically, tuberculosis treatment is provided by public health departments, often working in collaboration with other provide centers, correctional facilities, hospitals, hospices, long-term care facilities, and homeless shelters. Private providers and pub setting that is not only mutually agreeable but also enables access to tuberculosis expertise and resources that might otherwis more structured public/private partnership, often defined by a contract, to assure completion of therapy. Regardless of the me complete therapy rests with the public health system.

2.1. Role of the Health Department

The responsibility of the health department in the control of tuberculosis is to ensure that all persons who are suspected of ha treatment is prescribed and completed successfully (*1*,*2*). A critical component of the evaluation scheme is access to proficie The responsibilities of the health department may be accomplished indirectly by epidemiologic surveillance and monitoring more directly by provision of diagnostic and treatment services, as well as by conducting epidemiologic investigations. Give mechanisms by which health care is delivered, the means by which the goals of the health department are accomplished may In dealing with individual patients, approaches that focus on each person's needs and characteristics should be used to determ plans are developed with the patient as an active participant together with the physician and/or nurse, outreach workers, socia of tuberculosis in the United States were born outside the United States (similar circumstances prevail in most other low-inci

ensure his/her participation in developing the treatment plan. Ideally, a specific case manager is assigned individual responsi
and revised as needed. These reviews may be accomplished in meetings between the patient and the assigned provider, as we
principle of using the least restrictive measures that are likely to achieve success. The full spectrum of measures that may be
outpatient setting to legally mandated hospitalization (*4*). Directly observed therapy (DOT) is the preferred initial means to a
stepwise fashion. Any approach must be balanced, ensuring that the needs and rights of the patient, as well as those of the pu
jointly by the health department and the private provider, and must address identified and anticipated barriers to adherence.

2.2. Promoting Adherence

Louis Pasteur once said, "The microbe is nothing...the terrain everything" (*5*). Assuming appropriate drugs are prescribed, th
treatment) becomes the most important consideration in completion of tuberculosis treatment. Many factors may be part of th
linguistic barriers to cooperation, lifestyle differences, homelessness, substance abuse, and a large number of other condition
tuberculosis (*6*). Barriers may be patient related, such as conflicting health beliefs, alcohol or drug dependence, or mental illn
lack of interpreters (*7*). Effective tuberculosis case management identifies and characterizes the terrain and determines an app
centered approach are that, by increasing communication with the patient, it provides opportunities for further education con
To maximize completion of therapy, patient-centered programs identify and utilize a broad range of approaches based on the
initial strategy and deserves special emphasis. Although DOT itself has not been subjected to controlled trials in low-inciden
strongly suggest that DOT, coupled with individualized case management, leads to the best treatment results (*8--10*). To date
showed no benefit and one (*13*) in which there was a significant advantage for DOT. What is clear from these studies is that
aggressive interventions when patients miss doses. Using DOT in this manner can only improve results.

DOT can be provided daily or intermittently in the office, clinic, or in the "field" (patient's home, place of employment, scho
personnel. DOT should be used for all patients residing in institutional settings such as hospitals, nursing homes, or correctio
observation of therapy (*14*). However, even in such supervised settings careful attention must be paid to ensuring that ingesti
regimens that use intermittent drug administration have all doses administered under DOT because of the potentially serious
drug reactions, and clinical worsening of tuberculosis. DOT provides a close connection to the health care system for a group
and management of other conditions.

The use of DOT does not guarantee ingestion of all doses of every medication (*15*). Patients may miss appointments, may no
patients, including those who are being treated by DOT, should continue to be monitored for signs of treatment failure. DOT
incentives and enablers described subsequently (*16--20*). Patients who are more likely to present a transmission risk to others
when resources are limited. When DOT is not being used, fixed-dose combination preparations (see Section 6.2, Fixed-Dose
patient taking only one drug and may help prevent the development of drug resistance. Combination formulations are easier
Depending on the identified obstacles to completion of therapy, the treatment plan may also include enablers and incentives
utilizes DOT in addition to other adherence-promoting tools (*9*,*21*,*22*). These studies demonstrate, as shown in Figure 3, that
completion rates (in excess of 90% across a range of geographic and socioeconomic settings), and reinforces the importance
Intensive educational efforts should be initiated as soon as the patient is suspected of having tuberculosis. The instruction sho
tuberculosis, expected outcomes of treatment, the benefits and possible adverse effects of the drug regimen, methods of supe
medication regimen must be explained in clear, understandable language and the verbal explanation followed with written in
same language. Materials should be appropriate for the culture, language, age, and reading level of the patient. Relevant info
The patient's clinical progress and the treatment plan must be reviewed at least monthly to evaluate the response to therapy a
based, that quantifies the dosage and frequency of medication administered, indicates AFB smear and culture status, and note
regular reviews and also provides data for cohort analyses. In addition, adherence monitoring by direct methods, such as the
counts or a medication monitor, should be a part of routine management, especially if the patient is not being given DOT.

Tracking patients is also a critical concern for those charged with assuring completion of treatment. It has been shown that pa
likely to default than patients who do not move (*24*). Factors that have been shown to be associated with moving/defaulting i
homelessness. Communication and coordination of services among different sources of care and different health departments
patients with no permanent home. Such communication may also be necessary across national boundaries, especially the Uni
tracking.

Some patients, for example those with tuberculosis caused by drug-resistant organisms, or who have comorbid conditions, su
hospitalized in a facility where tuberculosis expertise is available and where there are appropriate infection control measures
measures have failed (*25--27*). Public health laws exist in most states that allow the use of detainment under these circumstan
successfully in some states as a less costly alternative. The use of these interventions depends on the existence of appropriate
facilities. Health departments must be consulted to initiate legal action when it is necessary.

References

1. CDC Essential components of a tuberculosis prevention and control program. MMWR 1995;44(RR-11):1--16.
2. Simone PM, Fujiwara PI. Role of the health department: legal and public health implications. In: Schlossberg D, ed
   Saunders, 1999:130--9.
3. Etkind SC. The role of the public health department in tuberculosis control. Med Clin North Am 1993;77:1303--14.

4. National Tuberculosis Controllers Association, National TB Nursing Consultant Coalition. Tuberculosis nursing: a
and National Tuberculosis Nursing Consultant Coalition, 1997:69--84.
5. Delhoume L. De Claude Bernard a d'Arsonval. Paris: J.B. Baillière et Fils, 1939:595.
6. Moss AR, Hahn JA, Tulsky JP, Daley CL, Small PM, Hopewell PC. Tuberculosis in the homeless: a prospective stu
7. Sumartojo E. When tuberculosis treatment fails: a social behavioral account of patient adherence. Am Rev Respir D
8. Chaulk CP, Moore-Rice K, Rizzo R, Chaisson RE. Eleven years of community-based directly observed therapy for
9. Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of tuberculosis: census statement o
10. Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB, Gomez E, Foresman BH. The effect of directly obse
1994;330:1179--84.
11. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Randomised controlled trial of self-supervised a
12. Walley JD, Khan MR, Newell JN, Khan MH. Effectiveness of the direct observation component of DOTS for tuber
13. Kamolratanakul P, Sawert H, Lertmaharit S, Kasetjaroen Y, Akksilp S, Tulaporn C, Punnachest K, Na-Songkhla S,
with pulmonary tuberculosis in Thailand. Trans R Soc Trop Med Hyg 1999;5:552--7.
14. Snyder DC, Paz EA, Mohle-Boetani JC, Fallstad R, Balck RL, Chin DP. Tuberculosis prevention in methadone mai
-85.
15. Burman WJ, Cohn DL, Rietmeijer CA, Judson FN, Sbarbaro JA, Reves RR. Noncompliance with directly observed
1997;111:1168--73.
16. Volmink J, Matchaba P, Garner P. Directly observed therapy and treatment adherence. Lancet 2000;355:1345--50.
17. Bayer R, Stayton C, Desvarieux M, Healton C, Landesman S, Tsai W. Directly observed therapy and treatment com
1998;88:1052--8.
18. Poszik CJ. Compliance with tuberculosis therapy. Med Clin North Am 1993;77:1289--1300.
19. Lobue PA, Cass R, Lobo D, Moser K, Catanzaro A. Development of housing programs to aid in the treatment of tul
20. Black B, Bruce ME. Treating tuberculosis: the essential role of social work. Soc Work Health Care 1998;26:51--68.
21. Moore RD, Chaulk CP, Griffiths R, Cavalcante S, Chaisson RE. Cost-effectiveness of directly observed versus self-
22. Burman WJ, Dalton CB, Cohn DL, Butler RG, Reves RR. A cost-effectiveness analysis of directly observed therapy
23. Davidson H, Smirnoff M, Klein SJ, Burdick E. Patient satisfaction with care at directly observed therapy programs
24. Cummings KC, Mohle-Boetani J, Royce SE, Chin DP. Movement of tuberculosis patients and the failure to comple
25. Oscherwitz T, Tulsky JP, Roger S, Sciortino S, Alpers A, Royce S, Lo B. Detention of persistently nonadherent pat
26. Singleton L, Turner M, Haskal R, Etkind S, Tricarico M, Nardell E. Long term hospitalization for tuberculosis cont
27. Gasner MR, Maw KL, Feldman GE, Fujiwara PI, Frieden TR. The use of legal action in New York City to ensure t
28. Gostin LO. Controlling the resurgent tuberculosis epidemic: a 50 state survey of TB statutes and proposals for refor

3. Drugs in Current Use

Currently, there are 10 drugs approved by the United States Food and Drug Administration (FDA) for treating tuberculosis (
are used relatively commonly to treat tuberculosis caused by drug-resistant organisms or for patients who are intolerant of so
complex disease in patients with HIV infection but not approved for tuberculosis, is useful for treating tuberculosis in patient
and kanamycin, nearly identical aminoglycoside drugs used in treating patients with tuberculosis caused by drug-resistant or
Of the approved drugs isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) are considered first-lin
may also be considered first-line agents under the specific situations described below. Streptomycin (SM) was formerly cons
increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. The remaining dru
The drug preparations available currently and the recommended doses are shown in Tables 3, 4, and 5.

3.1. First-Line Drugs

3.1.1. Isoniazid

Role in treatment regimen. Isoniazid (INH) is a first-line agent for treatment of all forms of tuberculosis caused by organis
against rapidly dividing cells (*1,2*).

Dose. See Table 3.

Adults (maximum): 5 mg/kg (300 mg) daily; 15 mg/kg (900 mg) once, twice, or three times weekly.

Children (maximum): 10--15 mg/kg (300 mg) daily; 20--30 mg/kg (900 mg) twice weekly (*3*).

Preparations. Tablets (50 mg, 100 mg, 300 mg); syrup (50 mg/5 ml); aqueous solution (100 mg/ml) for intravenous or intra

Adverse effects.

Asymptomatic elevation of aminotransferases: Aminotransferase elevations up to five times the upper limit of normal occur i
enzyme levels usually return to normal even with continued administration of the drug.

Clinical hepatitis: (see Table 10.) Data indicate that the incidence of clinical hepatitis is lower than was previously thought. I
latent tuberculosis infection in an urban tuberculosis control program (*5*). Prior studies suggested a higher rate, and a meta-ar
(*6--8*). In the meta-analysis the rate of clinical hepatitis was 1.6% when INH was given with other agents, not including RIF.
For INH alone the risk increases with increasing age; it is uncommon in persons less than 20 years of age but is nearly 2% in
disease, in those with a history of heavy alcohol consumption, and, data suggest, in the postpartum period, particularly amon
Fatal hepatitis: A large survey estimated the rate of fatal hepatitis to be 0.023%, but more recent studies suggest the rate is s
continued administration of INH despite onset of symptoms of hepatitis (*12*).
Peripheral neurotoxicity (*13,14*)*:* This adverse effect is dose related and is uncommon (less than 0.2%) at conventional doses
neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as for pregnant and
these conditions to help prevent this neuropathy (*18*).
Central nervous system effects: Effects such as dysarthria, irritability, seizures, dysphoria, and inability to concentrate have b
Lupus-like syndrome (*19*)*:* Approximately 20% of patients receiving INH develop anti-nuclear antibodies. Less than 1% dev
Hypersensitivity reactions: Reactions, such as fever, rash, Stevens-Johnson syndrome, hemolytic anemia, vasculitis, and neu
Monoamine (histamine/tyramine) poisoning: This has been reported to occur after ingestion of foods and beverages with hig
avoid foods and drinks, such as certain cheeses and wine, having high concentrations of monoamines.
Diarrhea: Use of the commercial liquid preparation of INH, because it contains sorbitol, is associated with diarrhea.
Use in pregnancy. INH is considered safe in pregnancy, but the risk of hepatitis may be increased in the peripartum period (
pregnancy (*18*). It should be noted that multivitamin preparations have variable amounts of pyridoxine but generally less tha
CNS penetration. Penetration is excellent. Cerebrospinal fluid (CSF) concentrations are similar to concentrations achieved i
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) INH can be used safely without d
require chronic hemodialysis (*26*).
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The risk of drug accumulation and drug-induced hepatitis may b
hepatic disease. Laboratory and clinical monitoring should be more frequent in such situations.
Monitoring. Routine monitoring is not necessary. However, for patients who have preexisting liver disease or who develop
should be measured monthly and when symptoms occur. Serum concentrations of phenytoin and carbamazepine may be incr
serum concentrations of the anticonvulsants are limited by the decrease caused by RIF. Thus, it is important to measure seru
if necessary.

3.1.2. Rifampin

Role in treatment regimen. Rifampin (RIF) is a first-line agent for treatment of all forms of tuberculosis caused by organisms
dividing rapidly (early bactericidal activity) (*1*) and against semidormant bacterial populations, thus accounting for its steriliz
Dose. See Table 3.
Adults (maximum): 10 mg/kg (600 mg) once daily, twice weekly, or three times weekly.
Children (maximum): 10--20 mg/kg (600 mg) once daily or twice weekly.
Preparations. Capsules (150 mg, 300 mg); contents of capsule may also be mixed in an appropriate diluent to prepare an ora
Adverse effects (*28*).
Cutaneous reactions (*29*)*:* Pruritis with or without rash may occur in as many as 6% of patients but is generally self-limited (
may be possible. More severe, true hypersensitivity reactions are uncommon, occurring in 0.07--0.3% of patients (*17,31,32*).
Gastrointestinal reactions (nausea, anorexia, abdominal pain): The incidence is variable, but symptoms are rarely severe en
Flulike syndrome: This may occur in 0.4--0.7% of patients receiving 600 mg twice weekly but not with daily administration
a higher dose (*29,35*).
Hepatotoxicity: Transient asymptomatic hyperbilirubinemia may occur in as many as 0.6% of patients receiving the drug. M
Hepatitis is more common when the drug is given in combination with INH (2.7%) than when given alone (nearly 0%) or in
Severe immunologic reactions: In addition to cutaneous reactions and flulike syndrome, other reactions thought to be immun
thrombotic thrombocytopenic purpura. These reactions are rare, each occurring in less than 0.1% of patients (*31,32,37*).
Orange discoloration of bodily fluids (sputum, urine, sweat, tears): This is a universal effect of the drug. Patients should be
permanently stained.
Drug interactions due to induction of hepatic microsomal enzymes: There are a number of drug interactions (described in Se
concern are reductions, often to ineffective levels, in serum concentrations of common drugs, such as oral contraceptives, me
rifamycins and antiretroviral agents. Because information regarding rifamycin drug interactions is evolving rapidly, readers a
information.
Use in pregnancy. RIF is considered safe in pregnancy (*38*).
CNS penetration. Concentrations in the CSF may be only 10--20% of serum levels, but this is sufficient for clinical efficacy
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) RIF can be used safely without d
Use in hepatic disease. (see Section 8.8: Hepatic Disease.) Clearance of the drug may be impaired in the presence of liver di
rifampin in all short-course regimens, it generally should be included, but the frequency of clinical and laboratory monitoring

Monitoring. No routine monitoring tests are required. However, rifampin causes many drug interactions described in Sectio
the drugs in question.

3.1.3. Rifabutin

Role in treatment regimen. Rifabutin is used as a substitute for RIF in the treatment of all forms of tuberculosis caused by
reserved for patients who are receiving any medication having unacceptable interactions with rifampin (*41*) or have experien
Dose. See Table 3.
Adults (maximum): 5 mg/kg (300 mg) daily, twice, or three times weekly. The dose may need to be adjusted when there is co
rifabutin is used with efavirenz the dose of rifabutin should be increased to 450--600 mg either daily or intermittently. Becau
consult the CDC web site, http://www.cdc.gov/nchstp/tb/, to obtain the most up-to-date information.
Children (maximum): Appropriate dosing for children is unknown.
Preparations: Capsules (150 mg) for oral administration.
Adverse effects.
Hematologic toxicity: In a placebo-controlled, double-blind trial involving patients with advanced acquired immunodeficienc
with 20% in patients receiving placebo (p = 0.03). Neutropenia severe enough to necessitate discontinuation of the drug occu
The effect is dose related, occurring more frequently with daily than with intermittent administration of the same dose (*42*). I
thrombocytopenia was associated with rifabutin (*43--47*).
Uveitis: This is a rare (less than 0.01%) complication when the drug is given alone at a standard (300 mg daily) dose. The oc
macrolide antimicrobial agents that reduce its clearance (*48*). Uveitis may also occur with other drugs that reduce clearance s
Gastrointestinal symptoms: These symptoms occurred in 3% of patients with advanced HIV infection given 300 mg/day (pac
noted among patients taking rifabutin (*43,44,46--48*).
Polyarthralgias: This symptom occurred in 1--2% of persons receiving a standard 300-mg dose (package insert). It is more c
involving both HIV-infected and uninfected patients (*43,44,46,47*).
Hepatotoxity: Asymptomatic elevation of liver enzymes has been reported at a frequency similar to that of RIF (*48*). Clinical
Pseudojaundice (skin discoloration with normal bilirubin): This is usually self-limited and resolves with discontinuation of t
Rash: Although initially reported to occur in as many as 4% of patients with advanced HIV infection, subsequent studies sug
Flulike syndrome: Flulike syndrome is rare (less than 0.1%) in patients taking rifabutin.
Orange discoloration of bodily fluids (sputum, urine, sweat, tears): This is a universal effect of the drug. Patients should be v
permanently stained.
Use in pregnancy. There are insufficient data to recommend the use of rifabutin in pregnant women; thus, the drug should b
CNS penetration. The drug penetrates inflamed meninges (*50*).
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Rifabutin may be used without d
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The drug should be used with increased clinical and laboratory m
with severe liver dysfunction (*50*).
Monitoring. Monitoring is similar to that recommended for rifampin. Although drug interactions are less problematic with r

3.1.4. Rifapentine

Role in treatment regimen. Rifapentine may be used once weekly with INH in the continuation phase of treatment for HIV
negative sputum smears at completion of the initial phase of treatment (*51*).
Dose. See Table 3.
Adults (maximum): 10 mg/kg (600 mg), once weekly during the continuation phase of treatment. Data have suggested that a
(*52*).
Children: The drug is not approved for use in children.
Preparation. Tablet (150 mg, film coated).
Adverse effects.
The adverse effects of rifapentine are similar to those associated with RIF. Rifapentine is an inducer of multiple hepatic enzy
these enzymes (see Section 7: Drug Interactions).
Use in pregnancy. There is not sufficient information to recommend the use of rifapentine for pregnant women.
CNS penetration. There are no data on CSF concentrations of rifapentine.
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease .) The pharmacokinetics of rifapen
administered dose is excreted via the kidneys, the clinical significance of impaired renal function in the disposition of rifaper
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The pharmacokinetics of rifapentine and its 25-desacetyl metabc
from those in healthy volunteers, even though the elimination of these compounds is primarily via the liver (*53*). The clinical
metabolite is not known.
Monitoring. Monitoring is similar to that for RIF. Drug interactions involving rifapentine are being investigated and are like

3.1.5. Pyrazinamide

Role in treatment regimen. Pyrazinamide (PZA) is a first-line agent for the treatment of all forms of tuberculosis caused by

greatest activity against the population of dormant or semidormant organisms contained within macrophages or the acidic en
Dose. See Tables 3 and 4.
Adults: 20--25 mg/kg per day. Recommended adult dosages by weight, using whole tablets, are listed in Table 4.
Children (maximum): 15--30 mg/kg (2.0 g) daily; 50 mg/kg twice weekly (2.0 g).
Preparations. Tablets (500 mg, scored).
Adverse effects.
Hepatotoxicity: Early studies (*55,56*) using doses of 40--70 mg/kg per day reported high rates of hepatotoxicity. However, in
25 mg/kg per day or less (*15,34,57*). In one study, however, hepatotoxicity attributable to PZA used in standard doses occurr
Gastrointestinal symptoms (nausea, vomiting): Mild anorexia and nausea are common at standard doses. Vomiting and sever
Nongouty polyarthralgia: Polyarthralgias may occur in up to 40% of patients receiving daily doses of PZA. This rarely requi
other nonsteroidal antiinflammatory agents. In clinical trials of PZA in the initial intensive phase of treatment, athralgias wer
Asymptomatic hyperuricemia: This is an expected effect of the drug and is generally without adverse consequence (*15,62*).
Acute gouty arthritis: Acute gout is rare except in patients with preexisting gout (*63*), generally a contraindication to the use
Transient morbilliform rash: This is usually self-limited and is not an indication for discontinuation of the drug.
Dermatitis: PZA may cause photosensitive dermatitis (*59*).
Use in pregnancy. There is little information about the safety of PZA in pregnancy. However, when there are sound reasons
unquantified) risk. The WHO and the IUATLD recommend this drug for use in pregnant women with tuberculosis (see Secti
the IUATLD).
CNS penetration. The drug passes freely into the CSF, achieving concentrations equivalent to those in serum (*64*).
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) PZA is cleared primarily by the l
insufficiency (*65*). The dose may, therefore, need to be reduced in patients with renal insufficiency. It should be administered
renal disease (Table 15) (*26*). The risk of hyperuricemia caused by PZA is increased in patients with renal insufficiency.
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) Although the frequency is slightly lower than with INH or RIF, t
with underlying liver disease, laboratory and clinical monitoring should be increased.
Monitoring. Serum uric acid measurements are not recommended as a routine but may serve as a surrogate marker for comp
underlying liver disease or when it is used with rifampin in treating latent tuberculosis infection.
3.1.6. Ethambutol
Role in treatment regimen. Ethambutol (EMB) is a first-line drug for treating all forms of tuberculosis. It is included in init
to INH may be present. Ethambutol is generally not recommended for routine use in children whose visual acuity cannot be
to be caused by organisms that are resistant to either INH or RIF, EMB should be used (see Section 8.2: Children and Adole
Dose. See Tables 3 and 5.
Adults: 15--20 mg/kg per day: Table 5 lists recommended dosages for adults, using whole tablets.
Children (maximum): 15--20 mg/kg per day (2.5 g); 50 mg/kg twice weekly (2.5 g). The drug can be used safely in older chi
(generally less than 5 years of age) (*66*). In younger children EMB can be used if there is concern with resistance to INH or I
Preparations. Tablets (100 mg, 400 mg) for oral administration.
Adverse effects.
Retrobulbar neuritis: This is manifested as decreased visual acuity or decreased red-green color discrimination that may affe
No difference was found in the prevalence of decreased visual acuity between regimens that contained EMB at 15 mg/kg and
(18% of patients receiving more than 30 mg/kg per day) and in patients with renal insufficiency. Higher doses can be given s
Peripheral neuritis: This is a rare adverse effect (*69*).
Cutaneous reactions: Skin reactions requiring discontinuation of the drug occur in 0.2--0.7% of patients (*68*).
Use in pregnancy. EMB is considered safe for use in pregnancy (*70--72*).
CNS penetration. The agent penetrates the meninges in the presence of inflammation but does not have demonstrated effica
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) EMB is cleared primarily by the
70 ml/minute (*74*). EMB should be administered at a dose of 15--20 mg/kg three times a week by DOT after dialysis in patie
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) EMB can be used safely in patients with hepatic disease.
Monitoring. Patients should have baseline visual acuity testing (Snellen chart) and testing of color discrimination (Ishihara t
including blurred vision or scotomata. Monthly testing of visual acuity and color discrimination is recommended for patients
any patient with renal insufficiency. Patients should be instructed to contact their physician or public health clinic immediate
permanently if there are any signs of visual toxicity.
3.1.7. Fixed-dose combination preparations
Role in treatment regimen. Two combined preparations, INH and RIF (Rifamate®) and INH, RIF, and PZA (Rifater®), are
monotherapy, particularly when DOT is not possible, and, therefore, may decrease the risk of acquired drug resistance (*75*).
Constituent drugs are combined in proportions compatible with daily treatment regimens. Formulations for intermittent admi
Preparations and dose.

Rifamate®: As sold in North America, each capsule contains RIF (300 mg) and INH (150 mg); thus, the daily dose is two ca
of INH are used by some programs for intermittent therapy given twice weekly as DOT.
Rifater®: Each tablet contains RIF (120 mg), INH (50 mg), and PZA (300 mg). The daily dose is based on weight as follows
adequate dose of PZA in persons weighing more than 90 kg additional PZA tablets must be given.
Adverse effects. See comments under individual drugs above.
Use in pregnancy. Rifamate® may be used in daily treatment of pregnant women. Rifater® should not be used because it cc
CNS penetration. See comments under individual drugs above.
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Rifamate® may be used in perso
adjustment of the dose of PZA.
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) In patients with underlying hepatic disease it is advisable to treat
regimen established.

3.2. Second-Line Drugs

3.2.1. Cycloserine

Role in treatment regimen. Cycloserine (*76,77*) is a second-line drug that is used for treating patients with drug-resistant tu
be used on a temporary basis for patients with acute hepatitis in combination with other nonhepatotoxic drugs.
Dose. See Table 3.
Adults (maximum): 10--15 mg/kg per day (1,000 mg), usually 500--750 mg/day given in two doses. Clinicians with experien
concentration measurements aiming for a peak concentration of 20--35 mg/ml are often useful in determining the optimum d
Children (maximum): 10--15 mg/kg per day (1.0 g/day).
Preparations. Capsules (250 mg).
Adverse effects.
Central nervous system effects: The central nervous system effects range from mild reactions, such as headache or restlessne
seizure disorders or mental illness. Seizures have been reported to occur in up to 16% of patients receiving 500 mg twice dai
neurotoxic side effects and is usually given in a dosage of 100--200 mg/day (*79*). Rarely, cycloserine may cause peripheral n
Use in pregnancy. Cycloserine crosses the placenta. There are limited data on safety in pregnancy; thus, it should be used in
CNS penetration. Concentrations in CSF approach those in serum (*77*).
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) The drug can accumulate in patie
dose should be reduced and serum concentrations measured. Cycloserine should not be used in patients having a creatinine c
hemodialyzed the dose should be 500 mg three times a week or 250 mg daily (Table 15). Serum concentrations of the drug s
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) There are no precautions except for patients with alcohol-related
Monitoring. Neuropsychiatric status should be assessed at least at monthly intervals and more frequently if symptoms devel
dose is established. For patients taking phenytoin, serum concentrations of phenytoin should be measured.

3.2.2. Ethionamide

Role in treatment. Ethionamide (*76,77*) is a second-line drug that is used for patients with drug-resistant tuberculosis diseas
Dose: See Table 3.
Adults (maximum): 15--20 mg/kg per day (1.0 g/day), usually 500--750 mg/day in a single daily dose or two divided doses. T
intermittent dosing.
Children (maximum): 15--20 mg/kg per day (1.0 g/day).
Preparations: Tablets (250 mg).
Adverse reactions.
Gastrointestinal effects: Ethionamide commonly causes profound gastrointestinal side effects, including a metallic taste, nau
improve if doses are taken with food or at bedtime.
Hepatotoxicity: Ethionamide is similar in structure to INH and may cause similar side effects. Hepatotoxicity occurs in abou
Neurotoxicity: Neurotoxicity, including peripheral neuritis, optic neuritis, anxiety, depression, and psychosis, has been repor
prolonged treatment (*83,84*).
Endocrine effects: Endocrine disturbances, including gynecomastia, alopecia, hypothyroidism, and impotence, have been des
Use in pregnancy. Ethionamide crosses the placenta and is teratogenic in laboratory animals. It should not be used in pregna
CNS penetration. CSF concentrations are equal to those in serum (*77*).
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-stage Renal Disease.) For patients having a creatinine c
to 250--500 mg/day (Table 15).
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) Ethionamide should be used with caution in patients with underl
Monitoring. Liver function tests should be obtained at baseline and, if there is underlying liver disease, at monthly intervals.
measured at baseline and at monthly intervals.

3.2.3. Streptomycin

Role in treatment regimen. Streptomycin (SM) (*76,77,87--89*) and EMB have been shown to be approximately equivalent

likely to have acquired *M. tuberculosis* in a high-incidence country, the relatively high rate of resistance to SM limits its usef
Dose. See Table 3.
Adults (maximum): 15 mg/kg per day (1 g/day) parenterally, usually given as a single daily dose (5--7 days/week) initially, a
conversion, depending on the efficacy of the other drugs in the regimen (*90*). For persons over 59 years of age, the dose shou
15 mg/kg per dose two or three times per week) in persons with renal insufficiency (see below: Use in Renal Disease) (*91,92*
Children (maximum): 20--40 mg/kg per day (1 g/day).
Preparations. Aqueous solution in vials of 1 g (*93*).
Adverse effects.
Ototoxicity: The most important adverse reaction caused by SM is ototoxicity, including vestibular and hearing disturbances
ethacrynic acid). The risk of ototoxicity increases with increasing single doses and with the cumulative dose, especially abov
Neurotoxicity: SM relatively commonly causes circumoral parasthesias immediately after injection. Rarely, it may interact w
Nephrotoxicity: Nephrotoxicity occurs less commonly with SM than with amikacin, kanamycin, or capreomycin (*95*). Renal
Use in pregnancy. SM is contraindicated in pregnancy because of the risk of fetal hearing loss (*77,97,98*).
CNS penetration. There is only slight diffusion of SM into CSF, even in patients with meningitis (*77,99*)
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) SM should be used with caution
nephrotoxicity. Because clearance is almost exclusively by the kidney, dosing adjustments are essential in patients with unde
patients, the dosing frequency should be reduced to two or three times weekly, but the milligram dose should be maintained
(Table 15) (*91,92*). Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate D
monitored to avoid toxicity (*91*).
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) No precautions are necessary.
Monitoring. An audiogram, vestibular testing, Romberg testing, and serum creatinine measurement should be performed at
symptoms, should be performed monthly. An audiogram and vestibular testing should be repeated if there are symptoms of e

3.2.4. Amikacin and kanamycin

Role in treatment regimen. Amikacin and kanamycin (*76,77,101*) are two closely related injectable second-line drugs that a
susceptibility to the agents. There is nearly always complete cross-resistance between the two drugs, but most SM-resistant s
infections, amikacin may be more easily obtained, and serum drug concentration measurements are readily available.
Dose. See Table 3.
Adults (maximum): 15 mg/kg per day (1.0 g/day), intramuscular or intravenous, usually given as a single daily dose (5--7 day
after culture conversion, depending on the efficacy of the other drugs in the regimen (*90*). For persons greater than 59 years
reduced (i.e., 12--15 mg/kg per dose, two or three times per week) in persons with renal insufficiency (see below: Use in Ren
Children (maximum): 15--30 mg/kg per day (1 g/day) intramuscular or intravenous as a single daily dose.
Preparations. Aqueous solution for intramuscular or intravenous injection in vials of 500 mg and 1 g.
Adverse effects.
Ototoxicity: Amikacin and kanamycin may cause deafness, but they cause less vestibular dysfunction than SM (*103,104*). Ot
loss occurred in 24% of patients receiving amikacin, with higher rates occurring among those receiving longer treatment and
Nephrotoxicity: Amikacin and kanamycin may be more nephrotoxic than SM (*95*). Renal impairment was seen in 8.7% of pa
levels, patients receiving larger total doses, and patients receiving other nephrotoxic agents. A frequency of 3.4% was report
Use in pregnancy. Both amikacin and kanamycin are contraindicated in pregnant women because of risk of fetal nephrotoxi
CNS penetration. Only low concentrations of the drugs are found in CSF, although slightly higher concentrations have beer
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Amikacin and kanamycin should
both ototoxicity and nephrotoxicity. Because clearance is almost exclusively by the kidney, dosing adjustments are essential
hemodialysis. In such patients, the dosing frequency should be reduced to two or three times per week, but the dose should b
(Table 15) (*91,92*). Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate D
monitored to avoid toxicity (*91*).
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) No precautions are necessary.
Monitoring. Monitoring should be performed as described for SM. An advantage of amikacin is that serum concentration m
predisposition to hepato-renal syndrome, may be at greater risk for nephrotoxicity from amikacin/kanamycin and should hav

3.2.5. Capreomycin

Role in treatment. Capreomycin is a second-line injectable drug that is used for patients with drug-resistant tuberculosis cau
Dose. See Table 3.
Adults (maximum): 15 mg/kg per day (1.0 g/day), usually given as a single daily dose five to seven times a week, and reduce
on the efficacy of the other drugs in the regimen (*90*). For persons greater than 59 years of age the dose should be reduced to
three times per week in persons with renal insufficiency (see below: Use In Renal Disease) (*91,92*).
Children (maximum): 15--30 mg/kg per day (1 g/day) as a single daily or twice weekly dose.
Preparations. Capreomycin is available in vials of 1 g for both intramuscular and intravenous administration.

Adverse effects.
Nephrotoxicity: Nephrotoxic effects may result in reduced creatinine clearance or potassium and magnesium depletion. Prote
reported to occur in 20--25% of patients (*110,111*).
Ototoxicity: Vestibular disturbances, tinnitus, and deafness appear to occur more often in elderly persons or those with preex
Use in pregnancy. Capreomycin should be avoided in pregnancy because of risk of fetal nephrotoxicity and congenital hear
CNS penetration. Capreomycin does not penetrate into the CSF (*77*).
Use in renal disease. (see Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Capreomycin should be used with
ototoxicity and nephrotoxicity (*112*). Because capreomycin is nearly entirely cleared by the kidneys, dosing adjustments are
patients undergoing hemodialysis. In such patients, the dosing frequency should be reduced to two or three times weekly, bu
concentration-dependent bactericidal effect (Table 15) (*91,92*). Smaller doses may reduce the efficacy of this drug. The drug
(*100,113*). Serum drug concentrations should be monitored to avoid toxicity (*91*).
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) No precautions are necessary.
Monitoring. Monitoring should be performed as described for SM. In addition, serum potassium and magnesium concentrat
3.2.6. p-Aminosalicylic acid
Role in treatment. *p*-Aminosalicylic acid (PAS) is an oral agent used in treatment of drug-resistant tuberculosis caused by o
Dose. See Table 3.
Adults: 8--12 g/day in two or three doses. For PAS granules, 4 g three times daily has been the usual dosage (*114,115*). How
serum concentration (*116*).
Children: 200--300 mg/kg per day in two to four divided doses (*117*).
Preparations. The only available formulation in the United States is granules in 4-g packets (Paser Granules®) (*118*). It was
recent data suggest that this is not necessary (C. Peloquin, personal communication). Tablets (500 mg) are still available in s
Adverse effects.
Hepatotoxicity: In a review of 7,492 patients being treated for tuberculosis, 38 (0.5%) developed hepatitis, of which 28 cases
Gastrointestinal distress: This is the most common side effect of PAS (*122*). In a large study of INH and PAS 11% of patien
gastrointestinal side effects is less with lower doses (8 g daily) and with the granular formulation of the drug.
Malabsorption syndrome: This is characterized by steatorrhea and low serum folate levels (*123*).
Hypothyroidism: This is a common side effect, especially with prolonged administration or concomitant use of ethionamide.
Thyroid function returns to normal after discontinuation of the drug (*124*).
Coagulopathy: A doubling of the prothrombin time that seemed to be lessened by coadministration of streptomycin has been
Use in pregnancy. No studies have been done in humans; however, PAS has been used safely in pregnancy. The drug shoul
resistant tuberculosis.
CNS penetration. In the presence of inflamed meninges, PAS concentrations are between 10--50% of those achieved in seru
Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Approximately 80% of the drug i
insufficiency because of the accumulation of the acetylated form (*123,126,127*). Because both PAS and acetyl-PAS are remo
removal of the drug (*126*).
Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The clearance of PAS is not substantially altered in liver disease
monitoring (*127*).
Monitoring. Hepatic enzymes and thyroid function should be measured at baseline. With prolonged therapy (i.e., more than
3.2.7. Fluoroquinolones
Role in treatment regimen. Of the fluoroquinolones (*128--131*), levofloxacin, moxifloxacin, and gatifloxacin have the most
profile with long-term use of levofloxacin, this drug is the preferred oral agent for treating drug-resistant tuberculosis caused
cannot be used because of intolerance. Data on long-term safety and tolerability of moxifloxacin and gatifloxacin, especially
ciprofloxacin, ofloxacin, and levofloxacin and presumably is a class effect (*132*). Fluoroquinolones should not be considered
intolerant of first-line drugs.
Dose. (See Table 3.) The doses given are for levofloxacin.
Adults: 500--1,000 mg daily.
Children: The long-term (more than several weeks) use of fluoroquinolones in children and adolescents has not been approv
that the drug should be considered for children with MDR tuberculosis. The optimal dose is not known.
Preparations (Levofloxacin). Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500 mg) for intravenous administration
Adverse effects. The adverse effects (*133*) cited are for levofloxacin.
Gastrointestinal disturbance: Nausea and bloating occur in 0.5--1.8% of patients taking the drug.
Neurologic effects: Dizziness, insomnia, tremulousness, and headache occur in 0.5% of patients.
Cutaneous reactions: Rash, pruritis, and photosensitivity occur in 0.2--0.4% of patients.
Use in pregnancy. This class of drugs should be avoided in pregnancy because of teratogenic effects (*119,134*).
CNS penetration. The concentration in CSF after administration of a standard dose of levofloxacin is 16--20% of that in ser

Interference with absorption. Because antacids and other medications containing divalent cations markedly decrease absor
hours of such medications (see Section 7.1: Interactions Affecting Antituberculosis Drugs).
Use in renal disease. (See Section 8.7: Renal Insufficiency and End Stage Renal Disease.) The drug is cleared primarily (80
if creatinine clearance is less than 50 ml/minute (Table 15) (*136*). It is not cleared by hemodialysis; supplemental doses after
Use in hepatic disease. Drug levels are not affected by hepatic disease (*135*). It is presumed to be safe for use in the setting
References

1. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonar
2. Hafner R, Cohn JA, Wright DJ, Dunlap NE, Egorin MJ, Enama ME, Muth K, Peloquin CA, Mor N, Heifets LB. Ea 1997;156:918--923.
3. Hsu KHK. Thirty years after isoniazid: its impact on tuberculosis in children and adolescents. JAMA 1984;251:128
4. Mitchell JR, Zimmerman HJ, Ishak KG, Thorgeirsson UP, Timbrell JA, Snodgrass WR, Nelson SD. Isoniazid liver 192.
5. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy. JAMA 1999;281
6. Kopanoff DE, Snider DE, Caras GJ. Isoniazid-related hepatitis: a US Public Health Service cooperative surveillanc
7. Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid associated hepatitis in 114 patients. Gastroer
8. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. Chest 1991;99:465--471.
9. Franks AL, Binkin NJ, Snider DE Jr, Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hi
10. Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1
11. Salpeter S. Fatal isoniazid-induced hepatitis: its risk during chemoprophylaxis. West J Med 1993;159:560--564.
12. Moulding TS, Redeker AG, Kanel GC. Twenty isoniazid-associated deaths in one state. Am Rev Respir Dis 1989;1
13. Lubing HN. Peripheral neuropathy in tuberculosis patients treated with isoniazid. Am Rev Respir Dis 1953;68:458-
14. Biehl JP, Vilter RW. Effects of isoniazid on pyridoxine metabolism. JAMA 1954;156:1549--1552.
15. Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxici
16. Hong Kong Chest Service, Tuberculosis Research Centre MBMRC. A double-blind placebo-controlled clinical trial Am Rev Respir Dis 1992;145:36--41.
17. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatm
18. Snider DE. Pyridoxine supplementation during isoniazid therapy. Tubercle 1980;61:191--196.
19. Rothfield TG, Bierer WF, Garfield JW. Isoniazid induction of antinuclear antibodies. Ann Intern Med 1978;88:650-
20. Smith CK, Durack DT. Isoniazid and reaction to cheese. Ann Intern Med 1978;88:520--521.
21. Toutoungi M, Carroll RLA, Enrico J-F, Perey L. Cheese, wine, and isoniazid. Lancet 1985;ii:671.
22. Baciewicz AM, Self TH. Isoniazid interactions. South Med J 1985;78:714--718.
23. Ludford J, Doster B, Woolpert SF. Effect of isoniazid on reproduction. Am Rev Respir Dis 1973;108:1170--1174.
24. Weber WW, Hein DW. Clinical pharmacokinetics of isoniazid. Clin Pharmacokinet 1979;4:401--422.
25. Bowersox DW, Winterbauer RH, Stewart GL, Orme B, Barron E. Isoniazid dosage in patients with renal failure. N
26. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on isoniazid, rifampin, pyr
27. Dickinson JM, Mitchison DA. Experimental models to explain the high sterilizing activity of rifampin in the chemo
28. Girling DJ. Adverse reactions to rifampicin in antituberculous regimens. J Antimicrob Chemother 1977;3:115--132
29. Aquinas M, Allan WGL, Horsfall PAL, Jenkins PK, Wong HY, Girling D, Tall R, Fox W. Adverse reactions to dail 1972;1:765--771.
30. Villarino ME, Ridzon R, Weismuller PC, Elcock M, Maxwell RM, Meador J, Smith PJ, Carson ML, Geiter LJ. Rifa Respir Crit Care Med 1997;155:1735--1738.
31. Martinez E, Collazos J, Mayo J. Hypersensitivity reactions to rifampin. Medicine (Baltimore) 1999;78:361--369.
32. Brasil MT, Opromalla DV, Marzliak ML, Noguelra W. Results of a surveillance system for adverse effects in lepro
33. Dutt AK, Jones L, Stead WW. Short-course chemotherapy for tuberculosis with largely twice-weekly isoniazid--rif
34. Zierski M, Bek E. Side-effects of drug regimens used in short-course chemotherapy for pulmonary tuberculosis: a c
35. Poole G, Stradling P, Worlledge S. Potentially serious side effects of high-dose twice-weekly rifampicin. BMJ 1971
36. Sanders WEJ. Rifampin. Ann Intern Med 1976;85:82--86.
37. Lee C-H, Lee C-J. Thrombocytopenia: a rare but potentially serious side effect of initial daily and interrupted use of
38. Steen JS, Stainton-Ellis DM. Rifampicin in pregancy. Lancet 1977;ii:604--605.
39. Holdiness MR. Cerebrospinal fluid pharmacokinetics of the antituberculosis drugs. Clin Pharmacokinet 1985;10:53
40. Acocella G. Clinical pharmacokinetics of rifampicin. Clin Pharmacokinet 1978;3:108--127.
41. CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: princ
42. Griffith DE, Brown BA, Wallace RJ. Varying dosages of rifabutin affect white blood cell and platelet counts in hun pulmonary *Mycobacterium avium* complex disease. Clin Infect Dis 1996;23:1321--1322.
43. Grassi C, Peona V. Use of rifabutin in the treatment of pulmonary tuberculosis. Clin Infect Dis 1996;22:S50--S54.

44. Shafran SD, Singer J, Zarowny DP, Phillips P, Salit I, Walmsley SL, et al. A comparison of two regimens for the tr clarithromycin versus rifampin, ethambutol, clofazamine, and ciprofloxacin. N Engl J Med 1996;335:377--383.
45. Schwander S, Rüsch-Gerdes S, Mateega A, Lutalo T, Tugume S, Kityo C, et al. A pilot study of antituberculosis co Tuber Lung Dis 1995;76:210--218.
46. Dautzenberg B, Olliaro P, Ruf B, Esposito R, Opravil M, Hoy JF, et al. Rifabutin versus placebo in combination wi Clin Infect Dis 1996;22:705--708.
47. Griffith DE, Brown BA, Murphy DT, Girard WM, Couch L, Wallace RJ Jr. Initial (6-month) results of three-times- human immunodeficiency virus-negative patients. J Infect Dis 1998;178:121--126.
48. Griffith DE, Brown BA, Girard WM, Wallace RJ Jr. Adverse events associated with high-dose rifabutin in macrolic Infect Dis 1995;21:594--598.
49. Shafran SD, Deschenes J, Miller M, Phillips P, Toma E. Uveitis and pseudo-jaundice during a regimen of clarithror
50. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. Clin Infect Dis 1996;22:S15--S22.
51. enator D, Bhattacharya M, Bozeman L, Burman W, Catanzaro A, Chaisson R, et al. Rifapentine and isoniazid once tuberculosis in HIV-negative patients: a randomized clinical trial. Lancet 2002;360:528--534.
52. Bock NN, Sterling TR, Hamilton CD, Pachucki C, Wang YC, Conwell DS, et al. A prospective, randomized, doubl continuation phase of tuberculosis treatment. Am J Respir Crit Care Med 2002;165:1526--1530.
53. Keung AC, Eller MG, Weir SJ. Pharmacokinetics of rifapentine in patients with varying degrees of hepatic dysfunc
54. Girling DJ. The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. Tubercle 1984;65:1--4.
55. McDermott W, Ormond L, Muschenhein C, Deuschle K, McCune RM, Tompsett R. Pyrazinamide--isoniazid in tub
56. Campagna M, Calix AA, Hauser G. Observations on the combined use of pyrazinamide (aldinamide) and isoniazid
57. Steele MA, DesPrez RM. The role of pyrazinamide in tuberculosis chemotherapy. Chest 1988;94:845--850.
58. Døssing M, Wilcke JTR, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. T
59. Girling DJ. Adverse effects of antituberculous drugs. Drugs 1982;23:56--74.
60. Jenner PJ, Ellard GA, Allan WG, Singh D, Girling DJ, Nunn AJ. Serum uric acid concentrations and arthralgia amo Tubercle 1981;62:175--179.
61. Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapu Intern Med 1990;112:407--415.
62. Koumbaniou C, Nicopoulos C, Vassiliou M, Manda-Stachouli C, Sakellariou K, Demou GS, Constantopoulos SH. Dis 1998;2:675--678.
63. Cullen JH, Early LJ, Fiore JM. The occurrence of hyperuricemia during pyrazinamide--isoniazid therapy. Am Rev
64. Ellard GA, Humphries MJ, Gabriel M, Teoh R. Penetration of pyrazinamide into the cerebrospinal fluid in tubercul
65. Ellard GA. Absorption, metabolism, and excretion of pyrazinamide in man. Tubercle 1969;50:144--158.
66. Trebucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the l
67. Leibold JE. The ocular toxicity of ethambutol and its relation to dose. Ann N Y Acad Sci 1966;135:904--909.
68. Doster B, Murray FJ, Newman R, Woolpert SF. Ethambutol in the initial treatment of pulmonary tuberculosis. Am
69. Tugwell P, James SL. Peripheral neuropathy with ethambutol. Postgrad Med J 1972;48:667--670.
70. Bobrowitz ID. Ethambutol in pregnancy. Chest 1974;66:20--24.
71. Lewit T, Nebel L, Terracina S, Karman S. Ethambutol in pregnancy: observations on embryogenesis. Chest 1974;6
72. Snider DE, Layde PM, Johnson MW, Lyle MA. Treatment of tuberculosis during pregnancy. Am Rev Respir Dis 1
73. Pilheu JA, Maglio F, Cetrangolo R, Pleus AD. Concentrations of ethambutol in the cerebrospinal fluid after oral adı
74. Strauss I, Earhardt F. Ethambutol absorption, excretion, and dosage in patients with renal tuberuclosis. Chemothera
75. Moulding T, Dutt AK, Reichman LB. Fixed-dose combinations of antituberculous medications to prevent drug resis
76. Kucers A, Bennett NM. The use of antibiotics: a comprehensive review with clinical emphasis, 4th edition. Philade
77. United States Pharmacopeial Dispensing Information. Drug Information for the Health Care Professional. Vol. I. En
78. Murray FJ. A pilot study of cycloserine toxicity: a United States Public Health Service cooperative clinical investig
79. Swash M, Roberts AH, Murnaghan DJ. Reversible pellagra-like encephalopathy with ethionamide and cycloserine.
80. Weinstein HJ, Hallett WY, Sarauw AS. The absorption and toxicity of ethionamide. Am Rev Respir Dis 1962;86:5
81. Pernod J. Hepatic tolerance of ethionamide. Am Rev Respir Dis 1965;92:39--42.
82. Phillips S, Tashman H. Ethionamide jaundice. Am Rev Respir Dis 1963;87:896--898.
83. Lees AW. Ethionamide, 750mg daily, plus isoniazid, 450mg daily, in previously untreated cases of pulmonary tube
84. Narang RK. Acute psychotic reaction probably caused by ethionamide. Tubercle 1972;53:137--138.
85. Drucker D, Eggo MC, Salit IE, Burrow GN. Ethionamide-induced goitrous hypothyroidism. Ann Intern Med 1984;
86. Anonymous. Drugs for tuberculosis. BMJ 1968;3:664--667.
87. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. BMJ 1948;2:769--782.
88. Medical Research Council. Streptomycin treatment of tuberculous meningitis. Lancet 1948;i:582--596.

89. Medical Research Council. Streptomycin in the treatment of tuberculosis. Lancet 1949;i:1273--1276.
90. Andrews RH, Jenkins PA, Marks J, Pines A, Selkon JB, Somner AR. Treatment of isoniazid-resistant pulmonary tu
Wales. Tubercle 1974;55:105--113.
91. Peloquin CA. Using therapeutic drug monitoring to dose the antimycobacterial drugs. Clin Chest Med 1997;18:79--
92. Zhu M, Burman WJ, Jaresko GS, Berning SE, Jelliffe RW, Peloquin CA. Population pharmacokinetics of intraveno
-1045.
93. Morris JT, Cooper RH. Intravenous streptomycin: a useful route of administration. Clin Infect Dis 1994;19:1150--1
94. Cawthorne T, Ranger D. Toxic effect of streptomycin upon balance and hearing. BMJ 1957;1:1444--1446.
95. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents [second of three parts]. N Engl J Med 1977;296:72
96. Joint Committee on the Study of Streptomycin. The effects of streptomycin on tuberculosis in man. JAMA 1947;13
97. Conway N, Birt BD. Streptomycin in pregnancy: effect on the foetal ear. BMJ 1965;2:260--263.
98. Robinson GC, Cambon KG. Hearing loss in infants of tuberculous mothers treated with streptomycin during pregna
99. Anderson DG, Jewell M. The absorption, excretion, and toxicity of streptomycin in man. N Engl J Med 1945;210:4
100. Ellard GA. Chemotherapy of tuberculosis in patients with renal impairment. Nephron 1993;64:169--181.
101. Meyer RD. Amikacin. Ann Intern Med 1981;95:328--332.
102. Allen BW, Mitchison DA, Chan YC, Yew WW, Allan WG, Girling DJ. Amikacin in the treatment of pulmonary tul
103. Finegold SM. Kanamycin. AMA Arch Intern Med 1959;104:15--18.
104. Anonymous. Drug induced deafness. JAMA 1973;224:515--516.
105. Black RE, Lau WK, Weinstein RJ, Young LS, Hewitt WL. Ototoxicity of amikacin. Antimicrob Agents Chemother
106. Gooding PG, Berman E, Lane AZ, Agre K. A review of results of clinical trials with amikacin. J Infect Dis 1976;13
107. Lane AZ, Wright GE, Blair DC. Ototoxicity and nephrotoxicity of amikacin: an overview of Phase II and Phase III
108. Frieden TR, Sherman LF, Maw KL, Fujiwara PI, Crawford JT, Nivin B, et al. A multi-institutional outbreak of high
109. Garfield JW, Jones JM, Cohen NL, Daly JF, McClemont JH. The auditory, vestibular, and renal effects of capreomy
110. Hesling CM. Treatment with capreomycin, with special reference to toxic effects. Tubercle 1969;50:39--41.
111. Aquinas M, Citron KM. Rifampicin, ethambutol, and capreomycin in pulmonary tuberculosis, previously treated wi
165.
112. Black HR, Griffith RS, Peabody AM. Absorption, excretion, and metabolism of capreomycin in normal and disease
113. Lehmann CR, Garrett LE, Winn RE, Springberg PD, Vicks S, Porter DK, Pierson WP, Wolny JD, Brier GL, Black
Dis 1988;138:1312--1313.
114. Storey PB. A comparison of isoniazid--cycloserine with isoniazid--PAS in the therapy of cavitary pulmonary tuberc
115. Peloquin CA, Henshaw TL, Huitt GW, Berning SE, Nitta AT, James GT. Pharmacokinetic evaluation of para-amin
116. Peloquin CA, Berning SE, Huitt GW, Childs JM, Singleton MD, James GT. Once-daily and twice-daily dosing of *p*
117. American Academy of Pediatrics. Tuberculosis. In: Pickering LK, editor. Red book report of the Committee on Infe
593--613.
118. Anonymous. Paserâ granules. In: Physicians' desk reference, 54th edition. Montvale, NJ: Medical Economics Comp
119. Peloquin CA. Antituberculosis drugs: pharmacokinetics. In: Heifets LB, editor. Drug susceptibility in the chemothe
120. Fodor T, Pataki G, Schrettner M. PAS infusion in treatment of multidrug-resistant tuberculosis [letter]. Int J Tuberc
121. Rossouw JE, Saunders SJ. Hepatic complications of antituberculous therapy. Q J Med 1975;XLIV:1--16.
122. British Medical Research Council. Treatment of pulmonary tuberculosis with streptomycin and para-amino-salicyli
123. Jacobus DP. Para-amino-salicylic acid: multi-drug resistant [*sic*] *Mycobacterium tuberculosis*. Washington, DC.
124. Crofton J. Drug treatment of tuberculosis. I. Standard chemotherapy. BMJ 1960;2:370--373.
125. Tarnoky AL, Steingold L. The action of *p*-aminosalicylic acid on prothrombin time in man. J Clin Pathol 1951;4:47
126. Ogg CS, Toseland PA, Cameron JS. Pulmonary tuberculosis in patient on intermittent haemodialysis. BMJ 1968;2:
127. Held H, Fried F. Elimination of para-aminosalicylic acid in patients with liver disease and renal insufficiency. Chen
128. Gillespie SH, Kennedy N. Fluoroquinolones: a new treatment for tuberculosis? Int J Tuberc Lung Dis 1998;2:265--
129. Kennedy N, Fox R, Kisyombe GM, Saruni AO, Uiso LO, Ramsay AR, Ngowi FI, Gillespie SH. Early bactericidal a
1993;148:1547--1551.
130. Kennedy N, Berger L, Curram J, Fox R, Gutmann J, Kisyombe GM, et al. Randomized controlled trial of a drug reg
1996;22:827--833.
131. Fujiwara PI, editor. Clinical policies and protocols. New York: Bureau of Tuberculosis Control, New York City De
132. Sander CC. Review of preclinical studies with ofloxacin. Clin Infect Dis 1991;14:526--538.
133. Ball P, Tillotson G. Tolerability of fluorquinolone antibiotics: past, present, and future. Drug Saf 1995;13:343--358
134. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis 1999;
135. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet 1997;32:101--119.
136. Anonymous. Ofloxacin. Med Lett Drugs Ther 1991;33:71--73.

4. Principles of Antituberculosis Chemotherapy

4.1. Combination Chemotherapy

The primary goals of antituberculosis chemotherapy are to kill tubercle bacilli rapidly, prevent the emergence of drug resista
these goals, multiple antituberculosis drugs must be taken for a sufficiently long time. The theoretical model of chemotherap
host and on the specific activities of antituberculosis drugs. This model is supported by data from numerous in vivo and in vi
It is theorized that there are three separate subpopulations of *M. tuberculosis* within the host. These populations are defined b
subpopulations consists of rapidly growing extracellular bacilli that reside mainly in cavities. This subpopulation, because of
The frequency of these mutations that confer resistance is about 10^{-6} for INH and SM, 10^{-8} for RIF, and 10^{-5} for EMB; thus, t
simultaneous resistance to both drugs in an untreated patient a highly unlikely event (*2*).

INH has been shown to possess the most potent ability to kill rapidly multiplying *M. tuberculosis* during the initial part of th
in this regard by EMB, RIF, and SM. PZA has weak early bactericidal activity during the first 2 weeks of treatment (*3,6*). Dr
the bacillary population.

Early experience in clinical trials demonstrated that multiple agents are necessary to prevent the emergence of a drug-resistan
Shortly after the discovery of SM, it was demonstrated that treatment with this agent alone resulted in treatment failure and d
lessened the likelihood of acquired resistance and treatment failure (*8*). In modern regimens both INH and RIF have consider
SM are also effective in preventing the emergence of drug resistance, whereas the activity of PZA in this regard is poor (*9,10*
tuberculosis.

The rapidly dividing population of bacilli is eliminated early in effective therapy as shown by the early clinical responses and

subpopulations of *M. tuberculosis* account for treatment failures and relapses, especially when the duration of therapy is inad
acidic environment provided by areas of necrosis, and a group that is characterized by having spurts of growth interspersed v
mainly in these two subpopulations that persist beyond the early months of therapy, thus decreasing the risk of relapse (*1*). T
RIF and PZA have the greatest sterilizing activity followed by INH and SM (*11,12*). The sterilizing activity of RIF persists th
containing regimens, PZA provides additive sterilizing activity only during the initial 2 months of therapy. The sterilizing ac
regimens for MDR tuberculosis may include PZA for the full course of treatment if the isolate is susceptible to this agent.

4.2. Optimum Duration of Treatment

Truly effective chemotherapy for tuberculosis became available with the introduction of INH in the early 1950s. Adding INH
months (*13*). Eventually, EMB replaced PAS as the companion agent for INH (*14*). Subsequent investigations of combinatio
intermittently.

The British Medical Research Council (BMRC) in East Africa (*15*) conducted the first large-scale multicenter study of short-
regimen of daily SM and INH increased the proportion of patients whose sputum cultures were negative by 2 months after th
the short-course regimens was no greater than that of the standard 18-month regimen containing SM, INH, and thiacetazone
month regimen of SM, INH, and PZA daily, twice weekly, or three times weekly was associated with a relapse rate of only 5
supervised therapy and SM had to be used for the entire 9 months. Subsequent investigations conducted by the British Thora
achieve excellent results with a 9-month treatment duration, using INH and RIF throughout (*17,18*). The BMRC conducted s
therapy, thereby demonstrating that an all-oral regimen was effective (*19*).

The addition of PZA to a regimen containing INH and RIF enabled further shortening of the duration of therapy to 6 months
supplemented during the first 2 months with PZA and either EMB or SM, was as effective as a 9-month regimen of INH and
an RIF-containing regimen had no additional benefit. The efficacy of the treatment regimens was similar regardless of wheth
Subsequent studies of 6-month regimens have served to refine the approach used currently. USPHS Trial 21 compared self-a
RIF for 9 months (*21*). EMB was added only if INH resistance was suspected. Patients taking the 6-month PZA-containing r
months without PZA and relapse rates were similar for the two regimens (3.5 versus 2.8%).

Investigators in Denver reported a low relapse rate (1.6%) when using a 62-dose, directly observed, 6-month regimen that co
weekly, and 18 weeks of twice weekly INH and RIF (*22*).

Regimens less than 6 months in duration have been shown to have unacceptably high relapse rates among patients with smea
with smear-negative, culture-positive tuberculosis, the relapse rate was about 2% when using a 4-month regimen of daily SM
only 1%. In Arkansas, patients with tuberculosis who had negative smears and cultures were treated with INH and RIF given
(2.4%) patients developed active tuberculosis during 3.5 years of follow-up. Thus, it appears that a 4-month, INH- and RIF-c
Pulmonary Tuberculosis in Adults).

4.3. Intermittent Drug Administration

Nonadherence to the antituberculosis treatment regimen is well known to be the most common cause of treatment failure, rel
opposed to daily dosing, facilitates supervision of therapy, thereby improving the outcome. The concept of intermittent admi
by subsequent laboratory investigations. First, it was noted that a single daily dose of 400 mg of INH was more effective tha
investigators demonstrated that fully supervised twice weekly therapy could be delivered to nonhospitalized patients and that
findings, plus the laboratory results noted below, led to a series of clinical trials that compared daily and intermittent dosing
to be as effective as daily regimens and no more toxic (*20*).

In the laboratory it was noted that in vitro exposure of tubercle bacilli to drugs was followed by a lag period of several days b
maintaining continuous inhibitory drug concentrations was not necessary to kill or inhibit growth of *M. tuberculosis*. Studies
efficacy; however, there was a significant decrease in activity with an 8-day dosing interval (*30,31*).

The concept of intermittent drug administration continues to evolve. Studies have demonstrated that the frequency of drug ad
INH and rifapentine for certain highly selected patients (*32--34*). Because of the newness of these findings the data are prese

The results from three open-label, randomized clinical trials indicate that rifapentine given with INH once a week is safe and
tuberculosis. In a study performed in Hong Kong, patients with pulmonary tuberculosis were allocated at random to receive
weeks for 4 months after completion of a standard 2-month initial phase (*32*). Overall, about 11% of patients in the two rifap
who received three times weekly INH--RIF (control arm) in the continuation phase of treatment. Omitting every third dose o
nonadherence may have a negligible effect. Multivariate analyses showed that the significant prognostic factors were treatme
men). The frequency of failures and relapses was also greater in all three arms if the 2-month culture was positive.

The pivotal study for drug registration was conducted in North America and South Africa among HIV-negative patients with
weekly rifapentine together with daily self-administered INH, PZA, and EMB in the initial 2 months, followed by 4 months
standard four-drug initial phase, followed by twice weekly INH--RIF. Relapse rates during 2 years of follow-up were similar
control arm), and cavitary disease, sputum culture positivity at the end of the initial phase, and nonadherence with INH, EMB
relapse.

The third study was conducted by the CDC Tuberculosis Trials Consortium, and employed a design similar to the Hong Kon
standard 2-month initial phase therapy (*34*). Again, results, as measured by rates of failure/relapse, were remarkably similar t

with 5.6% in the control (INH--RIF twice weekly) arm. However, as in the South Africa study, relapse was significantly asso positivity at 2 months, both of which were more common in the rifapentine arm. With adjustment for these factors, the differ who did not have cavitary disease and had negative sputum cultures at 2 months were low in both treatment arms. However, rifapentine arm was 22% and in the twice weekly INH--RIF arm was 21% (Table 11). In all of the cited studies, rifapentine v A small number of HIV--positive patients were enrolled in the CDC study, but this arm was closed after the development of

References

1. Mitchison DA. Mechanisms of the action of drugs in short-course chemotherapy. Bull Int Union Tuberc 1985;60:36
2. David HL. Probability distribution of drug-resistant mutants in unselected populations of *Mycobacterium tuberculo*
3. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonar
4. Chan SL, Yew WW, Ma WK, Girling DJ, Aber VR, Felmingham D, Allen BW, Mitchison DA. The early bactericic tuberculosis. Tuber Lung Dis 1992;73:33--38.
5. Sirgel FA, Botha FJH, Parkin DP, Van de Wal BW, Donald PR, Clark PK, Mitchison DA. The early bactericidal ac new method of drug assessment. J Antimicrob Chemother 1993;32:867--875.
6. Botha FJH, Sirgel FA, Parkin DP, Van del Wal BW, Donald PR, Mitchison DA. The early bactericidal activity of e (Rifater) in patients with pulmonary tuberculosis. S Afr Med J 1996;86:155--158.
7. McDermott W, Muschenheim C, Hadley SF, Bunn PA, Gorman RV. Streptomycin in the treatment of tuberculosis i 1947;27:769--822.
8. Medical Research Council. Treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid. B
9. East African/British Medical Research Council Pyrazinamide Investigation. A controlled comparison of four regim 1969;50:81--112.
10. Matthews JH. Pyrazinamide and isoniazid used in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 196
11. East African/British Medical Research Council. Controlled clinical trial of four short-course (6-month) regimens of
12. Hong Kong Chest Service/British Medical Research Council. Five year follow-up of a controlled trial of five 6-mor 1342.
13. Medical Research Council. Long-term chemotherapy in the treatment of chronic pulmonary tuberculosis with cavit
14. Bobrowitz ID, Robins DE. Ethambutol--isoniazid versus PAS--isoniazid in original treatment of pulmonary tubercu
15. East African/British Medical Research Council. Controlled clinical trial of four short-course (6-month) regimens of
16. Hong Kong Chest Service/British Medical Research Council. Controlled trial of 6-month and 9-month regimens of Hong Kong. Am Rev Respir Dis 1977;115:727--735.
17. British Thoracic and Tuberculosis Association. Short-course chemotherapy in pulmonary tuberculosis: a controlled
18. British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis: second repo 1982;126:460--462.
19. Hong Kong Chest Service/British Medical Research Council. Five-year follow-up of a controlled trial of five 6-mor 1342.
20. Hong Kong Chest Service/British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Am Rev Respir Dis 1991;143:70
21. Combs DL, O'Brien RJ, Geiter LJ. USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity,
22. Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapu Med 1990;112:407--415.
23. East Africa/British Medical Research Council. Controlled clinical trial of five short-course (4 month) chemotherapy 1981;123:165--170.
24. Singapore Tuberculosis Service/British Medical Research Council. Long-term follow-up of a clinical trial of 6-mon Respir Dis 1986;133:779--783.
25. Hong Kong Chest Service/British Medical Research Council. A controlled trial of 3-month, 4-month, and 6-month Am Rev Respir Dis 1989;139:871--876.
26. Dutt AK, Moers D, Stead WW. Smear and culture negative pulmonary tuberculosis: four-month short course therap
27. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of isoniazid plus PAS with three regimens o World Health Organ 1960;23:535--585.
28. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of intermittent (twice weekly) isoniazid plus tuberculosis. Bull World Health Organ 1964;31:247.
29. Dickinson JM, Mitchison DA. *In vitro* studies on the choice of drugs for intermittent chemotherapy of tuberculosis.
30. Dickinson JM, Ellard GA, Mitchison DA. Suitability of isoniazid and ethambutol for intermittent administration in
31. Dickinson JM, Mitchison DA. Suitability of rifampicin for intermittent administration in the treatment of tuberculos
32. Tam CM, Chan SL, Kam KM, Goodall RL, Mitchison DA. Rifapentine and isoniazid in the continuation phase of t
33. Anonymous. Rifapentine (Priftin) data on file [package insert]. Kansas City, MO: Hoechst Marion Roussel; 1998.

34. Benator D, Bhattacharya M, Bozeman L, Burman W, Catanzaro A, Chaisson R, Gordin F, Horsburgh CR, Horton J isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tub
35. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-r 1847.

5. Recommended Treatment Regimens

5.1. Evidence-based Rating System

To assist in making informed treatment decisions based on the most credible research results, evidence-based ratings have be used in the recommendations for treating latent tuberculosis infection, in which a letter indicating the strength of the recomm recommendation, are assigned to each regimen (*1*). Thus, clinicians can use the ratings to differentiate among recommendati relevant clinical practice and scientific rationale for such practice when clinical trial data are not available.

5.2. Recommended Regimens

There are four basic regimens recommended for treating adults with tuberculosis caused by organisms that are known or pres depending on the circumstances, may not receive EMB in the initial phase of a 6-month regimen, but the regimens are otherv options for the continuation phase of either 4 or 7 months. In Table 2 the initial phase is denoted by a number (1, 2, 3, or 4) a designation (a, b, or c). DOT is the preferred initial management strategy for all regimens and should be used whenever feasi DOT.

5.2.1. Six-month regimens

The current minimal acceptable duration of treatment for all children and adults with culture-positive tuberculosis is 6 month period of INH, RIF, PZA, and EMB given daily throughout (Regimen 1), daily for 2 weeks followed by two times weekly fo specified in Table 2. On the basis of substantial clinical experience, 5 day-a-week drug administration by DOT is considered Although administration of antituberculosis drugs by DOT at 5 days/week, rather than 7 days, has been reported in a large nu therefore is rated AIII.

The recommendation that a four-drug regimen be used initially for all patients is based on the current proportion of new tube supported by a retrospective analysis of data from various BMRC studies indicating that in the presence of INH resistance th PZA, and EMB, was used in the initial phase (*3*). However, if therapy is being initiated after drug susceptibility test results a discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to the first-line ag The continuation phase of treatment should consist of INH and RIF given for a minimum of 4 months (18 weeks). Patients sl regimen (Table 2). The continuation phase can be given daily (Regimen 1a), twice weekly (Regimens 1b and 2a), or three tir for patients who have cavitation on the initial or follow-up chest radiograph and are culture-positive at the time of completio cavities on the chest radiograph, and who have negative sputum AFB smears at completion of the initial phase of treatment r the culture of the sputum obtained at 2 months is positive, observational data and expert opinion suggest that the continuatio

5.2.2. Nine-month regimen

If PZA cannot be included in the initial regimen, or if the isolate is determined to be resistant to PZA (an unusual circumstan and EMB should be given for the initial 2 months (Regimen 4) followed by INH and RIF for 7 months given either daily or t

5.2.3. Alternative regimens

In some cases, either because of intolerance or drug resistance, the above-described regimens cannot be used. In these instan
clinical trials conducted by the BMRC it was concluded that, in the presence of initial resistance to INH, if a four-drug regim
continuation phase there were no treatment failures and 7% relapses compared with 4% relapses among patients with fully su
resistance results are better when PZA is used throughout (*5*). On the basis of these data, when INH cannot be used or the org
as an INH-containing regimen (Rating BI) (*3*). Alternatively, RIF and EMB for 12 months may be used, preferably with PZA
should be given for a minimum of 12--18 months supplemented with PZA during at least the initial 2 months (Rating BIII). A
extensive disease or to shorten the duration (e.g., to 12 months), (*7,8*).

Levofloxacin, moxifloxacin, or gatifloxacin may be useful in alternative regimens, but the potential role of a fluoroquinolone
first-line agents cannot be used because of intolerance, regimens based on the principles described for treating multiple drug-
Organisms) should be used.

5.3. Deciding to Initiate Treatment

The decision to initiate combination chemotherapy for tuberculosis should be based on epidemiologic information, clinical a
(preferably three) and, subsequently, cultures for mycobacteria. Rapid amplification tests, if used, can also confirm the diagn
that a given patient has tuberculosis can be estimated. For example, a patient who has emigrated recently from a high-incider
radiograph should be considered highly likely to have tuberculosis. In such situations combination drug therapy should be in
with a four-drug regimen should be initiated promptly when a patient is seriously ill with a disorder that is thought possibly t
for patients in whom tuberculosis is suspected and who have a life-threatening condition. Disseminated (miliary) tuberculosi
suspected tuberculosis and a high risk of transmitting *M. tuberculosis* if, in fact, she or he had the disease, combination chem
minimize potential transmission.

A positive AFB smear provides strong inferential evidence for the diagnosis of tuberculosis. If the diagnosis is confirmed by
from clinical or radiographic improvement consistent with a response to treatment, the regimen can be continued to complete
initial evaluation, but a negative test does not exclude the diagnosis of active tuberculosis. However, a positive skin test supp
chest radiographs consistent with inactive tuberculosis, a diagnosis of latent tuberculosis infection (see below).

If the cultures are negative, the PPD-tuberculin skin test is positive (5 mm or greater induration), and there is no response to
least 2 months; 2) continue treatment with RIF, with or without INH, for a total of 4 months; or 3) continue treatment with IN
with prior tuberculosis once active disease has been excluded.

If clinical suspicion for active tuberculosis is low, the options are to begin treatment with combination chemotherapy or to de
months) (Figure 2, top). Even when the suspicion of active tuberculosis is low, treatment for latent tuberculosis infection wit

In low-suspicion patients not initially treated, if cultures remain negative, the PPD-tuberculin skin test is positive (5 mm or g
options (Figure 2, top) (*11*). The preferred options are INH for 9 months or RIF, with or without INH, for 4 months. RIF and
who can be monitored closely. However, this last regimen has been associated with an increased risk of hepatotoxicity and sl
of combination chemotherapy is that, once active disease is excluded by negative cultures and lack of clinical or radiographic
can be applied to the total duration of treatment recommended for latent tuberculosis infection (Figure 2, bottom).

5.4. Baseline and Follow-Up Evaluations

Patients suspected of having tuberculosis should have appropriate specimens collected for microscopic examination and myc
obtained 8--24 hours apart. In patients who are not producing sputum spontaneously, induction of sputum using aerosolized h
may be necessary to obtain specimens. Susceptibility testing for INH, RIF, and EMB should be performed on an initial positi
in reference laboratories and be limited to specimens from patients who have had prior therapy, have been in contact of a pat
drugs, or who have positive cultures after more than 3 months of treatment.

At the time treatment is initiated, in addition to the microbiologic examinations, it is recommended that all patients with tube
suggesting a risk for hepatitis B or C, for example, injection drug use, birth in Asia or Africa, or HIV infection, should have s
lymphocyte count measurement. Measurements of AST, bilirubin, alkaline phosphatase, and serum creatinine and a platelet c
(Ishihara tests) should be performed when EMB is to be used.

During treatment of patients with pulmonary tuberculosis, at a minimum, a sputum specimen for AFB smear and culture sho
described subsequently, important decisions concerning the continuation-phase regimen hinge on the microbiological status a
critical, if sputum conversion to negative has not already been documented. For patients who had positive AFB smears at the
weeks until two consecutive specimens are negative) to provide an early assessment of the response to treatment, especially i
sputa are culture negative; this occurs most frequently among patients with far advanced cavitary tuberculosis after the first m
sign of treatment failure, even if noted later in treatment. However, repeat cultures should be obtained to confirm that the ear
Drug susceptibility tests should be repeated on isolates from patients who have positive cultures after 3 months of treatment.
months of treatment should be considered as having failed treatment and managed accordingly.

For patients with extrapulmonary tuberculosis the frequency and kinds of evaluations will depend on the sites involved and t
In addition to the microbiological evaluations, it is essential that patients have clinical evaluations at least monthly to identify
For patients with positive cultures at diagnosis, a repeat chest radiograph at completion of 2 months of treatment may be usef

which subsequent examinations can be compared, but, as with the 2-month examination, it is not essential. When the initial s
is noted, generally by the time 2 months of treatment has been completed. Thus, in patients with negative initial cultures, a cl
treatment is desirable. Generally, follow-up after completion of therapy is not necessary.
As a routine, it is not necessary to monitor liver or renal function or platelet count for patients being treated with first-line dru
measurements. Patients who have stable abnormalities of hepatic or renal function at baseline should have repeat measureme
worsening. Patients receiving EMB should be questioned regarding visual disturbances at monthly intervals; monthly repeat
exceeding 15--20 mg/kg (the recommended range) and for patients receiving the drug for more than 2 months. Monitoring te

5.5. Identification and Management of Patients at Increased Risk of Relapse

The result of a sputum culture at the conclusion of the initial phase of treatment (2 months) has been shown to correlate with
clinical trials performed by the BMRC, the regimens that had the highest proportion of patients with a positive sputum cultur
within 2 years (*17*). Of greater relevance to the current recommendations, data from USPHS Trial 22 comparing once weekly
patients who had a positive culture at 2 months in both study arms (*18*). Cavitation on the initial chest radiograph was also ar
presence of both cavitation and a positive culture at completion of 2 months of therapy was associated with a 21% rate of rel
reported in a retrospective analysis of data from BMRC trials (*17*) and from a USPHS trial conducted in Poland (*19*).
The most effective means of decreasing the likelihood of relapse for patients at increased risk has not yet been determined by
prolongation of the continuation phase from 4 to 6 months decreased the rate of relapse from 22 to 7% ($p < 0.025$) (*20*). Also
month initial phase did not improve the efficacy of RIF-containing regimens (*21*). It has been reported that for patients at hig
7 months resulted in significantly better results compared with patients in an earlier trial (*4*).
In view of this evidence and on the basis of expert opinion, it is recommended that treatment for patients who have cavitation
of therapy should be extended with INH and RIF for an additional 3 months for a total of 9 months (Rating AIII).
In USPHS Study 22 patients treated with INH and RIF twice weekly in the continuation phase who had *either* cavitation on t
relapse (Table 11) (*18*). This rate of adverse outcomes is not deemed to be sufficient to recommend prolongation of the conti
more closely and consideration given to lengthening treatment if there are suggestions of a poor response. Additional factors
culture at 2 months (but not both) might include being more than 10% underweight at diagnosis, having HIV infection, or ha
Patients with noncavitary pulmonary tuberculosis and a negative AFB smear at 2 months who are started on the once weekly
months should have treatment extended by an additional 3 months for a total of 9 months.

5.6. Definition of Completion of Therapy

Treatment for a defined duration without accounting for the number of doses taken can result in undertreatment. Therefore, t
doses taken---not solely on the duration of therapy (Table 2). For example, the 6-month daily (given 7 days/week) regimen s
administered by DOT at 5 days/week, the minimum number of doses is 130. A similar reduction in the target number of dose
In some cases, either because of drug toxicity or nonadherence to the regimen, the specified number of doses cannot be admi
number of doses for the initial phase be delivered within 3 months and those for the 4-month continuation phase be delivered
targets are not met the patient must be considered to have interrupted therapy and be managed as described below.

5.7. Interruptions in Therapy

Interruptions in therapy are common in the treatment of tuberculosis. When interruptions occur, the person responsible for su
intended originally. This decision depends in part on whether the interruption occurred during the initial or the continuation p
serious the effect and the greater the need to restart the treatment from the beginning. Continuous treatment is more importan
developing drug resistance is greatest. During the continuation phase, the number of bacilli is much smaller and the goal of t
status of the patient before and after the interruption are also important considerations.
There is no evidence on which to base detailed recommendations for managing interruptions in treatment, and no recommen
Figure 5), modified from the New York City Bureau of Tuberculosis Control Clinical Policies and Protocols (*22*), is presente
14 days or more in duration, treatment should be restarted from the beginning. However, if the lapse is less than 14 days, the
the initial phase should be given. If the interruption in treatment occurs during the continuation phase after the patient has rec
treatment may not be necessary if the patient's sputum was AFB smear negative on initial presentation. However, for patients
doses is warranted. If the patient has received less than 80% of the planned total doses and the lapse is 3 months or more in d
duration, treatment should be continued to complete a full course.
At the time the patient is returned to treatment sputum cultures should be obtained and repeat drug susceptibility testing perfo
cultures are negative the patient could be treated as having culture-negative tuberculosis and given an additional 4 months of
should be used. If the patient was already being managed with DOT, additional measures will be necessary to ensure comple
Consultation with an expert is recommended to assist in managing treatment interruptions.

References

1. Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Purpose of q
2. CDC. Reported tuberculosis in the United States, 2001. Atlanta, GA: US Department of Health and Human Service
3. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmo
4. Bock NN, Sterling TR, Hamilton CD, Pachucki C, Wang YC, Conwell DS, Mosher A, Samuels M, Vernon AA, Tu

tolerability of rifapentine 600, 900, and 1,200 mg plus isoniazid in the continuation phase of tuberculosis treatment.
5. Hong Kong Chest Service/British Medical Research Council. Five-year follow-up of a controlled trial of five 6-mor 1342.
6. Zierski M. Prospects of retreatment of chronic resistant pulmonary tuberculosis: a critical review. Lung 1977;154:9
7. Hong Kong Chest Service, British Medical Research Council. Controlled trial of 6-month and 9-month regimens of in Hong Kong. Am Rev Respir Dis 1977;115:727--35.
8. Bobrowitz ID. Ethambutol--isoniazid vs streptomycin--ethambutol--isoniazid in original treatment of cavitary tuber
9. Gillespie SH, Kennedy N. Fluoroquinolones: a new treatment for tuberculosis? Int J Tuberc Lung Dis 1998;2:265--
10. Alangaden GJ, Lerner SA. The clinical use of fluoroquinolones for the treatment of mycobacterial diseases. Clin Inf
11. CDC. Core curriculum on tuberculosis: what the clinician should know, 4th edition. Atlanta, GA: US Department o
12. CDC. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infec MMWR 2001;50:733--735.
13. Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, King MD, Kawamura LM, Hopew infection: a multucenter clinical trial. Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT
14. American Thoracic Society/CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J R
15. CDC. Recommendations for prevention of hepatitis C virus (HCV) infection and HCV chronic disease. MMWR 19
16. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. Semin Liver D
17. Mitchison DA. Assessment of new sterilizing drugs for treating pulmonary tuberculosis by culture at 2 months. Am
18. Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampin and isoniazid twice a week 2002;360:528--534.
19. Zierski M, Bek E, Long MW, Snider DE Jr. Short-course (6-month) cooperative tuberculosis study in Poland: result
20. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/ British Medical Research Council. A controlled patients with silicotuberculosis in Hong Kong. Am Rev Respir Dis 1991;143:262--267.
21. Hong Kong Chest Service/British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Am Rev Respir Dis 1991;143:70
22. Bureau of Tuberculosis Control. Clinical policies and protocols, 3rd edition. New York: Bureau of Tuberculosis Co

6. Practical Aspects of Treatment

6.1. Drug Administration

The first-line antituberculosis medications should be administered together as single dose rather than in divided doses. A sing Administering a single daily dose also facilitates using DOT. Ingestion with food delays or moderately decreases the absorpt agents, the effects of food are of little clinical significance. Thus, if patients have epigastric distress or nausea with the first-l dose or changing to a second-line drug. The absorption of INH can be substantially decreased when the drug is ingested with for flavor, rather than glucose or lactose. However, sorbitol can cause diarrhea, limiting the acceptability of the commercial I glucose, such as applesauce, has not been formally evaluated, but has been used successfully by many providers.

Antacids have minimal effects on the absorption of the first-line antituberculosis drugs. With the exception of fluoroquinolon antituberculosis drugs. In the absence of data, it is preferable to administer the drugs on an empty stomach if they are tolerate absorption of the fluoroquinolones, an interaction that has been associated with failure of antibiotic therapy (*2*,*3*). Therefore,

chewable tablet form of didanosine, sucralfate, iron, magnesium, calcium, zinc, or vitamins or dietary supplements (e.g., Ens
Parenteral therapy is indicated for severely ill patients who cannot take oral therapy and may be useful for the uncommon pa
aminoglycosides, capreomycin, and most fluoroquinolones are available for intravenous administration.

6.2. Fixed-Dose Combination Preparations

There are two fixed-dose combination preparations currently available for use in the United States, a combination of INH an
Current Use). (A four-drug combination of INH, RIF, EMB, and PZA is available in some countries.) Two tablets of Rifama
that is available in the United States contains INH (50 mg), RIF (120 mg), and PZA (300 mg). Six tablets of Rifater® would
typically in the United States because the RIF is less bioavailable in this formulation. These fixed-dose combinations have be
for twice weekly treatment. It should be noted that the dose of PZA in Rifater® is such that additional PZA tablets will be req
Although there is no evidence indicating that fixed-dose combination medications are superior to individual drugs, expert op
not possible. Moreover, they are strongly recommended in international recommendations of the WHO and IUATLD. The th
and the potential for reducing medication errors make them preferable to individual medications in many instances. When pr
the trade names of RIF (Rifadin®) and the fixed-dose combinations (Rifamate®, Rifater®).

6.3. Management of Common Adverse Effects

As is true with all medications, combination chemotherapy for tuberculosis is associated with a predictable incidence of adve
their frequency is described in Section 3: Drugs in Current Use.

Mild adverse effects can generally be managed with symptomatic therapy, whereas with more severe effects the offending dr
adverse effects it is at least equally important that first-line drugs not be stopped without adequate justification.

The following is a summary, based largely on clinical experience and expert opinion, of the approaches that should be taken
serious adverse reactions often requires expert consultation.

6.3.1. Gastrointestinal upset: nausea, vomiting, poor appetite, abdominal pain

Gastrointestinal reactions are common, particularly in the first few weeks of therapy. Many of the antituberculosis drugs can
bilirubin should be measured. If the AST level is less than three times the upper limit of normal, the symptoms are assumed r
of normal the symptoms should be assumed to represent hepatic toxicity, and the patient should be evaluated as described be
The initial approach to gastrointestinal intolerance, not associated with hepatic toxicity, is to change the hour of drug adminis
the drug administration should be altered, preferably to be closer to mealtime. Alternatively, food can be taken at the time of
receiving self-administered therapy can take the medications at bedtime. If gastrointestinal intolerance persists it may be best

6.3.2. Rash

All drugs used in treating tuberculosis can cause a rash. The response to a patient with a rash depends on its severity. The ras
case antihistamines should be given for symptomatic relief, but all antituberculosis medications can be continued. A petechia
checked and, if low, RIF hypersensitivity should be presumed to be the cause. RIF should be stopped and the platelet count r
erythematous rash, especially if it is associated with fever and/or mucous membrane involvement, all drugs should be stoppe
and two oral agents) should be started. When the rash is substantially improved the medications can be restarted one by one,
and it is the most important agent), followed by INH, and then EMB or PZA. If the rash recurs the last drug added should be
not be restarted unless the rash was relatively mild and the fourth drug is considered essential for therapy.

6.3.3. Drug fever

Recurrence of fever in a patient who has been receiving therapy for several weeks should suggest drug fever, especially if the
that fever from tuberculosis may persist for as long as 2 months after therapy has been initiated (*6*). Fever may also be a man
HIV Infection) (*7*). The clinical hallmark of drug fever is that the patient looks and feels well despite having a high fever (oft
present.

The first step in management of a possible drug fever is to ensure that there is no superinfection or worsening of tuberculosis
will resolve within 24 hours. Patients with severe tuberculosis should be given at least three new drugs in the interim. Once t
a rash should be followed.

6.3.4. Hepatitis

(Management of patients with baseline abnormal liver function is described in Section 8.8: Hepatic Disease.) Three of the fir
level three or more times the upper limit of normal in the presence of symptoms, or five or more times the upper limit of nor
normal, toxicity can be considered mild, an AST level 5--10 times normal defines moderate toxicity, and an AST level greate
occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with r
It is important to note that an asymptomatic increase in AST concentration occurs in nearly 20% of patients treated with the s
because of modest asymptomatic elevations of AST, but the frequency of clinical and laboratory monitoring should be increa
However, if AST levels are more than five times the upper limit of normal (with or without symptoms) or more than three tir
the patient evaluated carefully. Similarly, a significant increase in bilirubin and/or alkaline phosphatase is cause for a prompt
questioned carefully regarding symptoms suggestive of biliary tract disease and exposures to other potential hepatotoxins, pa
exclusion but in view of the frequency with which other possible causes are present in any given patient, determining the cau
Because the schedule for restarting antituberculosis medications is slower with hepatitis than for rash or drug fever it is gene

of hepatotoxicity can be determined and an appropriate longer term regimen begun. The suspect antituberculosis medications upper limit of normal. (In patients with elevated baseline AST from preexisting liver disease, drugs should be restarted when than is INH or PZA (Table 10) (*10*) and is the most effective agent, it should be restarted first. If there is no increase in AST increase. If symptoms recur or AST increases the last drug added should be stopped. If RIF and INH are tolerated, and hepat circumstance, depending on the number of doses of PZA taken, severity of disease, and bacteriological status, therapy might

6.4. Serum Drug Concentration Measurements

The first-line drugs (INH, RIF, PZA, and EMB) have relatively predictable pharmacokinetics (*11,12*) and are highly efficaci altered metabolism of the first-line drugs, resulting in failure of therapy (*15,16*) Second-line agents have a much narrower th rarely causing toxicity) than the first-line drugs, and the consequences of treatment failure of drug-resistant tuberculosis may therapeutic drug monitoring may be helpful: 1) patients with treatment failure that is not explained by nonadherence or drug the first-line drugs, and 3) the management of multidrug-resistant tuberculosis with second-line drugs. Be aware, however, th treatment. An important limitation is the lack of sufficient data to formulate clinically validated therapeutic ranges for antitub rifamycins is to use the distribution of concentrations achieved in healthy volunteers as the therapeutic range. However, in pa line drugs among HIV-infected patients with active tuberculosis are frequently lower than those in healthy volunteers (*17,18* The disadvantages of therapeutic drug monitoring are as follows: 1) the time necessary, from both patients and providers, to concentrations.

Until more data are available, it seems prudent to restrict therapeutic drug monitoring for the first-line drugs to patients who evidence of severe gastrointestinal or metabolic abnormalities. Examples of such circumstances include severe gastroparesis described above, patients with HIV-related tuberculosis may have an increased incidence of malabsorption of antituberculosi lower drug concentrations among patients with HIV-related tuberculosis is not sufficient to warrant routine therapeutic drug

References

1. Burman W, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of HIV-related
2. Sahai J, Gallicano K, Oliveras L, Khaliq S, Hawley-Foss N, Garber G. Cations in didanosine tablet reduce ciproflox
3. Lomaestro BM, Bailie GR. Effect of multiple staggered doses of calcium on the bioavailability of ciprofloxacin. An
4. CDC. Core curriculum on tuberculosis: what the clinician should know, 4th edition. Atlanta, GA: US Department o
5. Mehta YS, Jijina FF, Badakere SS, Pathare AV, Mohanty D. Rifampin-induced immune thrombocytopenia. Tuberc
6. Kiblawi SS, Jay SJ, Stonehill RB, Norton J. Fever response of patients on therapy for pulmonary tuberculosis. Am l
7. Chien JW, Johnson JL. Paradoxical reactions in HIV and pulmonary TB. Chest 1998;114:933--936.
8. Ormerod LP. Hepatotoxicity of antituberculosis drugs. Thorax 1996;51:111--113.
9. World Health Organization Collaborating Center for International Drug Monitoring. Adverse drug reaction termino
10. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. Chest 1991;99:465
11. Acocella G, Nonis A, Perna G, Patane E, Gialdroni-Grassi G, Grassi C. Comparative bioavailability of isoniazid, rif designed for daily use in antituberculosis chemotherapy. Am Rev Respir Dis 1988;138:886--890.
12. Peloquin CA, Vernon A, Burman W, Benator D. Pharmacokinetics of rifapentine, rifampin, and isoniazid in TB pat
13. Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapu Med 1990;112:407--415.
14. Hong Kong Chest Service/British Medical Research Council. Controlled trial of 4 three-times-weekly regimens and to 24 months. Tubercle 1982;63:89--98.
15. Kimerling ME, Phillips P, Patterson P, Hall M, Robinson CA, Dunlap NE. Low serum antimycobacterial drug level
16. Berning SE, Huitt GA, Iseman MD, Peloquin CA. Malabsorption of antituberculosis medications by a patient with A
17. Sahai J, Gallicano K, Swick L, Tailor S, Garber G, Seguin I, Oliveras L, Walker S, Rachlis A, Cameron DW. Reduc Med 1997;127:289--293.
18. Peloquin CA, Nitta AT, Burman WJ, Brudney KF, Miranda-Massari JR, McGuinness ME, Berning SE, Gerena GT 1996;30:919--925.
19. Chaisson RE, Clermont HC, Holt EA, Cantave M, Johnson MP, Atkinson J, Davis H, Boulos R, Quinn TC, Halsey HIV infection. Am J Respir Crit Care Med 1996;154:1034--1038.
20. El-Sadr W, Perlman DC, Matts JP, Nelson ET, Cohn DL, Salomon N, et al. Evaluation of an intensive intermittent- Clin Infect Dis 1998;26:1148--1158.
21. Choudri SH, Hawken M, Gathau S, Minyiri GO, Watkins W, Sahai J, Sitar DS, Aoki FY, Long R. Pharmacokinetic 1997;25:104--111.
22. Taylor J, Smith PJ. Does AIDS impair the absorption of antituberculosis agents? Int J Tuberc Lung Dis 1998;2:670-

7. Drug Interactions

7.1. Interactions Affecting Antituberculosis Drugs

Drug--drug interactions can result in changes in the concentrations of one or both of the drugs involved. In the case of the an concentrations of the antituberculosis drugs; much more often the antituberculosis drugs cause clinically relevant changes in

fluoroquinolones.

Rifabutin is partially metabolized by cytochrome P450 (CYP) 3A. Inhibitors of CYP3A increase serum concentrations of rifa example, administration of ritonavir, a potent CYP3A inhibitor, with the standard daily dose of rifabutin (300 mg) increases increase) (*1*) and is associated with increased rates of leukopenia, arthralgias, skin discoloration, and uveitis (*2*), all recogniz rifabutin with a CYP3A inducer decreases its concentrations, perhaps to ineffective levels. For example, efavirenz, a potent a Recommendations for making dose adjustments of rifabutin when it is given with commonly used CYP3A inhibitors and ind nature of antiretroviral therapy strongly suggest that the management of cases of HIV-related tuberculosis should involve a p Absorption of the fluoroquinolones is markedly decreased by ingestion with medications containing divalent cations (calciur (*10*), sucralfate (*11*); and the chewable tablet formulation of didanosine (*12*). These drug interactions can be avoided by assu fluoroquinolones (*13*).

7.2. Effects of Antituberculosis Drugs on Other Drugs

7.2.1. Drug interactions due to rifamycins

The drugs used to treat tuberculosis affect the metabolism of many other drugs, and can result in a lack of efficacy (interactio the clinically relevant drug--drug interactions involving the antituberculosis drugs are due to the effect of the rifamycins (rifa inducers of a variety of metabolic pathways, particularly those involving the various isozymes of the cytochrome P450 syste decrease in the serum concentrations of many drugs, sometimes to levels that are subtherapeutic. The rifamycins differ subst intermediate, and rifabutin is the least potent enzyme inducer (*19*).

The well-described, clinically relevant drug--drug interactions involving the rifamycins are presented in Table 12 (*1,5,15,20-* have not been investigated fully and additional clinically relevant interactions undoubtedly will be described. Therefore, it is interactions with rifamycins.

Some of these drug--drug interactions can be managed with close clinical or laboratory monitoring and dose increases of the decrease in concentrations of a concomitant medication may be such that serum concentrations cannot be restored by a dose critical to remember that the dose of this drug will probably need to be decreased within the 2 weeks after the rifamycin is di In some situations, rifabutin can sometimes be used in place of rifampin, if there is an unacceptable drug--drug interaction be inhibitors (*89*). All the rifamycins may cause unacceptable decreases in the serum concentrations of certain drugs, such as de

7.2.2. Drug interactions due to isoniazid

Isoniazid is a relatively potent inhibitor of several cytochrome P450 isozymes (CYP2C9, CYP2C19, and CYP2E1) (*92*), but some drugs to the point of toxicity. The clearest examples of toxicity due to the inhibitory activity of isoniazid are the antico of benzodiazepines metabolized by oxidation, such as diazepam (*85*) and triazolam (*97*), but not those metabolized by conjug serum concentrations of many of these drugs. The available data demonstrate that the inductive effect of rifampin outweighs isoniazid is a decrease in the concentrations of drugs such as phenytoin (*59*) and diazepam (*85*).

Isoniazid may increase toxicity of other drugs---acetaminophen (*98*), valproate (*99*), serotonergic antidepressants (*100*), disu been well studied.

7.2.3. Drug interactions due to fluoroquinolones

Ciprofloxacin (*104*) inhibits the metabolism of theophylline and can cause clinical theophylline toxicity (*105*). However, lev metabolism.

References

(Includes references cited in Table 12.)

1. Cato A, Cavanaugh J, Shi H, Hsu A, Leonard J, Granneman GR. The effect of multiple doses of ritonavir on the pha
2. Sun E, Heath-Chiozzi M, Cameron DW, Hsu A, Granneman RG, Maurath CJ, Leonard JM. Concurrent ritonavir an International Conference on AIDS, Vancouver, Canada, July 7--12, 1996;11:18.
3. Torseth J, Bhatia G, Harkonen S, Child C, Skinner M, Robinson WS, Blaschke TF, Merigan TC. Evaluation of the a
4. Griffith DE, Brown BA, Girard WM, Wallace RJ Jr. Adverse events associated with high-dose rifabutin in macrolic 1995;21:594--598.
5. Benedeck IH, Fiske WD, White SJ, Stevenson D, Joseph JL, Kornhauser DM. Pharmacokinetic interaction between Infectious Diseases Society of America. Denver, CO: Infectious Diseases Society of America; 1998.
6. CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: princi
7. CDC. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among inhibitors. MMWR 2000;49:185--189.
8. Nix DE, Watson WA, Lener ME, Frost RW, Krol G, Goldstein H, Lettieri J, Schentag JJ. Effects of aluminum and 1989;46:700--705.
9. Frost RW, Lasseter KC, Noe AJ, Shamblen EC, Lettieri JT. Effects of aluminum hydroxide and calcium carbonate
10. Polk RE, Healy DP, Sahai J, Drwal L, Racht E. Effect of ferrous sulfate and multivitamins with zinc on absorption
11. Lehto P, Kivisto KT. Effect of sucralfate on absorption of norfloxacin and ofloxacin. Antimicrob Agents Chemothe
12. Sahai J, Gallicano K, Oliveras L, Khaliq S, Hawley-Foss N, Garber G. Cations in didanosine tablet reduce ciproflox

13. Lomaestro BM, Bailie GR. Effect of multiple staggered doses of calcium on the bioavailability of ciprofloxacin. An
14. Gharaibeh MN, Gillen LP, Osborne B, Schwartz JI, Waldman SA. Effect of multiple doses of rifampin on the [^{14}C *l*
495.
15. Dilger K, Greiner B, Fromm MF, Hofmann U, Kroemer HK, Eichelbaum M. Consequences of rifampicin treatment
1999;9:551--559.
16. Bachmann KA, Jauregui L. Use of single sample clearance estimates of cytochrome P450 substrates to characterize
17. Caraco Y, Sheller J, Wood AJ. Pharmacogenetic determination of codeine induction by rifampin: the impact on cod
18. Greiner B, Eichelbaum M, Fritz P, Kreichgauer HP, von Richter O, Zundler J, Kroemer HK. The role of intestinal P
19. Li AP, Reith MK, Rasmussen A, Gorski JC, Hall SD, Xu L, Kaminski DL, Cheng LK. Primary human hepatocytes
potential of xenobiotics: evaluation of rifampin, rifapentine, and rifabutin. Chem Biol Interact 1997;107:17--30.
20. Indinavir Pharmacokinetic Study Group. Indinavir (MK 639) drug interactions studies. In: XI International Confere
21. Kerr B, Lee C, Yuen G, Anderson R, Daniels R, Greitenberger H, et al. Overview of in-vitro and in-vivo drug intera
the 4th Conference on Retroviruses and Opportunistic Infections, Washington, DC, January 22--26, 1997. Foundati
22. Kerr BM, Daniels R, Clendeninn N. Pharmacokinetic interaction of nelfinavir with half-dose rifabutin [abstract]. Ca
23. Moyle J, Buss NE, Goggin T, Snell P, Higgs C, Hawkins DA. Interaction between saquinavir soft-gel and rifabutin
24. Moreno S, Podzamczer D, Blazquez R, Tribarren JA, Ferror B, Reparez J, Pena JM, Cabrero E, Usan L. Treatment
of ritonavir and rifampin. AIDS 2001;15:1185--7.
25. Polk RE, Brophy DF, Israel DS, Patron R, Sadler BM, Chittick GE, Symonds WT, Lou Y, Kristoff D, Stein DS. Ph
Antimicrob Agents Chemother 2001;45:502--508.
26. Borin MT, Chambers JH, Carel BJ, Gagnon S, Freimuth WW. Pharmacokinetic study of the interaction between rif
27. Borin MT, Chambers JH, Carel BJ, Freimuth WW, Aksentijevich S, Piergies AA. Pharmacokinetic study of the inte
1997;35:53--63.
28. Robinson P, Lamsom M, Gigliotti M, Myers M. Pharmacokinetic interaction between nevirapine and rifampin. Inte
29. Benedek IH, Joshi A, Flake WD, White SJ, Stevenson D, Bawerjee G, Kornhauser DM. Pharmacokinetic interactio
Switzerland, 1998;829.
30. Hafner R, Bethel J, Power M, Landry B, Banach M, Mole L, et al. Tolerance and pharmacokinetic interactions of ri
Agents Chemother 1998;42:631--639.
31. Wallace RJJ, Brown BA, Griffith DE, Girard W, Tanaka K. Reduced serum levels of clarithromycin in patients trea
intracellulare infection. J Infect Dis 1995;171:747--750.
32. Apseloff G, Foulds G, LaBoy-Garol L, Willavize S, Vincent J. Comparison of azithromycin and clarithromycin in t
33. Colmenero JD, Fernandez-Gallardo LC, Agundez JA, Sedeno J, Benitez J, Valverde E. Possible implications of dox
1994;38:2798--2802.
34. Drayton J, Dickinson G, Rinaldi MG. Coadministration of rifampin and itraconazole leads to undetectable levels of
35. Doble N, Shaw R, Rowland-Hill C, Lush M, Warnock DW, Keal EE. Pharmacokinetic study of the interation betwe
36. Nicolau DP, Crowe HM, Nightingale CH, Quintiliani R. Rifampin--fluconazole interaction in critically ill patients.
37. Jaruratanasirikul S, Sriwiriyajan S. Effect of rifampicin on the pharmacokinetics of itraconazole in normal voluntee
38. Jaruratanasirikul S, Kleepkaew A. Lack of effect of fluconazole on the pharmacokinetics of rifampicin in AIDS pat
39. Sadler BM, Caldwell P, Scott JD, Rogers M, Blum MR. Drug interaction between rifampin and atovaquone in HIV
Agents and Chemotherapy, San Francisco, CA, September 17--20, 1995.
40. Prober CG. Effect of rifampin on chloramphenicol levels (letter). N Engl J Med 1985;312:788--789.
41. Ridtitid W, Wongnawa M, Mahatthanatrakul W, Chaipol P, Sunbhanich M. Effect of rifampin on plasma concentra
42. Barditch-Crovo P, Trapnell CB, Ette E, Zacur HA, Coresh J, Rocco LE, Hendrix CW, Flexner C. The effects of rifa
contraceptive. Clin Pharmacol Ther 1999;65:428--438.
43. Gupta KC, Ali MY. Failure of oral contraceptive with rifampicin. Med J Zambia 1980;15:23.
44. LeBel M, Masson E, Guilbert E, Colborn D, Paquet F, Allard S, Vallee F, Narang PK. Effects of rifabutin and rifam
1998;38:1042--1050.
45. Kivisto KT, Villikka K, Nyman L, Anttila M, Neuvonen PJ. Tamoxifen and toremifene concentrations in plasma ar
46. Nolan SR, Self TH, Norwood JM. Interaction between rifampin and levothyroxine. South Med J 1999;92:529--531.
47. Christensen HR, Simonsen K, Hegedus L, Hansen BM, Dossing M, Kampmamn JP, Hansen JM. Influence of rifam
(Copenh) 1989;121:406--410.
48. Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin-induced methadone withdrawal. N Engl J Med 1976;294
49. Brown LS, Sawyer RC, Li R, Cobb MN, Colborn DC, Narang PK. Lack of a pharmacologic interaction between rif
1996;43:71--77.
50. Romankiewicz JA, Ehrman M. Rifampin and warfarin: a drug interaction. Ann Intern Med 1975;82:224--225.
51. Vandevelde C, Chang A, Andrews D, Riggs W, Jewesson P. Rifampin and ansamycin interactions with cyclosporin

52. Hebert MF, Roberts JP, Prueksaritanont T, Benet LZ. Bioavailability of cyclosporine with concomitant rifampin ad
1992;52:453--457.
53. Chenhsu RY, Loong CC, Chou MH, Lin MF, Yang WC. Renal allograft dysfunction associated with rifampin--tacr
54. Kyriazopoulou V, Parparousi O, Vagenakis AG. Rifampicin-induced adrenal crisis in addisonian patients receiving
55. Perucca E, Grimaldi R, Frigo GM, Sardi A, Monig H, Ohnhaus EE. Comparative effects of rifabutin and rifampicin
599.
56. Lin FL. Rifampin-induced deterioration in steroid-dependent asthma. J Allergy Clin Immunol 1996;98:1125.
57. Carrie F, Roblot P, Bouquet S, Delon A, Roblot F, Becq-Giraudon B. Rifampin-induced nonresponsiveness of giant
58. McAllister WA, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of p
59. Kay L, Kampmann JP, Svendsen TL, Vergman B, Hansen JE, Skovsted L, Kristensen M. Influence of rifampin and
60. Ebert U, Thong NQ, Oertel R, Kirch W. Effects of rifampicin and cimetidine on pharmacokinetics and pharmacody
61. Barbarash RA, Bauman JL, Fischer JH, Kondos GT, Batenhorst RL. Near-total reduction in verapamil bioavailabili
62. Holtbecker N, Fromm MF, Kroemer HK, Ohnhaus EE, Heidemann H. The nifedipine--rifampin interaction: evidenc
1123.
63. Yoshimoto H, Takahashi M, Saima S. [Influence of rifampicin on antihypertensive effects of dihydropiridine calciu
64. Herman RJ, Nakamura K, Wilkinson GR, Wood AJ. Induction of propranolol metabolism by rifampicin. Br J Clin I
65. Bennett PN, John VA, Whitmarsh VB. Effect of rifampicin on metoprolol and antipyrine kinetics. Br J Clin Pharma
66. Kandiah D, Penny WJ, Fraser AG, Lewis MJ. A possible drug interaction between rifampicin and enalapril. Eur J C
67. Williamson KM, Patterson JH, McQueen RH, Adams KF Jr, Pieper JA. Effects of erythromycin or rifampin on losa
68. Gault H, Longerich L, Dawe M, Fine A. Digoxin--rifampin interaction. Clin Pharmacol Ther 1984;35:750--754.
69. Poor DM, Self TH, Davis HL. Interaction of rifampin and digitoxin. Arch Intern Med 1983;143:599.
70. Damkier P, Hansen LL, Brosen K. Rifampicin treatment greatly increases the apparent oral clearance of quinidine.
71. Ahmad D, Mathur P, Ahuja S, Henderson R, Carruthers G. Rifampicin--quinidine interaction. Br J Dis Chest 1979;
72. Pentikainen PJ, Koivula IH, Hiltunen HA. Effect of rifampicin treatment on the kinetics of mexiletine. Eur J Clin Pl
73. Rice TL, Patterson JH, Celestin C, Foster JR, Powell JR. Influence of rifampin on tocainide pharmacokinetics in hu
74. Gillum JG, Sesler JM, Bruzzese VL, Israel DS, Polk RE. Induction of theophylline clearance by rifampin and rifabu
75. Self TH, Morris T. Interaction of rifampin and chlorpropamide. Chest 1980;77:800--801.
76. Zilly W, Breimer DD, Richter E. Induction of drug metabolism in man after rifampicin treatment measured by incre
77. Surekha V, Peter JV, Jeyaseelan L, Cherian AM. Drug interaction: rifampicin and glibenclamide. Natl Med J India
78. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ, Kivisto KT. Rifampin decreases the plasma concentrations and
79. Niemi M, Kivisto KT, Backman JT, Neuvonen PJ. Effect of rifampicin on the pharmacokinetics and pharmacodyna
80. Kyrklund C, Backman JT, Kivisto KT, Neuvonen M, Laitila J, Neuvonen PJ. Rifampin greatly reduces plasma simv
81. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. Clin Pharmacokinet 2001;40:263--281.
82. Self T, Corley CR, Nabhan S, Abell T. Case report: interaction of rifampin and nortriptyline. Am J Med Sci 1996;3
83. Kim YH, Cha IJ, Shim JC, Shin JG, Yoon YR, Kim YK, et al. Effect of rifampin on the plasma concentration and t
Psychopharmacol 1996;16:247--252.
84. Misra LK, Erpenbach JE, Hamlyn H, Fuller WC. Quetiapine: a new atypical antipsychotic. S D J Med 1998;51:189
85. Ochs HR, Greenblatt DJ, Roberts GM, Dengler HJ. Diazepam interaction with antituberculosis drugs. Clin Pharmac
86. Yuan R, Flockhart DA, Balian JD. Pharmacokinetic and pharmacodynamic consequences of metabolism-based drug
87. Villikka K, Kivisto KT, Luurila H, Neuvonen PJ. Rifampin reduces plasma concentrations and effects of zolpidem.
88. Kivisto KT, Lamberg TS, Neuvonen PJ. Interactions of buspirone with itraconazole and rifampicin: effects on the p
Toxicol 1999;84:94--97.
89. Narita M, Stambaugh JJ, Hollender ES, Jones D, Pitchenik AE, Ashkin D. Use of rifabutin with protease inhibitors
2000;30:779--783.
90. Cox SR, Herman BD, Batta DH, Carel BJ, Carberry PA. Delavirdine and rifabutin: pharmacokinetic evaluation in H
and Opportunistic Infections, February 1--5, Chicago, IL, 1998. p. 144.
91. Smith JA, Hardin TC, Patterson TF, Rinaldi MG, Graybill JR. Rifabutin decreases itraconazole plasma levels in pat
January 29--February 2, 1995;26.
92. Self TH, Chrisman CR, Baciewicz AM, Bronze MS. Isoniazid drug and food interactions. Am J Med Sci 1999;317:
93. Kutt H, Brennan R, Dehajia H, Verebely K. Dephenylhydantoin intoxiciation: a complication of isoniazid therapy.
94. Miller RR, Porter J, Greenblatt DJ. Clinical importance of the interaction of phenytoin and isoniazid: a report from
95. Block SH. Carbamazepine--isoniazid interaction. Pediatrics 1982;69:494--495.
96. Valsalan VC, Cooper GL. Carbamazepine intoxication caused by interaction with isoniazid. BMJ 1982;285:261--26
97. Ochs HR, Greenblatt DJ, Knuchel M. Differential effect of isoniazid on triazolam oxidation and oxazepam conjugat
98. Murphy R, Swartz R, Watkins PB. Severe acetaminophen toxicity in a patient receiving isoniazid. Ann Intern Med

99. Jonville AP, Gauchez AS, Autret E, Billard C, Barbier P, Nsabiyumva F, Breteau M. Interaction between isoniazid
100. Judd FK, Mijch AM, Cockram A, Norman TR. Isoniazid and antidepressants: is there cause for concern? Int Clin Ps
101. Whittington HG, Grey L. Possible interaction between disulfiram and isoniazid. Am J Psychiatry 1969;125:1725--1
102. Rosenthal AR, Self TH, Baker ED, Linden RA. Interaction of isoniazid and warfarin. JAMA 1977;238:2177.
103. Torrent J, Izquierdo I, Cabezas R, Jane F. Theophylline--isoniazid interaction. DICP 1989;23:143--145.
104. Robson RA, Begg EJ, Atkinson HC, Saunders DA, Frampton CM. Comparative effects of ciprofloxacin and lomefl
105. Raoof S, Wollschlager C, Khan FA. Ciprofloxacin increases serum levels of theophylline. Am J Med 1987;82:115--
106. Gisclon LG, Curtin CR, Fowler CL, Williams RR, Hafkin B, Natarajan J. Absence of a pharmacokinetic interaction 1997;37:744--750.
107. Niki Y, Hashiguchi K, Miyashita N, Nakajima M, Matsushima T. Influence of gatifloxacin, a new quinolone antiba
108. Balfour JA, Wiseman LR. Moxifloxacin. Drugs 1999;57:363--373; 374 [discussion].

8. Treatment in Special Situations

8.1. HIV Infection

Treatment of tuberculosis in patients with HIV infection follows the same principles as treatment of HIV-uninfected patients infection. These differences include the potential for drug interactions, especially between the rifamycins and antiretroviral a the development of acquired resistance to rifamycins when treated with highly intermittent therapy.

8.1.1. Clinical trials of treatment for tuberculosis in HIV-infected patients

There have been seven prospective studies of 6-month regimens for the treatment of pulmonary tuberculosis in patients with controlled trials (*1--4*), and three were observational in nature (*5,6*). These studies differed somewhat in design, patient popu therefore, it is difficult to provide meaningful cross-study comparisons. All of the studies reported a good early clinical respo treatment failure rates were similar to these indices of treatment efficacy in patients without HIV infection.

Recurrence rates have varied among studies, with most reporting rates of 5% or less (*2,3,5,6*). In one study from the Democr compared with 3% in the 12-month arm, nonadherence in the continuation phase and/or exogenous reinfection may have co versus twice weekly INH--RIF in the continuation phase of therapy, 5 of 30 (17%) HIV-infected patients receiving treatment -RIF arm (*4*). Four of the five relapsed patients in the once weekly group had resistance to rifampin alone compared with no it is difficult to interpret the relapse rate of 10%.

In an observational study of twice weekly INH--rifabutin among HIV-infected tuberculosis patients also receiving antiretrov failure/relapse was low (4.6%), *M. tuberculosis* isolated from all five of these patients was resistant to RIF alone. The pheno RIF therapy, albeit at a lower rate (*3*). In all of these studies, acquired RIF resistance occurred only among patients with CD4 was given daily.

A consistent finding in the treatment studies has been a high mortality rate among HIV-seropositive patients. In most studies tuberculosis, but deaths during the continuation phase of therapy are usually due to other AIDS-related conditions. Mortality advanced HIV disease (*1,3,6,8*). However, the use of effective antiretroviral therapy during the treatment of tuberculosis in p described subsequently (*9*).

A major concern in treating tuberculosis in the setting of HIV infection is the interaction of RIF with antiretroviral agents (se against *M. tuberculosis* but has less of an effect in inducing hepatic microsomal enzymes than RIF. Data from clinical trials s colleagues (*10*) reported the first randomized clinical trial comparing rifabutin (150 and 300 mg) with RIF in a 6-month regi there were few adverse reactions.

Investigators from South Africa reported a randomized, open-label trial comparing rifabutin with RIF in a standard four-drug the HIV seroprevalence was reportedly low at the time of the study. In the continuation phase, the medications were given tw of those given rifabutin had negative sputum cultures. The relapse rate was 3.8% in the RIF group versus 5.1% in the rifabut Only one study examining the effectiveness of rifabutin included HIV-infected patients (*12*). A single blind randomized stud rifabutin together with INH, EMB, and PZA. Time to sputum conversion was similar between groups when controlling for b Investigators in Uganda have reported a higher mortality rate among HIV-infected patients treated with regimens that did no associated with shortened survival compared with an RIF-based regimen. In addition to the higher mortality associated with the setting of HIV infection (*14,15*). Thus, every effort should be made to use a rifamycin-based regimen for the entire cours

8.1.2. Treatment recommendations

Recommendations for the treatment of tuberculosis in HIV-infected adults are, with two exceptions, identical to those for HI EMB given for 2 months followed by INH and RIF for 4 months when the disease is caused by organisms that are known or intermittent administration as listed in Table 1 and described in Section 5.2: Recommended Regimens. However, on the basi cell counts <100/μl, it is recommended that patients with advanced HIV disease be treated with daily or three times weekly t continuation phase should not be used in patients with $CD4^+$ cell counts <100/μl. Twice weekly therapy may be considered i administration of INH--rifapentine in the continuation phase should not be used in any patient with HIV infection.

Six months should be considered the minimum duration of treatment for adults, even for patients with culture-negative tuber 2 months of therapy), prolongation of the continuation phase to 7 months (a total of 9 months treatment) should be strongly c

HIV-related tuberculosis. Although there are no data on which to base recommendations, the American Academy of Pediatri
(*17*).

All patients with tuberculosis should be advised to undergo voluntary counseling and HIV testing. Efforts should be made to
tuberculosis. Ideally, patients should be managed by physicians who are expert in the treatment of tuberculosis/HIV coinfect
communication between them is essential and should occur frequently throughout the course of treatment.

8.1.3. Safety and tolerability

The frequency of antituberculosis drug-related toxicity in patients with HIV infection has varied from study to study. In a ret
change of regimen because of adverse drug reactions (*18*). RIF was the drug implicated most commonly, producing an adver
patients developed a rash but in none was the treatment interrupted (*1*). Paresthesia developed in 21% of the cases, suggestin
Other investigators have reported low rates of significant adverse reactions (*3,5,6,19*). In the three times weekly regimen stuc
patients (*6*). In HIV-infected patients it is often difficult to distinguish an adverse reaction to antituberculosis drugs from the
taken concurrently. Because of the difficulties in diagnosing a drug reaction and in determining the responsible agent, the firs
strong evidence that the antituberculosis drug was the cause of the reaction. In such situations consultation with an expert in
In a study reported by Ungo and associates (*20*), it was demonstrated that the relative risk of developing drug-induced hepatc
respectively, compared with a 14-fold relative risk in patients with both hepatitis C virus and HIV infections. This finding wa
greater in patients with HIV and hepatitis C virus who were given INH (*21*). Current IDSA and USPHS guidelines recomme
probably prudent to provide more frequent clinical and laboratory monitoring, as described for patients with preexisting liver
tuberculosis.

8.1.4. Concurrent administration of antiretroviral agents and rifamycins

Most patients with tuberculosis have relatively advanced HIV disease and, thus, antiretroviral therapy is indicated (*23*). Anti
tuberculosis, if it is otherwise indicated. Nevertheless, it is not advisable to begin both antiretroviral therapy and combinatior
new drugs with interactions and overlapping toxicities that would be difficult to evaluate. Although there are few data on wh
initiated first.

Although antiretroviral therapy has a dramatic effect in decreasing progression of HIV disease (decreasing $CD4^+$ cell counts,
antiretroviral therapy in the setting of tuberculosis therapy is complex. In those patients not already receiving antiretroviral th
associated with a high incidence of side effects and paradoxical reactions, some severe enough to warrant discontinuation of
in a short time period may present a tremendous adherence challenge for patients adjusting to the diagnoses of both tuberculc
antituberculosis therapy has the potential advantages of being better able to ascribe a specific cause for a drug side effect, dec
patient. Until there have been controlled studies evaluating the optimal time for starting antiretroviral therapy in patients with
initial response to treatment for tuberculosis, occurrence of side effects, and ready availability of multidrug antiretroviral ther
initiated at any time after tuberculosis treatment was begun, based on current recommendations (*23*). For patients who are alr
regimen may need to be modified on the basis of the risk of drug--drug interactions, as described in Section 7: Drug Interacti
Even though drug interactions are common, a rifamycin should not be excluded from the tuberculosis treatment regimen for
treatment regimen is likely to delay sputum conversion, will prolong the duration of therapy, and possibly result in a poorer c
and should be used if these categories of antiretroviral agents are being administered.

The categories of antiretroviral agents available currently are nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide
(NNRTIs), and protease inhibitors (PIs). The NRTIs and NtRTIs do not have clinically significant drug interactions with the
rifamycins without any dose adjustment being necessary. However, the PIs and NNRTIs, depending on the specific drug, ma
the serum concentration of rifabutin, as described in Section 7.1: Interactions Affecting Antituberculosis Drugs.

When rifabutin is combined with antiretroviral agents, its dose and the dose of the antiretroviral agents may require adjustme
PIs (*25*). All 25 patients became culture negative by 2 months and no relapses were reported after a median follow-up of 13 r
achieving viral loads of less than 500 copies/ml. Thus, it appears that both tuberculosis and HIV can be treated successfully v
Previous guidelines from CDC specifically stated that RIF was contraindicated in patients who were taking any PI or NNRTI
certain combinations of antiretroviral agents (*27,28*). As recommended by CDC (*27*), rifampin can be used with a regimen of
(either hard-gel or soft-gel capsule), and with a triple nucleoside regimen. As new antiretroviral agents and more pharmacoki
recommendations are frequently revised, obtaining the most up-to-date information from the CDC website, http://www.cdc.g
compiled by Medscape, can be found at http://www.medscape.com/updates/quickguide.

When starting NNRTIs or PIs for tuberculosis patients receiving RIF, a 2-week "washout" period is generally recommended
enzyme-inducing activity of RIF. During this time, rifabutin may be started to ensure that the tuberculosis treatment regimen
tuberculosis is begun, an assessment of the antiretroviral regimen should be undertaken and, if necessary, changes made to en
determination of whether to use RIF and the dose of the rifamycin must take into account the antiretroviral regimen.

8.1.5. Paradoxical reaction

On occasion, patients have a temporary exacerbation of symptoms, signs, or radiographic manifestations of tuberculosis (par
patients without HIV infection, especially with lymphadenitis, but it is more common among HIV-infected patients. These re
brought about by antiretroviral therapy or, perhaps, by treatment of the tuberculosis itself. Narita and colleagues (*29*) reporte

paradoxical worsening after beginning treatment for tuberculosis compared with 7% of those who were not taking antiretrovi
with tuberculosis developed paradoxical worsening and the reactions were not associated with antiretroviral therapy. Signs o
lymph nodes, new lymphadenopathy, expanding central nervous system lesions, worsening of pulmonary parenchymal infilt
reaction only after a thorough evaluation has excluded other possible causes, especially tuberculosis treatment failure.
A paradoxical reaction that is not severe should be treated symptomatically without a change in antituberculosis or antiretrov
airway compromise from enlarging lymph nodes, enlarging serosal fluid collections, and sepsis syndrome, have not been stu
1 mg/kg and gradually reduced after 1 to 2 weeks.

References

1. Perriens JH, St. Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, Portaels F, Willame JC, Mandala JK, Kabo treatment for either 6 or 12 months. N Engl J Med 1995;332:779--784.
2. Kennedy N, Berger L, Curram J, Fox R, Gutmann J, Kisyombe GM, Ngowi FI, Ramsay ARC, Saruni AOS, Sam N that includes ciprofloxacin for the treatment of pulmonary tuberculosis. Clin Infect Dis 1996;22:827--833.
3. El-Sadr WM, Perlman DC, Matts JP, Nelson ET, Cohn DL, Salomon N, Olibrice M, et al. Evaluation of an intensiv immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for Clinical Research o 1158.
4. Vernon, A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-t Consortium. Lancet 1999;353:1843--1847.
5. Kassim S, Sassan-Morokro M, Ackah A, Abouya LY, Digbeu H, Yesso G, et al. Two year follow-up of persons wit West Africa. AIDS 1995;9:1185--1191.
6. Chaisson RE, Clermont HC, Holt EA, Cantave M, et al. JHU-CDS Research Team. Six-months supervised intermit Care Med 1996;154:1034--1038.
7. CDC. Notice to readers: acquired rifamycin resistance in persons with advanced HIV disease being treated for activ
8. Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. Human immunodeficiency virus and the outcome of treat Med 1999;159:733--740.
9. Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, et al. Treatment of tuberculosis in HIV-infecte
10. Gonzalez-Montaner LJ, Natal S, Yonchaiyud P, Olliaro P. Rifabutin for the treatment of newly-diagnosed pulmona Dis 1994;75:341--347.
11. McGregor MM, Olliaro P, Womarans L, Mabuza B, Bredell M, Felten MK, Fourie PB. Efficacy and safety of rifabu Care Med 1996;154:1462--1467.
12. Schwander S, Rusch-Gerdes S, Mateega A, Lutalo T, Tugume S, Kityo C, Rubaramira R, Mugyenyi P, Okwera A, of patients with newly diagnosed pulmonary tuberculosis. Tuber Lung Dis 1995;76:210--218.
13. Wallis RS, Helfand MS, Whalen CC, Johnson JL, Mugerwa RD, Vjecha M, Okwera A, Ellner JJ. Immune activatio 1996;77:516--523.
14. Hawken M, Nunn P, Gathua S, Brindle R, Godfrey-Faussett P, Githui W, et al. Increased recurrence of tuberculosis
15. Perriens JH, Colebunders RL, Karahunga C, Willame J-C, Jeugmans J, Kaboto M, et al. Increased mortality and tub compared with HIV seronegative patients with pulmonary tuberculosis in Kinshasa, Zaire. Am Rev Respir Dis 199
16. CDC. Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis wit
17. American Academy of Pediatrics. Tuberculosis. In: Pickering LJ, editor. Red book report of the Committee on Infec -613.
18. Small PM, Schecter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC. Treatment of tuberculosis in patien
19. Jones BE, Otaya M, Antoniskis D, Sian S, Wang F, Mercado A, Davidson PT, Barnes PF. A prospective evaluation Respir Crit Care Med 1994;150:1499--1502.
20. Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D, Albanese AP, Pitchenik AE. Antituberculosis drug-induc Respir Crit Care Med 1998;157:1871--1876.
21. Sadaphal P, Astemborski J Graham NM, Sheely L, BondsM, Madison A, Vlahov D, Thomas DL, Sterling TR. Ison users infected with *Mycobacterium tuberculosis* Clin Infect Dis 2001;33:1687--1691.
22. United States Public Health Service (USPHS), Infectious Diseases Society of America (IDSA). USPHS/IDSA guid virus. November 28, 2001. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=69
23. Yeni PG, Hammer SM, Carpenter CCJ, Cooper DA, Fischl MA, Gatell JM, Gazzard BG, Hirsch MS, Jacobsen DM recommendations of the International AIDS Society---USA panel. JAMA 2002;288:222--235.
24. Okwera A, Whalen C, Byekwaso F, Vjecha J, Johnson J, Huebner R, Mugerwa R, Ellner J. Randomized trial of thia Ugandans. Makere University--Case Western Reserve University Research Collaboration. Lancet 1994;344:1323--1
25. Narita M, Stambaugh JJ, Hollender ES, Jones D, Pitchenik AE, Ashkin D. Use of rifabutin with protease inhibitors 2000;30:779--783.
26. CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: princi

27. CDC. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among inhibitors. MMWR 2000;49:185--200.
28. Burman WJ, Jones BE. Treament of HIV-related tuberculosis in the era of effective antiretroviral therapy. Am J Re
29. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral th
30. Wendel KA, Alwood KS, Gachuhi R, Chaisson RE, Bishai WR, Sterling TR. Paradoxical worsening of tuberculosis

8.2. Children and Adolescents

Children most commonly develop tuberculosis as a complication of the initial infection with *M. tuberculosis* (primary tuberc and lower lung zone infiltrates, and the absence of cavitation. However, children, occasionally, and adolescents, more freque sputum production). The lesions of primary tuberculosis have a smaller number of *M. tuberculosis* organisms than those of a resistance are rare phenomena among children.

Because it is more difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis than from an adult, it is frequ person presumed to be the source of the infection in the child to guide the choice of drugs for the child. In children in whom organisms via three early morning gastric aspirations (optimally during hospitalization), bronchoalveolar lavage, or tissue bi Because tuberculosis in infants and children younger than 4 years of age is more likely to disseminate, treatment should be st tuberculin skin test and an abnormal chest radiograph (atelectasis, parenchymal infiltrate, or hilar adenopathy) should receive Several controlled and observational trials of 6-month therapy in children with pulmonary tuberculosis caused by organisms months of therapy with INH and RIF has been shown to be effective for hilar adenopathy and pulmonary disease caused by c INH and RIF, supplemented during the first 2 weeks to 2 months with PZA. This three-drug combination has a success rate c times weekly therapy from the beginning with good results (*1,7*).

Many experts prefer to treat children with three (rather than four) drugs in the initial phase because the bacillary population i drugs, and because of the difficulty in performing visual acuity tests in young children who are being treated with EMB. In c susceptible, the initial phase should consist of INH, RIF, and PZA. If the susceptibility of the presumed infecting strain is no three drugs. However, children and adolescents with adult-type pulmonary tuberculosis, as defined above, should be treated (*10*). When epidemiologic circumstances (Table 6) suggest an increased risk of drug-resistant organisms being present, EME

routine eye testing. Older children should have monthly evaluations of visual acuity and color discrimination while taking Et
The usual doses for daily and twice weekly treatment in children are listed in Section 3, Drugs in Current Use, and shown in
recommended for infants, children, and adolescents who are being treated with INH and who have nutritional deficiencies, s
DOT should be used for all children with tuberculosis. The lack of pediatric dosage forms of most antituberculosis medicatic
tolerance of the medications must be monitored closely. Parents should not be relied on to supervise DOT.
Because of the difficulties in isolating *M. tuberculosis* from children, bacteriological examinations are less useful in evaluati
importance. However, hilar adenopathy and resultant atelectasis may require 2--3 years to resolve. Thus, a persisting abnorm
Recognition of treatment failure or relapse in a child is subject to the same difficulties as making a diagnosis. Thus, clinical a
cultures. A decision to modify the drug regimen should not be made lightly, but often must be made on clinical grounds only
In general, extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. Exceptions
month therapy. A fourth drug is recommended in the initial phase when there is disseminated tuberculosis. The recommende
The optimal treatment of pulmonary tuberculosis in children and adolescents with HIV infection is unknown. The American
(INH and RIF, plus PZA for the first 2 months), and the total duration of therapy should be at least 9 months (*11*).

References

1. Te Water Naude JM, Donald PR, Hussey GD, Kibel MA, Louw A, Perkins DR, Schaaf HS. Twice weekly vs. daily
2. Tsakalidis D, Pratsidou P, Hitoglou-Makedou A, Tzouvelekis G, Sofroniadis I. Intensive short course chemotherapy
3. Kumar L, Dhand R, Singhi PO, Rao KL, Katariya S. A randomized trial of fully intermittent vs. daily followed by i 1990;9:802--806.
4. Biddulph J. Short course chemotherapy for childhood tuberculosis. Pediatr Infect Dis J 1990;9:794--801.
5. Reis FJC, Bedran MBM, Moura JAR, Assis I, Rodrigues ME. Six-month isoniazid-rifampin treatment for pulmonar
6. Jacobs RF, Abernathy RS. The treatment of tuberculosis in children. Pediatr Infect Dis J 1985;4:513--517.
7. Varudkar B. Short course chemotherapy for tuberculosis in children. Indian J Pediatr 1985;52:593--597.
8. Ibanez Quevedo S, Ross Bravo G. Quimioterapia abreviada de 6 meses en tuberculosis pulmonar infantil. Rev Chil
9. Al-Dossary FS, Ong LT, Correa AG, Starke JR. Treatment of childhood tuberculosis using a 6-month, directly obse
10. Trebucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the l
11. American Academy of Pediatrics. Tuberculosis. In: Pickering LJ, editor. Red book report of the Committee on Infec -613.

8.3. Extrapulmonary Tuberculosis

Tuberculosis can involve virtually any organ or tissue in the body. Nonpulmonary sites tend to be more common among chil
tuberculosis, appropriate specimens including pleural fluid; pericardial or peritoneal fluid; pleural, pericardial, and peritonea
cerebrospinal fluid should be obtained for AFB staining, mycobacterial culture, and drug susceptibility testing (*1*). Tissue sp
absence of AFB and of granulomas or even failure to culture *M. tuberculosis* does not exclude the diagnosis of tuberculosis.
limited by the difficulty in obtaining follow-up specimens. Thus, response often must be judged on the basis of clinical and r
The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease
tuberculosis, compared with pulmonary disease, increasing evidence, including some randomized controlled trials, suggests t
patients with extrapulmonary tuberculosis, a 6- to 9-month regimen (2 months of INH, RIF, PZA, and EMB followed by 4--7
strongly suspected of being resistant to the first-line drugs. If PZA cannot be used in the initial phase, the continuation phase
The exception to the recommendation for a 6- to 9-month regimen is tuberculous meningitis, for which the optimal length of
Although in extrapulmonary tuberculosis there have not been controlled trials of the various patterns of intermittent drug adn
INH--rifapentine once weekly in the continuation phase. Given the lack of experience with this regimen, it is not recommend
Corticosteroid treatment is a useful adjunct in treating some forms of extrapulmonary tuberculosis, specifically meningitis ar
duration of treatment for extrapulmonary tuberculosis and the use of corticosteriods are shown in Table 13.

8.3.1. Lymph node tuberculosis

A 6-month regimen as described in Section 5, Recommended Treatment Regimens, and Table 2 is recommended for initial t
6). Affected lymph nodes may enlarge while patients are receiving appropriate therapy or after the end of treatment without a
after treatment as well. Therapeutic lymph node excision is not indicated except in unusual circumstances. For large lymph n
drainage appears to be beneficial, although this approach has not been examined systematically (Rating BIII). It should be no
States are caused by nontuberculous mycobacteria.

8.3.2. Bone and joint tuberculosis

Several studies have examined treatment of bone and joint tuberculosis and have shown that 6- to 9-month regimens contain
of the difficulties in assessing response, however, some experts tend to favor the 9-month duration. A randomized trial perfo
Tuberculosis of the Spine (*13*) demonstrated no additional benefit of surgical debridement or radical operation (resection of t
chemotherapy alone. Myelopathy with or without functional impairment most often responds to chemotherapy. In two Medic
patients in an earlier study (*19*) had complete resolution of myelopathy or complete functional recovery when treated medica
situations include failure to respond to chemotherapy with evidence of ongoing infection, the relief of cord compression in pa

8.3.3. Pericardial tuberculosis

For patients with pericardial tuberculosis, a 6-month regimen is recommended. Corticosteroids are recommended as adjuncti randomized, double-blind, controlled trial, patients in the later effusive--constrictive phase who received prednisolone had a treated patients also had a lower mortality (2 of 53 [4%] versus 7 of 61 [11%]) and needed pericardiectomy less frequently (1 (*8*). Prednisolone did not reduce the risk of constrictive pericarditis. In a second prospective, double-blind, randomized trial o disease), prednisolone reduced the need for repeated pericardiocentesis (7 of 76 [9%] versus 17 of 74 [23%]; p <0.05) and w prednisolone compared with 10 of 74 [14%] among those not given prednisolone; p <0.05) (*9*). As before, there was no statis additional small randomized trial by Hakim and associates (*20*) performed in HIV-infected patients with tuberculous pericar On the basis of these studies, it is recommended that daily adjunctive prednisolone or prednisone treatment be given to adult equivalent dose of prednisolone) given for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks, and finally their weight, beginning with about 1 mg/kg body weight and decreasing the dose as described for adults.

8.3.4. Pleural tuberculosis

A 6-month regimen is also recommended for treating pleural tuberculosis. A number of studies have examined the role of co double blind, and randomized (*7,22*). In both of these studies, prednisone (or prednisolone) administration did not reduce the pleural tuberculosis who received prednisone had a significantly more rapid resolution of symptoms such as fever, chest pain radiographic resolution of the effusions. In the study by Wyser and colleagues (*7*), all patients had complete drainage of the e to receive adjunctive oral prednisone or placebo for 6 weeks. The complete drainage led to a rapid resolution of symptoms, a Tuberculous empyema, a chronic, active infection of the pleural space containing a large number of tubercle bacilli, usually requiring a surgical procedure) and antituberculous chemotherapy. Surgery, when needed, should be undertaken by experien tuberculosis has not been established.

8.3.5. Tuberculous meningitis

Before the advent of effective antituberculosis chemotherapy, tuberculous meningitis was uniformly fatal. Tuberculous meni mortality, despite prompt initiation of adequate chemotherapy (*24--29*). HIV-infected patients appear to be at increased risk f similar to those in patients without HIV infection (*24--26,29*). Patients presenting with more severe neurologic impairment s mortality. Chemotherapy should be initiated with INH, RIF, PZA, and EMB in an initial 2-month phase. INH and RIF, as we forms for patients with altered mental status who may not be able to take oral medications.

After 2 months of four-drug therapy for meningitis caused by susceptible strains, PZA and EMB may be discontinued, and II chemotherapy is not defined, and there are no data from randomized, controlled trials to serve as the basis of recommendatio glucose, and protein, especially in the early course of therapy.

Differences in regimens among patient groups and in the use of corticosteroid therapy have made meta-analysis of published years (*28,31*), whereas others have suggested that short-course RIF-based regimens for 6 to 9 months may be adequate therap develop tuberculomas during therapy, perhaps as a form of paradoxical reaction; however, this does not necessarily indicate

A number of investigators have examined the role of adjunctive corticosteroid therapy in the treatment of tuberculous menin not include RIF. There are no large, prospective, randomized, controlled trials of adjunctive corticosteroid use for tuberculou benefit of corticosteroid therapy in terms of survival, frequency of sequelae, or both. In the study conducted by Girgis and co presentation (4 of 27 [15%] of those who received dexamethasone died versus 14 of 35 [40%] in the control group; p <0.02). between those who received dexamethasone and control patients (28 of 44 [64%] mortality for the dexamethasone group ver finding an effect. Likewise, there were too few patients with Stage I disease (alert) on entry to determine the effectiveness of On the basis of the available data, albeit limited, adjunctive corticosteroid therapy with dexamethasone is recommended for a meningitis. The recommended regimen is dexamethasone in an initial dose of 8 mg/day for children weighing less than 25 kg 3 weeks and then decreased gradually during the following 3 weeks.

8.3.6. Disseminated tuberculosis

A 6-month regimen is recommended for tuberculosis at multiple sites and for miliary tuberculosis, although there are limited treatment for children with disseminated tuberculosis.) Expert opinion suggests that corticosteroid therapy may be useful for its use.

8.3.7. Genitourinary tuberculosis

Renal tuberculosis is treated primarily with medical therapy (*12,42--46*), and a 6-month regimen is recommended. If ureteral hydronephrosis and progressive renal insufficiency due to obstruction, renal drainage by stenting or nephrostomy is recomm is discussed in the urologic literature but the efficacy of steroids in this setting is unclear. Nephrectomy is not usually indicat nonfunctioning or poorly functioning kidney, particularly if hypertension or continuous flank pain is present. Tuberculosis o needed only for residual large tubo-ovarian abscesses.

A positive urine culture for *M. tuberculosis* occurs relatively commonly as an incidental finding among patients with pulmon in the absence of any abnormalities on urinalysis and does not necessarily represent genitourinary tract involvement.

8.3.8. Abdominal tuberculosis

A 6-month regimen is recommended for patients with peritoneal or intestinal tuberculosis (*47,48*). There are insufficient data

In a small study of peritoneal tuberculosis alternate patients received adjunctive corticosteroid therapy for 4 months (total of in none of those in the steroid group (23 patients), but the difference was not statistically significant.

8.3.9. Other sites of involvement

As noted above, tuberculosis can involve any organ or tissue. In treating tuberculosis in sites other than those mentioned, the individual patients.

References

1. American Thoracic Society, Centers for Disease Control and Prevention. Diagnostic standards and classificationof t at http://www.thoracic.org/adobe/statements/tbadult1-20.pdf.
2. Yuen APW, Wong SHW, Tam CM, Chan SL, Wei WI, Lau SK. Prospective randomized study of the thrice weekly Otolaryngol Head Neck Surg 1997;116:189--192.
3. British Thoracic Society Research Committee. Six-months versus nine-months chemotherapy for tuberculosis of ly
4. Jawahar MS, Sivasubramanian S, Vijayan VK, Ramakrishnan CV, Paramasivan CN, Selvakumar V, Paul S. Short c
5. Campbell IA, Ormerod LP, Friend PA, Jenkins R, Prescott J. Six months versus nine months chemotherapy for tube
6. Cheung WL, Siu KF, Ng A. Six-month combination chemotherapy for cervical tuberculous lymphadenitis. J R Coll
7. Wyser C, Walzl G, Smedema JP, Swart F, van Schalkwyk M, van de Wal BW. Corticosteroids in the treatment of t 338.
8. Strang JI, Kakaza HH, Gibson DG, Girling DJ, Nunn AJ, Fox W. Controlled trial of prednisolone as adjuvant in tre
9. Strang JI, Kakaza HH, Gibson DG, Allen BW, Mitchison DA, Evans DJ, Girling DJ, Nunn AJ, Fox W. Controlled pericardial effusion in Transkei. Lancet 1988;2:759--764.
10. Donald PR, Schoeman JF, Van Zyl LE, De Villiers JN, Pretorius M, Springer P. Intensive short course chemotherap
11. Rajeswari R, Balasubramanian R, Venkatesan P, Sivasubramanian S, Soundarapandian S, Shanmugasundaram TK, follow-up. Int J Tuberc Lung Dis 1997;1:152--158.
12. Dutt KA. Short-course chemotherapy for extrapulmonary tuberculosis: nine years experience. Ann Intern Med 1986
13. Medical Research Council Working Party on Tuberculosis of the Spine. Five-year assessment of controlled trials of patients ambulatory from the start or undergoing radical surgery. Int Orthop 1999;23:73--81.
14. Medical Research Council Working Party on Tuberculosis of the Spine. Controlled trial of short-course regimens of in Korea. J Bone Joint Surg Br 1993;75:240--248.
15. Medical Research Council Working Party on Tuberculosis of the Spine. A controlled trial of six-month and nine-mo spine in Hong Kong. Tubercle 1986;67:243--259.
16. British Thoracic Society Research Committee. Short course chemotherapy for tuberculosis of lymph nodes: a contro
17. Campbell IA, Dyson AJ. Lymph node tuberculosis: a comparison of various methods of treatment. Tubercle 1977;5
18. Campbell IA, Dyson AJ. Lymph node tuberculosis: a comparison of treatments 18 months after completion of chem
19. Pattison PRM. Pott's paraplegia: an account of the treatment of 89 consecutive patients. Paraplegia 1986;24:77--91.
20. Hakim JG, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled t seropositive patients. Heart 2000;84:183--188.
21. Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal o
22. Lee CH, Wang WJ, Lan RS, Tsai YH, Chiang YC. Corticosteroids in the treatment of tuberculous pleurisy: a doubl
23. Sahn SA, Iseman MD. Tuberculous empyema. Semin Respir Infect 1999;14:82--87.
24. Dube MP, Holtom PD, Larsen RA. Tuberculous meningitis in patients with and without human immunodeficiency
25. Berenguer J, Moreno S, Laguna F, Vicente T, Adrados M, Ortega A, Gonzalez-LaHoz J, Bouza E. Tuberculous me 1992;326:668--672.
26. Porkert MT, Sotir M, Moore PP, Blumberg HM. Tuberculous meningitis at a large inner-city medical center. Am J
27. Yechoor VK, Shandera WX, Rodriguez P, Cate TR. Tuberculous meningitis among adults with and without HIV in
28. Girgis NI, Sultan Y, Farid Z, Mansour MM, Erian MW, Hanna LS, Mateczun AJ. Tuberculosis meningitis, Abbassi Med Hyg 1998;58:28--34.
29. Karstaedt AS, Valtchanova S, Barriere R, Crewe-Brown HH. Tuberculous meningitis in South African urban adults
30. Thwaites G, Chau TTH, Mai NTH, Brobniewski F, McAdam K, Farrar J. Tuberculous meningitis. J Neurol Neurosu
31. Goel A, Pandya S, Satoskar A. Whither short-course chemotherapy for tuberculous meningitis? Neurosurgery 1990
32. Jacobs RF, Sunakorn P, Chotpitayasunonah T, Pope S, Kelleher K. Intensive short course chemotherapy for tubercu
33. Phuapradit P, Vejjajiva A. Treatment tuberculous meningitis: role of short-course chemotherapy. Q J Med 1987;62:
34. Girgis NI, Farid Z, Kilpatrick ME, Sultan Y, Mikhail IA. Dexamethasone adjunctive treatment for tuberculous men
35. Girgis NI, Farid Z, Hanna LS, Yassin MW, Wallace CK. The use of dexamethasone in preventing ocular complicati
36. Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK. Randomized controlled trial of dexamethasone in tubercu
37. Lepper MH, Spies HW. The present status of the treatment of tuberculosis of the central nervous system. Ann N Y
38. Escobar JA, Belsey MA, Duenas A, Medinea P. Mortality from tuberculous meningitis reduced by steroid therapy.

39. O'Toole RD, Thornton GF, Mukherjee MK, Nath RL. Dexamethasone in tuberculous meningitis: relationship of cer
40. Ashby M, Grant H. Tuberculous meningitis treatment with cortisone. Lancet 1955;i:65--66.
41. Voljavec BF, Corpe RF. The influence of corticosteriod hormones in the treatment of tuberculous meningitis in Neg
42. Carl P, Stark L. Indications for surgical management of genitourinary tuberculosis. World J Surg 1997;21:505--510
43. Skutil V, Varsa J, Obsitnik M. Six-month chemotherapy for urogenital tuberculosis. Eur Urol 1985;11:170--176.
44. Gow JG. Genitourinary tuberculosis: a study of the disease in one unit over a period of 24 years. Ann R Coll Surg E
45. Christensen WI. Genitourinary tuberculosis: review of 102 cases. Medicine (Baltimore) 1974;53:377--390.
46. Simon HB, Weinstein AJ, Pasternak MS, Swartz MN, Kunz LJ. Genitourinary tuberculosis: clinical features in a ge
47. Bastani B, Shariatzadeh MR, Dehdashti F. Tuberculous peritonitis: report of 30 cases and review of the literature. Q
48. Demir K, Okten A, Kaymakoglu S, Dincer D, Besisik F, Cevikbas U, Ozdil S, Bostas G, Mungan Z, Cakaloglu Y. T
Gastroenterol Hepatol 2001;13:581--585.
49. Singh MM, Bhargava AN, Jain KP. Tuberculous peritonitis: an evaluation of pathogenetic mechanisms, diagnostic

8.4. Culture-Negative Pulmonary Tuberculosis in Adults

Failure to isolate *M. tuberculosis* from appropriately collected specimens in persons who, because of clinical or radiographic tuberculosis. For the United States as a whole, about 17% of the reported new cases of pulmonary tuberculosis have negative expelled, and errors in specimen processing all may result in failure to isolate organisms from patients who have active tuber appropriate diagnostic studies undertaken in patients who have what appears to be culture-negative tuberculosis. At a minimu (using sputum induction with hypertonic saline if necessary) for AFB smears and cultures for mycobacteria as part of the dia testing, such as bronchoscopy with bronchoalveolar lavage and biopsy, should be considered before making a presumptive d Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have pulmonary tuberculosis should negative. If *M. tuberculosis* is isolated in culture, treatment for active disease should be continued. Patients who have negativ follow-up clinical and radiographic evaluation at the time 2 months of therapy has been completed to determine whether ther or radiographic improvement and no other etiology is identified, treatment should be continued for active tuberculosis. A 4-m successful with only 1.2% relapses during an average follow-up of 44 months (*2*). However, because the results of cultures n two-drug therapy with INH and RIF alone is not recommended, but the continuation phase can be shortened to 2 months usir On occasion, patients who are being evaluated for pulmonary tuberculosis will be found to have positive AFB smears but ne possibilities that the acid-fast organisms are nontuberculous and difficult to culture, that they are nonviable tubercle bacilli, a individualized on the basis of clinical and radiographic findings. If suspicion of tuberculosis is high and the patient has positi using one of the recommended regimens.

References

1. CDC. Reported tuberculosis in the United States, 2000. Atlanta, GA: US Department of Health and Human Service
2. Dutt AK, Moers D, Stead WW. Smear- and culture-negative pulmonary tuberculosis: four-month short-course chem

8.5. Radiographic Evidence of Prior Tuberculosis: Inactive Tuberculosis

Persons with a positive tuberculin PPD skin test who have radiographic findings consistent with prior pulmonary tuberculosi development of active tuberculosis (*2--4*). The radiographic findings that constitute evidence of prior tuberculosis are apical were about 2.5 times those of persons infected with *M. tuberculosis* who did not have chest radiographic abnormalities (*3*). P pulmonary nodules, calcified hilar lymph nodes, and pleural thickening) are not at increased risk for tuberculosis compared v Patients should not be classified as having radiographic evidence of prior tuberculosis if another disease is found to account f chest radiograph, and unless there are previous radiographs showing that the abnormality has not changed, it is recommende possibility of active tuberculosis. Once active tuberculosis has been excluded by sputum culture, these persons are high-prior The optimum treatment for patients with latent tuberculosis infection and abnormal chest radiographs consistent with prior tu IUATLD (*2*) compared the efficacy of 3, 6, and 12 months of INH in preventing active tuberculosis for persons with latent tu tuberculosis. Among those receiving INH for at least 6 months, the incidence of tuberculosis was significantly reduced comp given for 12 months was significantly better than 6 months (89 versus 67% reduction). A reanalysis of data from a communi showed that the efficacy of INH decreased significantly if less than 9 months of the drug was taken, but that further protectio data, guidelines for treatment of latent tuberculosis infection recommend 9 months of INH for persons with abnormal chest r without INH) for 4 months, and RIF and PZA for 2 months (for persons who are unlikely to complete a longer course and wh and RIF with INH alone in treating this category of patient showed that 4 months of INH and RIF was cost saving compared resistant to INH increased (*7*).

Instances of severe and fatal liver disease have been reported in patients taking RIF and PZA for treatment of latent tubercul RIF--PZA than with INH alone (7.7% Grade 3 or 4 hepatotoxicity with RIF--PZA compared with 1% for INH; p = 0.001) (9 measuring serum AST and bilirubin at baseline and after 2, 4, and 6 weeks of treatment. RIF--PZA is not recommended for p hepatotoxicity from INH. The regimen should be reserved for patients who are not likely to complete a longer course of treat

References

1. American Thoracic Society, CDC. Diagnostic standards and classification of tuberculosis in adults and children. An

2. International Union Against Tuberculosis Committee on Prophylaxis. The efficacy of varying durations of isoniazic Health Organ 1982;60:555--564.
3. Grzybowski S, Fishaut H, Rowe J, Brown A. Tuberculosis among patients with various radiologic abnormalities, fo
4. Comstock GW, Woolpert SF. Preventive treatment of untreated, nonactive tuberculosis in an Eskimo population. A
5. American Thoracic Society, CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J R
6. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int
7. Jasmer RM, Snyder DC, Chin DP, Hopewell PC, Cuthbert SC, Paz EA, Daley CL. Twelve months of isoniazid com previous tuberculosis: an outcome and cost-effectiveness analysis. Am J Respir Crit Care Med 2000;162:1648--165
8. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infec 735.
9. Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, King MD, Kawamura LM, Hopew infection: a multicenter clinical trial. Ann Intern Med 2002;137:640--647.

8.6. Pregnancy and Breastfeeding

Untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does treatment of the disease. I to women without tuberculosis and, rarely, the infant may acquire congenital tuberculosis (*1--3*). Thus, treatment of a pregna moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. SM should *not* be substituted for EM IUATLD (*5*), the drug has not been recommended for general use in pregnant women in the United States because of insuffi have used PZA in pregnant women without reported adverse events (*1*). If PZA is not included in the initial treatment regime pregnant women who are receiving INH.

INH, RIF, and EMB cross the placenta, but none has been shown to have teratogenic effects (*6*). SM, the only antituberculos the ear and may cause congenital deafness. In 40 pregnancies among women being treated with SM, 17% of the babies had e Kanamycin, amikacin, and capreomycin presumably share this toxic potential; however, there is little specific information o was no indication of teratogenicity among babies whose mothers had received these two drugs (*2*). There are not enough data teratogenic effects attributed to ethionamide (*8*). The fluoroquinolones have been associated with arthropathies in young anir In general, administration of antituberculosis drugs is not an indication for termination of pregnancy (*2*). However, in women should be provided because of the known and unknown risks of the second-line agents.

Breastfeeding should not be discouraged for women being treated with first-line agents, because the small concentrations of in breast milk should not be considered to serve as effective treatment for active tuberculosis or latent tuberculosis infection i INH. The administration of the fluoroquinolones during breastfeeding is not recommended, although, as of 1998, there have

References

1. Davidson PT. Managing tuberculosis during pregnancy. Lance*t* 1995;346:199--200.
2. Snider DE, Layde PM, Johnson MW, Lyle MA. Treatment of tuberculosis during pregnancy. Am Rev Respir Dis 1
3. Jana N, Vasishta K, Jindal SK, Khunnu B, Ghosh K. Perinatal outcome in pregnancies complicated by pulmonary tu
4. World Health Organization. Treatment of tuberculosis: guidelines for national programmes, 2nd edition. WHO/TB/ http://www.who.int/gtb/publications/ttgnp/PDF/tb97_220.pdf
5. Enarson DA, Rieder HL, Arnodottir T, Trebucq A. Tuberculosis guide for low income countries, 4th edition. Paris:
6. Briggs GG, Freeman RK, Yaffe SJ, editors. Drugs in pregnancy and lactation, 5th edition. Baltimore, MD: William
7. Varpela E, Hietalalahti J, Aro M. Streptomycin and dihidrostreptomycin during pregnancy and their effect on the ch
8. Potworowska M, Sianozecko E, Szuflodowica R. Ethionamide treatment and pregnancy. Pol Med J 1966;5:1153--1
9. Snider DE, Powell KE. Should women taking antituberculosis drugs breast-feed? Arch Intern Med 1984;144:589--5

8.7. Renal Insufficiency and End-stage Renal Disease

Renal insufficiency complicates the management of tuberculosis because some antituberculosis medications are cleared by th agents via hemodialysis. Thus, some alteration in dosing antituberculosis medications is commonly necessary in patients with Decreasing the dose of selected antituberculosis drugs may not be the best method of treating tuberculosis because, although decreasing the dose of the antituberculosis agent, increasing the dosing interval is recommended (*1*). The general approach d of drugs that are cleared by the kidneys to patients having a creatinine clearance of less than 30 ml/minute and those receivin Peloquin, personal communication). There are insufficient data to guide dosing recommendations for patients having a reduc used, but measurement of serum concentrations should be considered to avoid toxicity.

RIF and INH are metabolized by the liver, so conventional dosing may be used in the setting of renal insufficiency (*1--5*). PZ acid) may accumulate in patients with renal insufficiency (*3,6*). EMB is about 80% cleared by the kidneys and may accumul week administration is recommended for PZA and EMB (*3,7*). INH, EMB, and PZA (as well as its metabolites) are cleared b significant degree (*3*). RIF is not cleared by hemodialysis because of its high molecular weight, wide distribution into tissues dosing is not necessary for INH, RIF, or EMB. If PZA is given after hemodialysis, supplemental dosing is not required. In ge during hemodialysis, and to facilitate DOT.

Doses of streptomycin, kanamycin, amikacin, and capreomycin must be adjusted in patients with renal failure because the ki

hemodialysis when these drugs are given just before hemodialysis (*8*). Far less drug is likely to be removed once the drugs h
anticipated. As with EMB and PZA, the dosing interval should be increased. In general, the dose should not be reduced beca
reduce drug efficacy. Ethionamide is not cleared by the kidneys, nor is the drug removed with hemodialysis, so no dose adju
acetyl-PAS, is substantially removed by hemodialysis; twice daily dosing (4 g) should be adequate if the granule formulation
cleared by hemodialysis (56%). Thus, an increase in the dosing interval is necessary to avoid accumulation between hemodia
fluoroquinolones undergo some degree of renal clearance that varies from drug to drug. For example, levofloxacin undergoes
dosing recommendations for end-stage renal disease provided by the manufacturers were developed for treating pyogenic ba
in patients with end-stage renal disease.

As noted above, administration of all antituberculosis drugs immediately after hemodialysis will facilitate DOT (three times
concentrations in persons with renal insufficiency who are taking cycloserine, EMB, or any of the injectable agents to minim
patients with end-stage renal disease may have additional clinical conditions, such as diabetes mellitus with gastroparesis, th
medications that interact with these drugs. Under these circumstances a careful clinical and pharmacologic assessment is nec
determining the optimum dose of the antituberculosis drugs (*9*). Finally, data currently do not exist for patients receiving per
peritoneal dialysis, it cannot be assumed that all of the recommendations in Table 15 will apply to peritoneal dialysis. Such p
antituberculosis drugs.

References

1. Peloquin CA. Antituberculosis drugs: pharmacokinetics. In: Heifets L, editor. Drug susceptibility in the chemothera
2. Ellard GA. Chemotherapy of tuberculosis for patients with renal impairment. Nephron 1993;64:169--181.
3. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on isoniazid, rifampin, pyr
4. Bowersox DW, Winterbauer RH, Stewart GL, Orme B, Barron E. Isoniazid dosage in patients with renal failure. N
5. Acocella G. Clinical pharmacokinetics of rifampicin. Clin Pharmacol 1978;13:108--127.
6. Ellard GA. Absorption, metabolism, and excretion of pyrazinamide in man. Tubercle 1969;50:144--158.
7. Strauss I, Erhardt F. Ethambutol absorption, excretion and dosage in patients with renal tuberculosis. Chemotherapy
8. Matzke GR, Halstenson CE, Keane WF. Hemodialysis elimination rates and clearance of gentamicin and tobramyci
9. Peloquin CA. Using therapeutic drug monitoring to dose the antimycobacterial drugs. Clin Chest Med 1997;18:79--
10. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on cycloserine, ethionamid
11. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet 1997;32:101--119.

8.8. Hepatic Disease

The treatment of tuberculosis in patients with unstable or advanced liver disease is problematic for several reasons. First, the
hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening. Finally, fluctuations in the b
disease confound monitoring for drug-induced hepatitis. Thus, clinicians may consider regimens with fewer potentially hepa
advisable in treating such patients. It should be noted that tuberculosis itself may involve the liver, causing abnormal liver fu
causes other than tuberculosis. The hepatic abnormalities caused by tuberculosis will improve with effective treatment.

Possible treatment regimens in the setting of liver disease include the following.

8.8.1. Treatment without INH

As described in Section 5.2, Alternative Regimens, analysis of data from several studies conducted by the BMRC in patients
regimens despite in vitro resistance to INH so long as the initial phase contained four drugs and RIF was used throughout the
that results were improved when PZA was used throughout the 6 months (*2*). Thus, it is reasonable to employ an initial phase
(Rating BII). Although this regimen has two potentially hepatotoxic medications, it has the advantage of retaining the 6-mon

8.8.2. Treatment without PZA

Although the frequency of PZA-induced hepatitis is slightly less than occurs with INH or RIF, the liver injury induced by thi
initial phase of INH, RIF, and EMB for 2 months followed by a continuation phase of INH and RIF for 7 months, for a total

8.8.3. Regimens with only one potentially hepatotoxic drug

For patients with advanced liver disease, a regimen with only one potential hepatotoxic drug might be selected. Generally, R
cycloserine, and injectable agents. The duration of treatment with such regimens should be 12--18 months, depending on the

8.8.4. Regimens with no potentially hepatotoxic drugs

In the setting of severe unstable liver disease, a regimen with no hepatotoxic agents might be necessary. Such a regimen mig
provide guidance as to the choice of agents or the duration of treatment or that indicate the effectiveness of such a regimen. I
CIII). Consultation should always be obtained before embarking on such a treatment plan.

References

1. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmo
2. Hong Kong Chest Service, British Medical Research Council. Five-year follow-up of a controlled trial of five 6-mo
1342.
3. United States Public Health Service. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. U
-387.

8.9. Other Associated Disorders

Tuberculosis commonly occurs in association with other diseases or conditions. An associated disorder may alter immune re occurs frequently in the same social and cultural milieu as tuberculosis. Examples of the former class of disorders include HI chronic renal failure, poorly controlled, insulin-dependent diabetes mellitus, and malnutrition. Silicosis, by impairing pulmo The latter group of disorders includes chronic alcoholism and its secondary effects, other substance abuse, and psychiatric ill outcome of therapy (discussed in Section 2: Organization and Supervision of Treatment). The response of immunocompromi immunity, although in patients with HIV infection the response to treatment is not impaired Nevertheless, therapeutic decisio severity of tuberculosis and the response to treatment. When possible, steps should be taken to correct the immune deficiency if the continuation phase is extended for at least 2 months (*1,2*).

References

1. Hong Kong Chest Service, Tuberculosis Research Centre, Madras/British Medical Research Council. A control tria silicotuberculosis in Hong Kong. Am Rev Respir Dis 1991;143:262--267.
2. Lin T-P, Suo J, Lee C-N, Lee J-J, Yang S-P. Short course chemotherapy of pulmonary tuberculosis in pneumoconio

9. Management of Relapse, Treatment Failure, and Drug Resistance

9.1. Relapse

Relapse refers to the circumstance in which a patient becomes and remains culture-negative while receiving antituberculosis experiences clinical or radiographic deterioration consistent with active tuberculosis. In such patients vigorous efforts should enable testing for drug resistance. True relapses are due to failure of chemotherapy to sterilize the host tissues, thereby enabl exogenous reinfection with a new strain of *M. tuberculosis* may be responsible for the apparent relapse (*1*).

Patients who are most likely to have true relapses are those with extensive tuberculosis whose sputum cultures remain positiv completion of therapy. In nearly all patients with tuberculosis caused by drug-susceptible organisms who were treated with r However, in patients who received self-administered therapy or a nonrifamycin regimen and who have a relapse, the risk of a performed and the patient fails or relapses with a rifamycin-containing regimen given by DOT, there is a high likelihood that Among patients who received self-administered therapy, the risk of erratic drug administration leading to relapse with resista regimens for patients with relapses should be based on the prior treatment scheme. For patients with tuberculosis that was ca retreatment using the standard four-drug initial phase regimen may be appropriate, at least until the results of susceptibility te treatment in the past, it is prudent to infer a higher risk of acquired drug resistance and begin an expanded regimen (see belo respiratory reserve, central nervous system involvement, or other life-threatening circumstances, that is, cases in which treatr For the relatively few patients in whom epidemiologic circumstances provide a strong suspicion of exogenous reinfection as pattern of the presumed source case. If the presumed source case is known to have tuberculosis caused by drug-susceptible o likely source case is known to have drug-resistant organisms, an empirically expanded regimen based on the resistance profi There are no clinical trials to guide the choice of agents to include in expanded empirical regimens for presumed drug resista and PZA plus an additional three agents, based on the probability of in vitro susceptibility. Usual agents would include EMB isolate was susceptible) amikacin, kanamycin or capreomycin, with or without other drugs.

9.2. Treatment Failure

Treatment failure is defined as continued or recurrently positive cultures in a patient receiving appropriate chemotherapy. An 90--95% will be culture-negative after 3 months of treatment with a regimen that contains INH and RIF. During this time the and weight gain. Thus, patients with persistently positive cultures after 3 months of chemotherapy, with or without on-going Patients whose sputum cultures remain positive after 4 months of treatment are considered to have failed treatment.

There are multiple potential reasons for treatment failure. If the patient is not receiving DOT, the most likely explanation for DOT, cryptic nonadherence (spitting out or deliberately regurgitating pills) or failure of the health care system to reliably del (Was initial drug-susceptibility testing done? Was it reported accurately?), malabsorption (prior resectional surgery of the sto that might bind or interfere with drug absorption (see Section 6.1: Drug Administration, and Section 7.1: Interactions Affecti "normal" patients may experience very protracted disease including persistently positive cultures or prolonged symptoms in considered as a possible reason for a positive culture in a patient who is doing well. Recent reports document cross contamin (*7,8*).

Clinicians should be alert, as well, to the possibility of transient clinical or radiographic worsening (paradoxical reactions), d inflammation at sites of lymphadenitis, worsened abnormalities on chest radiographs after several months of treatment, or th paradoxical worsening during treatment occurs more commonly but not exclusively in persons with HIV infection (*12--14*) (For patients who meet criteria for treatment failure, the possible reasons listed above should be addressed promptly. If clinici consultation with a specialty center is indicated. If treatment failure is presumed to be due to drug resistance and the patient c wait for drug susceptibility results from a recent isolate. If the patient is seriously ill or has a positive sputum AFB smear, an continued until susceptibility tests are available to guide therapy. For patients who have failed treatment, mycobacterial isola second-line drugs.

A fundamental principle in managing patients who have failed treatment is that a single new drug should never be added to a

generally prudent to add at least three new drugs to which susceptibility could logically be inferred to lessen the probability o
of an empirical regimen; however, expert opinion indicates that empirical retreatment regimens might include a fluoroquinol
was susceptible initially), amikacin, kanamycin, or capreomycin, and an oral agent such as PAS, cycloserine, or ethionamide
according to the results.

9.3. Management of Tuberculosis Caused by Drug-Resistant Organisms

Tubercle bacilli are continually undergoing spontaneous mutations that create resistance to individual antituberculosis drugs.
combination chemotherapy that is reliably ingested, clinically significant resistance will not develop (see Section 4.1: Combi
when there is a large bacillary population, such as in pulmonary cavities, when an inadequate drug regimen is prescribed (ina
the provider to ensure that an adequate regimen is taken (*16*). Rarely, malabsorption of one or more antituberculosis drugs m
pulmonary tuberculosis because of the immense number of rapidly multiplying bacilli in the cavity(ies) (*17*). During extende
resistance may transmit their strains to others who, if they develop tuberculosis, will have primary drug resistance.

Drug resistance in a patient with newly diagnosed tuberculosis may be suspected on the basis of historical (previous treatmer
region in which drug resistance is common) (*18,19*). In such situations it is prudent to employ an empirically expanded regin
can be proven only by drug-susceptibility testing performed in a competent laboratory (Table17). The steps taken when resis
tuberculosis resistant to both INH and RIF (MDR) are at high risk for treatment failure and further acquired resistance; they
centers. Patients with strains resistant to RIF alone have a better prognosis than MDR cases, but also are at increased risk for
scrutiny.

Definitive randomized or controlled studies have not been performed among patients with the various patterns of drug resista
of general principles, extrapolations and expert opinion. The WHO and IUATLD have formulated standard algorithmic regir
listed below, as well as on expert opinion (*20,21*). This approach is best suited to regions without in vitro susceptibility testir
industrialized nations with more ample resources (*22,23*).

Guidelines for management of patients with tuberculosis caused by drug-resistant organisms are based on the following guid

- A single new drug should never be added to a failing regimen.
- When initiating or revising therapy, always attempt to employ at least three previously unused drugs to which there
- Do not limit the regimen to three agents if other previously unused drugs that are likely to be active are available. In
  and RIF, regimens employing four to six medications appear to be associated with better results (*24--26*).
- Patients should receive either hospital-based or domiciliary DOT. The implications of treatment failure and further a
- Intermittent therapy should not be used in treating tuberculosis caused by drug-resistant organisms, except perhaps f
- The use of drugs to which there is demonstrated in vitro resistance is not encouraged because there is little or no eff
  are available. However, the clinical significance and effectiveness of the use of INH in the setting of low-level INH
  better survival rates in patients with the strain-W variety of MDR *M. tuberculosis* that was susceptible to higher con
- Resistance to RIF is associated in nearly all instances with cross-resistance to rifabutin and rifapentine (*28*). Rare st
  mutations of the RNA-polymerase locus in the bacillus (*29*). However, unless in vitro susceptibility to rifabutin is d
  between RIF and rifapentine appears almost universal (*28*).
- There is no cross-resistance between SM and the other injectable agents: amikacin, kanamycin, and capreomycin (a
  amikacin and kanamycin is universal (*24*). Simultaneous use of two injectable agents is not recommended due to the
- Determination of resistance to PZA is technically problematic and, thus, is not made in many laboratories. Howeve
  monoresistance to PZA is observed, consideration must be given to the possibility that the etiologic agent is *M. bovi*
  M. tuberculosis by nucleic acid hybridization--probe assays that are commonly used for identification).

Table 16 contains regimens suggested for use in patients with various patterns of drug-resistant tuberculosis.

9.4. Role of Surgery in MDR Tuberculosis

The role of resectional surgery in the management of patients with extensive pulmonary MDR tuberculosis has not been esta
having resistance to more than 5 drugs) appeared to benefit from the resection of cavitary or badly damaged lung tissue wher
drug resistance having similar cure rates without surgery (*25,32*). The disparity in these reports may be due to long-standing
performed by an experienced surgeon after the patient has received several months of intensive chemotherapy. Even with suc
demonstrated susceptibility, should be given.

References

1. van Rie A, Warren R, Richardson M, Victor TC, Gie RP, Enarson DA, Beyers N, van Helden PD. Exogenous reinfe
   1179.
2. Catanzaro A, Horsburgh R. TBTC Study 22: risk factors for relapse with once-weekly isoniazid/rifapentine (HP) in
3. Tam CM, Chan SL, Kam KM, Goodall RL, Mitchison DA. Rifapentine and isoniazid in the continuation phase of tr
4. Hong Kong Chest Service/British Medical Research Council. Five-year follow-up of a controlled trial of five 6-mor
5. Hong Kong Chest Service/British Medical research Council. Controlled trial of 2,4, and 6-months of pyrazinamide
   assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide: results at 30 months. Am Rev Resp
6. Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis. Int J Tuberc Lung Dis 2000;4:796--80

7. Burman WJ, Stone BL, Reves RR, Wilson ML, Yang Z, El-Hajj H, Bates JH, Cave MD. The incidence of false-pos
8. Braden CR, Templeton GL, Stead WW, Bates JH, Cave MD, Valway SE. Retrospective detection of laboratory cros Clin Infect Dis 1997;24:35--40.
9. Carter JE, Mates S. Sudden enlargement of a deep cervical lymph node during and after treatment of pulmonary tub
10. Onwubalili JK, Scott GM, Smith H. Acute respiratory distress related to chemotherapy of advanced pulmonary tube
11. Matthay RA, Neff TA, Iseman MD. Tuberculous pleural effusions developing during chemotherapy for pulmonary
12. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral th
13. Crump JA, Tyrer MJ, Lloyd-Owen SJ, Han LY, Lipman MC, Johnson MA. Miliary tuberculosis with paradoxical e patient receiving highly active antiretroviral therapy. Clin Infect Dis 1998;26:1008--1009.
14. Wendel KA, Alwood KS, Gachuhi R, Chaisson RE, Bishai WR, Sterling TR. Paradoxical worsening of tuberculosis
15. David HL, Newman CM. Some observations on the genetics of isoniazid resistance in the tubercle bacilli. Am Rev
16. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis: common errors and their association wi
17. Canetti G. The J. Burns Amberson Lecture: present aspects of bacterial resistance in tuberculosis. Am Rev Respir D
18. Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, et al. Global trends in resistance to antituberc Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 2001;344:1294--1303.
19. Dye C, Espinal MA, Watt CJ, Mbiaga C, Williams BG. Worldwide incidence of multidrug-resistant tuberculosis. J
20. World Health Organization. Treatment of tuberculosis: guidelines for national programmes. Geneva: World Health
21. Enarson DA, Rieder HL, Arnadottir T, Trébucq A. Management of tuberculosis: a guide for low income countries. http://www.iuatld.org/assets/images/Management-of-TB.
22. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, Baez J, Kochi A, Dye C, Raviglione MC countries. JAMA 2000;283:2537--2545.
23. García-García M, Ponce-de-León A, Jiménez-Corona ME, Jiménez-Corona A, Palacios-Martinez M, Balandrano-C southern Mexico. Arch Intern Med 2000;160:630--636.
24. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR Jr. Treatment of 171 patients with pulmor
25. Park SK, Kim CT, Song SD. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to iso
26. Geerligs WA, van Altena R, de Lange WCM, van Soolingen D, van der Werf TS. Multidrug-resistant tuberculosis:
27. Frieden TR, Sherman LF, Maw KL, Fujiwara PI, Crawford JT, Nivin B, et al. A multi-institutional outbreak of high
28. Moghazeh SL, Pan X, Arain T, Stover CK, Musser JM, Kreiswirth BN. Comparative antimicrobial activities of rifa *tuberculosis* isolates with known rpoB mutations. Antimicrob Agents Chemother 1996;40:2655--2657.
29. Bodmer T, Zürcher G, Imboden I, Telenti A. Molecular basis of rifabutin susceptibility in rifampicin-resistant *M. tu*
30. Moore M, Onorato IM, McCray E, Castro KG. Trends in drug-resistant tuberculosis in the United States, 1993--199
31. Pomerantz BJ, Cleveland JC Jr, Olson HK, Pomerantz M. Pulmonary resection for multi-drug resistant tuberculosis
32. Farmer PE, Bayona J, Shin S, Becerra M, et al. Preliminary results of community-based MDRTB treatment in Lima

9.5 Laboratory Considerations in Determining Drug Resistance

Susceptibility testing of *M. tuberculosis* is critical for appropriate patient management and should be performed on an initial routinely will perform susceptibility testing on initial isolates but, often, private laboratories do not perform such testing unle should be repeated if the patient still has a positive culture result after 3 months of therapy or again develops positive culture using a standard methodology, such as that recommended by the National Committee for Clinical Laboratory Standards (*3*). was published by the National Committee for Clinical Laboratory Standards in 2000 (*3*).

Susceptibility of *M. tuberculosis* is determined by evaluating the ability of an isolate to grow on agar or in broth containing a the reference method for all antituberculosis drugs except pyrazinamide, in which case the BACTEC broth-based methodolo on the drug-containing plate that is more than 1% of the growth on the non--drug-containing plate (*4*). Because the agar meth *M. tuberculosis* isolates to first-line antituberculosis drugs be performed using more rapid broth-based methods (e.g., BACTI line drugs) available within 28 days of receipt of a clinical specimen (*5*). The critical concentrations recommended by the Na

concentrations for broth-based testing methods are shown in Table 17 (*2,3*).
The National Committee for Clinical Laboratory Standards recommends that susceptibility testing be performed for INH (tw initial *M. tuberculosis* isolates. Pyrazinamide testing may be done if there is a sufficiently high prevalence of PZA resistance there is resistance to RIF alone or to two or more drugs. Testing of second-line drugs is performed using the agar proportion are capreomycin, ethionamide, kanamycin (which also predicts amikacin susceptibility), ofloxacin (used to assess fluoroquin of EMB is also recommended. Susceptibility testing for cycloserine is not recommended because of the technical problems a

References

1. American Thoracic Society and CDC. Diagnostic standards and classification of tuberculosis in adults and children.
2. Woods GL. Susceptibility testing for mycobacteria. Clin Infect Dis 2000;31:1209--1215.
3. National Committee for Clinical Laboratory Standards (NCCLS). Susceptibility testing of mycobacteria, *Nocardia*, Committee for Clinical Laboratory Standards; 2000. Available at http://www.nccls.org/microbiology.htm.
4. Kent PT, Kubica GP. Antituberculosis chemotherapy and drug susceptibility testing. In: Kent PT, Kubica GP. Publi Control; 1985:159--184.
5. Tenover FC, Crawford JT, Huebner RE, Geiter LJ, Horsburgh CR Jr, Good RC. The resurgence of tuberculosis: is y

10. Treatment Of Tuberculosis in Low-Income Countries: Recommendations and Guidelines of th

This brief summary of the differences between the recommendations for treatment of tuberculosis in high-income, low-incid context for the ATS/CDC/IDSA guidelines. As tuberculosis in low-incidence countries, such as the United States, becomes r care providers in low-incidence countries have an understanding of the differences in the approaches used and the reasons fo high-incidence countries (*1*). As noted at the outset of this document, the ATS/CDC/IDSA recommendations cannot be assu tuberculosis and the resources with which to confront it to an important extent determine the approaches used.
A number of differences exist between these new ATS/CDC/IDSA recommendations, and the current tuberculosis treatment Rather than being recommendations per se, the IUATLD document presents a distillation of IUATLD practice, validated in t mycobacterial culture and susceptibility testing and radiographic examinations are not widely available. These organizations Course) in which direct observation of therapy ("DOT" in the current statement) is only one of five key elements (*4*). The bo Selected important differences among the recommendations are summarized below. Some of the differences arise from varia weekly regimens, arise from different interpretations of common elements, for example, whether DOT is used throughout th

10.1. Microbiological Tests for Diagnosis and Evaluation of Response

The WHO and the IUATLD recommend diagnosis and classification of cases and assessment of response based on sputum A in many countries. In addition, the AFB smear identifies patients who are most likely to transmit the organism. Susceptibility facilities. However, susceptibility testing is recommended by the WHO for patients who fail (sputum smear--positive in mon

those who fail a supervised retreatment regimen. Regarding follow-up, it is recommended by the WHO and the IUATLD tha and at completion of treatment (either 6 or 8 months). The IUATLD recommends that for patients who have positive smears

10.2. Use of Chest Radiographs in Diagnosis and Follow-Up of Patients Being Treated

In many parts of the world radiographs are not readily available. Moreover, because the highest priority for treatment is the h radiographic findings alone is an inefficient use of resources. Thus, chest radiography is recommended by both the WHO an follow-up.

10.3. Initial Treatment Regimens

The WHO recommends a single initial phase of daily INH, RIF, PZA, and EMB (or SM) for 2 months followed by a continu daily INH and EMB for 6 months (self-administered). The WHO specifically discourages programs from using twice weekly The IUATLD recommends a 2-month initial phase of INH, RIF, PZA, and EMB given by DOT, followed by a 6-month cont the IUATLD recommends EMB in place of thiaocetazone. The IUATLD also recommends a 12-month regimen with a 2-mo of daily INH and thioacetazone. This regimen is intended to be used for patients who have negative smears or when the 8-mo The rationale for the 8-month regimen recommendation is that it is felt that RIF should always be given by DOT; yet, many p treatment. The 8-month regimen is less efficacious in patients with drug-susceptible tuberculosis, but use of this regimen wil 8-month regimen's continuation phase of INH and EMB costs about 27% less than a 4-month continuation phase of daily IN

10.4. Approach to Previously Treated Patients

The WHO and the IUATLD recommend a standardized regimen for patients who have relapsed, had interrupted treatment, o at the WHO.) The regimen consists of an initial phase of INH, RIF, PZA, EMB, and SM given daily for 2 months and then 1 INH, RIF, and EMB.

Patients who have failed supervised retreatment are considered "chronic" cases and are highly likely to have tuberculosis cau based on the test results are recommended by the WHO, if testing and second-line drugs are available (*5*). The IUATLD recc The issue of chronic cases is an area of considerable controversy (*6*). In countries with sufficient resources, such as the Unite in Section 9, Management of Relapse, Treatment Failure, and Drug Resistance, are recommended. However, in countries wit Nevertheless, at least one group has demonstrated that in a high-incidence, low-income country (Peru) treatment with indivic

10.5. Monitoring of Outcomes of Therapy

Both the WHO and the IUATLD recommend a formal system for monitoring outcomes of treatment that classifies all cases i transferred out). The assessment of cure is based on clinical response and on sputum AFB smear (or culture when available) identification of programmatic shortcomings.

10.6. Recommended Doses of Antituberculosis Drugs

The WHO recommends 10 mg/kg as the dose for three times weekly INH, whereas the ATS/CDC/IDSA recommend 15 mg/ to a maximum of 300 mg/day), but the ATS/CDC/IDSA recommend a higher dose for children (10--15 mg/kg per day), base the number of pills required for three weight ranges resulting in a dose of about 5 mg/kg up to 300 mg/day.

The clinical trials of the BMRC that established the efficacy of three times weekly regimens all used an INH dose of 15 mg/k IUATLD (with assistance from global experts), and was chosen to maintain the weekly amount of INH approximately equal

10.7. Drugs/Preparations Not Available in the United States

Thioacetazone, which formerly was commonly used, is still available in most parts of the world, but is used less frequently. I component of the recommended IUATLD first-line regimen. Combination preparations not available in the United States bu thioacetazone (50 mg); and INH (75 mg), RIF (150 mg), PZA (400 mg), and EMB (275 mg). The IUATLD recommends usi

10.8. Treating Pregnant Women

Both the WHO and the IUATLD include PZA in the regimen for treating pregnant women, in the absence of data indicating

10.9. Management of Common Adverse Reactions

Neither baseline nor follow-up testing is recommended by the WHO and the IUATLD. It is recommended that patients be ta

References

1. CDC. Reported tuberculosis in the United States, 2001. Atlanta, GA: US Department of Health and Human Service
2. World Health Organization. Treatment of tuberculosis: guidelines for national programmes, 2nd edition. WHO/TB/
3. International Union against Tuberculosis and Lung Disease. Management of tuberculosis: a guide for low income c http://www.iuatld.org/pdf/en/guides_publications/management_of_tb.pdf
4. World Health Organization. What is DOTS? A guide to understanding the WHO-recommended TB control strategy Organization; 1999. Available at http://www.who.int/gtb/dots.
5. World Health Organization. An Expanded DOTS framework for effective tuberculosis control. WHO/CDS/TB/200 http://www.who.int/gtb/dots.
6. Farmer P. DOTS and DOTS-plus: not the only answer. Ann N Y Acad Sci 2001;953:165--84.
7. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F, Sanchez E, Barria M, Becerra M, Fawzi MC, Kapiga resistant tuberculosis in Lima, Peru. N Engl J Med 2003;348:119--128.

11. Research Agenda for Tuberculosis Treatment

11.1. New Antituberculosis Drugs

New antituberculosis drugs are needed for three reasons: to shorten or otherwise simplify treatment of tuberculosis caused by
provide more effective and efficient treatment of latent tuberculosis infection (LTBI) (*1*). Although treatment regimens for d
to achieve optimal results. Nonadherence to this relatively lengthy course of treatment remains a major problem. To address
standard of care worldwide. However, the administrative and financial burden of providing DOT for all patients is considera
are drugs that could enable effective treatment to be given at dosing intervals of 1 week or more.

Rates of multidrug-resistant tuberculosis are alarmingly high in several countries (*2*), and even in countries, such as the Unit
difficult treatment problem (see Section 9: Management of Relapse, Treatment Failure, and Drug Resistance). Current treatm
more expensive than those used for standard treatment. Moreover, these treatment regimens often have to be given for 18--2
solve the problem of drug resistance, their judicious use would greatly improve the treatment for many patients.

Finally, the United States and several other low-incidence countries have embarked on plans to eliminate tuberculosis. An im
LTBI who are at high risk of developing tuberculosis (*3*). In the United States the most commonly used LTBI treatment regi
limitation on its effectiveness. A shorter LTBI treatment regimen with RIF and PZA appears to be effective, but reports have
effective "short-course" LTBI treatment are a major need.

No truly novel compounds that are likely to have a significant impact on tuberculosis treatment are presently available for cl
regimens and investigate the role of newer fluoroquinolones in the treatment of drug-susceptible tuberculosis is warranted. A
HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum smears at completion of 2 month
by experimental studies: increasing the rifapentine dosage (*5*), and adding moxifloxacin as a companion drug to provide bett
regimen (*6*). Other data from a clinical trial of ofloxacin suggest that fluoroquinolones have the potential to significantly sho
tuberculosis, moxifloxacin appears to be the most promising.

Other compounds that might become available for clinical evaluation in the future include the nitroimidazopyrans that are ch
suggested; oxazolidinones such as linezolid; and drugs that target isocitrate lyase, an enzyme that may be necessary for the e
bactericidal activity comparable to that of INH and appears to act as well on bacilli maintained in an anaerobic environment
begin. Although linezolid, a drug that is marketed for the treatment of selected acute bacterial infections, does have demonst

treatment of tuberculosis (*10*).

11.2. Other Interventions To Improve the Efficacy of Treatment

A number of other approaches have been suggested that might lead to improved treatment outcome, including alternative dru
Experimental studies have demonstrated that effective serum concentrations of INH and PZA can be provided through incor
(*11*). However, there has been little apparent commercial interest in pursuing this approach. Liposomal encapsulation of anti
infection (i.e., the macrophage) providing for more effective and better tolerated therapy, as well as for more widely spaced t
requirements, minimize toxicity, and deliver drug to infected alveolar macrophages. Although experimental studies have sug
(*11,12*).

Because of possible detrimental effects of the cytokine, tumor necrosis factor-a, in HIV-associated tuberculosis, there has be
necrosis factor-a production. Studies have shown that administration of thalidomide improves weight gain in both HIV-posit
reductions in circulating HIV viral load in patients with tuberculosis (*14*). However, the potential side effects of these drugs
"protective" cytokines, such as aerosolized interferon-g and subcutaneous interleukin-2, that have shown activity as adjuncts
immunomodulation, the use of heat-killed preparations of *M. vaccae* as a therapeutic vaccine, has not shown clinically signif
continues to be interest in this approach, especially for patients with advanced drug-resistant tuberculosis. Other vaccines tha
experimental studies (*18*). Finally, a study suggested that the administration of Vitamin A and zinc to patients with pulmonar
chest radiographs (*19*). Further assessment of nutritional supplements in tuberculosis treatment may be indicated.

11.2.1. Better methods to identify and manage high- and low-risk patients

As noted above, sputum culture positivity at 2 months appears to be a marker for an increased risk of relapse for patients wit
greater sensitivity and specificity for a poor outcome could better select high risk patients for more intensive or longer therap
have shown promise and deserve further evaluation (*20*). Conversely, markers that reliably identify patients at lower risk of a
treatment. Whether or not low-risk patients can be treated with shorter regimens using currently available drugs is a topic of

11.2.2. Health services research to facilitate treatment administration and improve treatment outcome

Although DOT (as a component of DOTS) is widely advocated as a universal standard of care for tuberculosis treatment, ma
Moreover, some programs have achieved excellent results by targeting DOT to patients known or suspected of being at incre
Finally, although limited work has been done in the area of behavioral studies of tuberculosis patients and providers, an amb
revisited (21).

References

1. O'Brien RJ, Nunn PP. The need for new drugs against tuberculosis: obstacles, opportunities, and next steps. Am J R
2. Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, Hoffner S, Rieder HL, Binkin N, Dye C, Wil
Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Dru
3. American Thoracic Society, CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J R
4. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infec
-735.
5. Daniel N, Lounis N, Ji B, O'Brien RJ, Vernon A, Geiter LJ, Szpytma M, Truffot-Pernot C, Hejblum G, Grosset J. A
effectiveness with 6- and 8-month treatment regimens. Am J Respir Crit Care Med 2000;161:1572--1577.
6. Lounis N, Bentoucha A, Truffot-Pernot C, Ji B, O'Brien RJ, Vernon A, Roscigno G, Grosset J. Effectiveness of onc
Antimicrob Agents Chemother 2001;45:3482--3486.
7. Tuberculosis Research Centre. Shortening short course chemotherapy: a randomised clinical trial for the treatment c
Indian J Tuber 2002;49:27--38.
8. McKinney JD, Honer zu Bentrup K, Munoz-Elias EJ, Miczak A, Chen B, Chan WT, Swenson D, Sacchettini JC, Ja
requires the glyoxylate shunt enzyme isocitrate lyase. Nature 2000;406:683--685.
9. Stover CK, Warrener P, VanDevanter DR, Sherman DR, Arain TM, Langhorne MH, et al. A small-molecule nitroir
10. Cynamon MH, Klemens SP, Sharpe CA, Chase S. Activities of several novel oxazolidinones against *Mycobacteriu*
11. Gangadharam PR, Geeta N, Hsu YY, Wise DL. Chemotherapy of tuberculosis in mice using single implants of ison
12. Sharma R, Saxena D, Dwivedi AK, Misra A. Inhalable microparticles containing drug combinations to target alveol
13. Tramontana JM, Utaipat U, Molloy A, Akarasewi P, Burroughs M, Makonkawkeyoon S, Johnson B, Klausner JD, I
enhances weight gain in patients with pulmonary tuberculosis. Mol Med 1995;1:384--397.
14. Wallis RS, Nsubuga P, Whalen C, Mugerwa RD, Okwera A, Oette D, Jackson JB, Johnson JL, Ellner JJ. Pentoxifyl
randomized, controlled trial. J Infect Dis 1996;174:727--733.
15. Condos R, Rom WN, Schluger NW. Treatment of multidrug-resistant pulmonary tuberculosis with interferon-g via
16. Johnson B, Bekker LG, Ress S, Kaplan G. Recombinant interleukin 2 adjunctive therapy in multidrug-resistant tube
17. Durban Immunotherapy Trial Group. Immunotherapy with *Mycobacterium vaccae* in patients with newly diagnosec
18. Moreira AL, Tsenova L, Murray PJ, Freeman S, Bergtold A, Chiriboga L, Kaplan G. Aerosol infection of mice with
Microb Pathog 2000;29:175--185.
19. Karyadi E, West CE, Schultink W, Nelwan RH, Gross R, Amin Z, Dolmans WM, Schlebusch H, van Der Meer JW

tuberculosis in Indonesia: effects on clinical response and nutritional status. Am J Clin Nutr 2002;75:720--727.
20. Desjardin LE, Perkins MD, Wolski K, Haun S, Teixeira L, Chen Y, et al. Measurement of sputum *Mycobacterium t* Med 1999;160:203--210.
21. CDC. Improving tuberculosis treatment and control: an agenda for behavioral, social, and health services research. Bethesda, MD, August 28--30, 1994. Atlanta, GA: US Department of Health and Human Services, CDC; 1995.

Acknowledgment
The Committee thanks Elisha Malanga of the American Thoracic Society for excellent administrative support. The Committe Elimination, National Center for HIV, STD, and TB Prevention, CDC, for their thorough review and helpful comments. The Holcombe, M.P.P.A., James Lamberti, M.D., Evelyn Lancaster, R.N., Kathleen Moser, M.D., M.P.H., James McDaniel, M.I Ray, M.D., Jon Tillinghast, M.D., M.P.H., Victor Tomlinson, Jr., M.D., and Charles Wallace, Ph.D.

Joint Committee of the American Thoracic Society (ATS), the Infectious
Membership List*

Co-chairs: Henry M. Blumberg, M.D., IDSA; Philip C. Hopewell, M.D., ATS; Richard J. O'Brien, M.D., CDC.
Members: William J. Burman, M.D.; Richard E. Chaisson, M.D.; Charles L. Daley, M.D.; Wafaa El Sadr, M.D., M.P.H.; Su Grzemska, M.D.; Michael D. Iseman, M.D.; Robert M. Jasmer, M.D.; Venkatarama R. Koppaka, M.D., Ph.D.; Richard I. Me M.D.; Jeffrey R. Starke, M.D.; Andrew A. Vernon, M.D., M.H.S.
* Charles Peloquin, Pharm.D., also made substantial contributions to the document.

Table 1

Return to top.

Figure 1

Morbidity and Mortality Weekly Report
Centers for Disease Control and Prevention
1600 Clifton Rd, MailStop E-90, Atlanta, GA 30333, U.S.A