

Practical Pharmacy

For Developing Countries

NOTE TO OUR READERS:

The goal of *Practical Pharmacy* is to provide accessible and accurate information on medicines issues for front-line health workers who may not have any pharmaceutical training. This issue of *Practical Pharmacy* would be best used as a supplement to your national Tuberculosis (TB) guidelines. It is extremely important for all people involved in TB care to have access to the national treatment guidelines. We therefore encourage you to get in contact with your National TB Program Centre for these resources. We are aware, however, that in some countries it may be difficult to obtain copies of these guidelines; in some cases they may not even be available at all.

Aside from national guidelines, another "must have" is the *WHO Treatment of Tuberculosis Guidelines for National Programs 2003* (see the reference section on the final page). These guidelines provide a comprehensive information on all aspects of TB treatment.

What is Tuberculosis

Tuberculosis (TB) infection is caused by bacteria – bacilli called *Mycobacterium Tuberculosis*. When a person with TB infection coughs or sneezes, they release tiny particles containing TB bacilli into the air. A person who is exposed to the bacilli becomes infected if they inhale the airborne bacilli into their lungs.

TB infection or **non-active TB** means that TB bacilli are in the body, but the immune system is keeping them under control. **Active TB**, on the other hand, develops when the immune system cannot keep the TB bacilli under control and the bacilli begin to multiply rapidly. When the bacteria become active, a person becomes ill with TB, and this can occur when the person's immunity goes down or is reduced. Conditions that can reduce a person's immunity include: HIV, malnutrition, advancing age, or some other diseases.

People who have TB infection (non-active TB disease) are **NOT** infectious. However, people with untreated active TB are infectious, and must be treated as soon as possible.

How is Tuberculosis treated?

According to the World Health Organization (WHO), the aims of TB treatment are:

- to cure the patient of TB,
- to prevent death from active TB or its late effects,
- to prevent relapse of TB,
- to decrease transmission of TB to others,
- to prevent the development of acquired drug resistance.

QUICK TIP!

The common symptoms of active TB disease are persistent cough, bloody sputum, weight loss or loss of appetite, fatigue, fever, or night sweats.

QUICK TIP!

If not treated, a person with active TB can infect on average 10 to 15 people every year.

Treatment of TB is carried out according to your national guidelines. You should refer to the national guidelines for specific details about treatment regimens and procedures of your country. We have summarised the most common treatment regimens [see page 3]. These regimens are based on the characteristics and proven efficacy of the medicines, although regimens may deviate from this under some circumstances (e.g. known resistance, pregnancy, treatment of children), or according to local guidelines.

Reminder: Commonly used abbreviations

Isoniazid	H	INH
Rifampicin (aka Rifampin)	R	RIF
Pyrazinamide	Z	PZA
Ethambutol	E	EMB
Streptomycin	S	SM

Standard adult treatment regimens start with an initial (or intensive) phase of two months, normally consisting of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. [See table 1, page 2] During the initial phase, TB bacilli are killed rapidly, infectious patients quickly become non-infectious (usually within 2 weeks) and symptoms improve. This is followed by a continuation phase of 4 to 6 months, normally consisting of Isoniazid and Rifampicin (although sometimes Isoniazid and Ethambutol are used). During the continuation phase, the medicines eliminate remaining bacilli and prevent subsequent relapse.

Dosing frequency

Treatment may be administered daily, five-times per week (Monday to Friday), or three-times per week (usually Monday, Wednesday and Friday). This is decided by each national TB program. It must be noted that twice-weekly regimens are no longer recommended. *continued on page 2...*

Table 1: Common treatment regimens

	Initial Phase		Continuation Phase
New Cases	2 months HRZE		4 months HR or 6 months HE
Retreatment Cases	2 months HRZE S	1 month HRZE	5 months HRE
Chronic Cases and Drug-resistant TB	According to your national guidelines		

Retreatment

If a patient has undergone a course of TB treatment, and is found to have TB infection either at the end of the course (failure), or at some time in the future (relapse), they will need to be considered for **retreatment**. This is an important time for you to update the patient’s understanding of their TB treatment, and to reassess and reinforce medication adherence.

The most common retreatment regimen is shown in the table above, and involves two months of an additional agent, the injectable aminoglycoside Streptomycin. However, some retreatment cases may have drug-resistant TB, so retreatment policies are entirely dependant on your national TB program and the laboratory resources that are available in your area. The best programs perform drug-susceptibility testing (DST), and this should be performed before each patient begins a retreatment regimen. The treatment regimen can later be adjusted according to DST results and available second-line agents.

QUICK TIP!
Empowerment of TB patients can also be assisted by encouraging patients to interact with one another, such as through the daily visits to the health facility for DOT

Adherence and DOT

Adherence to TB treatment is not easy due to the heavy pill burden, the potential side-effects and the long duration of treatment. Empowering the patients (and their families) with information about TB is essential to allow them to take positive control of their health and to give them the best chance of treatment success. From a public health point of view it is critical to stop both the spread of TB to others, and the development of drug resistance.



Credit: Lung Health Image Library/Pierre Viriot

A TB patient takes his medication

Directly Observed Treatment (DOT) is currently the most recommended adherence method. DOT entails having a patient’s treatment fully observed by a treatment supporter. This ensures that every TB patient has the support of another concerned individual and guarantees better treatment adherence.

QUICK TIP!
Providing a supportive and efficient service in your facility is one of the best aids to treatment adherence.



Credit: Lung Health Image Library/ J. P. Zellweger

Supervision of drug intake at the TB hospital in Cotonou, Benin

“Because of the length of time the patient has to take treatment, completing TB treatment is a special challenge and requires an unyielding sense of commitment. This may be easy to sustain while the patient feels sick. However, after a few weeks of taking treatment, patients often feel better and see no reason for continuing their treatment. It is thus essential for health workers or treatment supporters to be supportive and use the initial period to bond with the patient. This will enable them to build a strong relationship in which the patient believes and trusts advice given by the treatment supporter.”

(Source: South African Guidelines)

Reminder: DOT vs DOTS

- DOT** stands for **Directly Observed Treatment**, and is the strategy of having all of a TB patient’s medicine doses observed by a designated person (health care worker, or trained and supervised community member) to help ensure adherence to therapy.
- DOTS** stands for **Directly Observed Treatment Short-course** refers to WHO’s comprehensive “Internationally recommended policy package for TB control” to which countries are recommended to adapt their TB programs (DOT is one element of DOTS).

Tuberculosis Medicines

Table 2: Adult and children weight-based doses of first-line medicines

Medication (common presentation)	Potency	ONCE DAILY		THREE TIMES WEEKLY	
		Dose and range (mg/kg)		Dose and range (mg/kg)	Maximum Dose (mg)
Isoniazid (H) (100, 300mg)	High	5 (4-6)		10 (8-12)	600
Rifampicin (R) (150, 300mg)	High	10 (8-12)		10 (8-12)	600
Ethambutol (E) (100, 400mg)	Low	Adult: 15 (15-20)	Child: 20 (15-25)	30 (25-35)	2400
Pyrazinamide (Z) (400mg)	Low	25 (20-30)		35 (30-40)	3000
Streptomycin (S) (1g vial)	Low	15 (12-18)		15 (12-18)	1000

Note: 1. Doses are based on WHO Guidelines (doses differ in some guidelines, but may be based on differently resourced settings)
2. Retreatment doses may be higher – refer to your national guidelines or WHO Drug-Resistant TB Guidelines

Credit: Lung Health Image Library/Pierre Virot



Thiacetazone causes serious, sometimes fatal, side effects in many HIV positive patients

- Pyridoxine (Vitamin B6) 10-30mg daily should always be given with isoniazid
- WHO now discourages the use of thioacetazone because of the risk of side effects, especially for people living with HIV
- For second-line medicines refer to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis 2006 (available at <http://www.who.int/tb/publications/en/>)
- No new TB medicines have been developed for the standard regimen since the 1960s. This highlights the urgent need for medicines development for TB and other neglected diseases

Fixed-Dose Combination tablets (FDCs)

The use of FDCs makes TB treatment easier for both patients and healthcare workers.

- For patients, FDCs reduce the number of tablets to take and help to minimise dosing errors, thereby improving adherence and reducing the chance of developing resistance or side effects.
- For healthcare workers, FDCs simplify dosing recommendations and weight-based dose-adjustments, thereby helping to reduce prescribing errors.

QUICK TIP!
Soon after TB treatment is initiated, a patient's health improves and their infectiousness declines.

NOTE: The most useful dosing table for practical purposes is one that follows your national treatment regimen and incorporates the specific FDC formulations available in your country. It should provide weight-based recommendations of how many tablets to take for each formulation. Below (Table 3) is an example of Kenya's national guidelines for adults:

Table 3: Kenya's national guidelines for adults

Medicine and Strength	Formulation	Dosing (number of tablets) based on pre-treatment weight		
		over 55kg	40-54kg	30-39kg
Rifampicin 150mg + Isoniazid 75mg + Pyrazinamide 400mg + Ethambutol 275mg	4-FDC tablet RHZE	4	3	2
Isoniazid 150mg + Ethambutol 400mg	2-FDC tablet EH	2	2	2
Rifampicin 150mg + Isoniazid 75mg + Ethambutol 275mg	3-FDC tablet RHE	4	3	2
Rifampicin 150mg + Isoniazid 75mg + Pyrazinamide 400mg	3-FDC tablet RHZ	4	3	2

QUICK TIP!
Treatment is always based on multidrug chemotherapy (antibiotic treatment), which is the only way of preventing the emergence of resistant bacteria.

A table like this could be created for your own setting (if one is not already available) as well as one for children's doses, which would need more detail. *continued on page 4...*

Medication Counselling

- Through supportive counselling, the patient and the treatment observer should both know what to expect while undergoing TB treatment. This information is best supplemented with cultural- and language-appropriate written information.
- Patients should be asked and encouraged to report any and all symptoms at each clinic visit.

Essential Medicine Information

- Once a patient has started treatment he or she will start to feel much better very quickly, even so the patient must complete the entire course of medication exactly as advised by the health worker in order to kill all the TB bacteria and cure the disease.
- When on TB treatment, the patient must check with the doctor and pharmacist before taking any other medicine (whether modern or traditional medicines, and including birth control pills) as they can affect how the TB medication works.
- People on TB treatment *should not* drink a lot of alcohol.
- It is normal for a TB patient to get the following mild symptoms, but they should be reported to the healthcare provider at the next clinic visit:
 - Nausea, mild stomach pains
 - Orange/red urine or tears (check that the patient does not use soft contact lenses as they may stain)
 - Pain, tingling or numbness in hands or feet
 - Some joint pain.
- The patient should immediately report to the clinic if any of the above symptoms become severe, or upon noticing any of the following:
 - Rash, yellow skin or eyes, or dark-coloured urine
 - Changes in vision or eyes
 - Any other severe or unusual illness
- Patients being treated with Streptomycin should be asked to immediately report any changes in hearing or balance



Credit: Lung Health Image Library/Jan van den Hombergh

Children reading an information leaflet on TB

QUICK TIP!
Because of the importance of tuberculosis to public health, all TB treatment services should be provided free of charge

Interactions

Interactions are very common among TB medicines. This is largely due to the enzyme-inducing effects of rifampicin, but also due to the potential additive side effects of all TB medicines. As a result, ALL other medicines should be checked by pharmacist to ensure their safe use with TB medicines. Below is a summary of some common and significant interactions:

Table 4: Common interactions

Interacting substance	Effect	General recommendations
Food	Delayed or reduced absorption of some TB medicines	Recommend taking entire regimen on an empty stomach, however, the patient may take the medicines with a small meal to reduce stomach side-effects
Antacids	Reduced levels of some TB medicines	Do not administer antacids together with TB medicines; take antacids at least 4 hours after taking TB medicines
Alcohol	Possible increased risk of liver problems	Avoid excessive alcohol during TB treatment
Medicines with additive toxicities (liver, kidney, stomach, eye, ear)	Increase/additive risk of specific side effects	Avoid combinations as much as possible. If used together, monitor very carefully for potential side effects (e.g. monitor the liver if using antiretrovirals (ARVs); monitor kidneys and hearing if using streptomycin)

Table 5: Clinically significant medicines interactions involving Rifampicin

<i>Class of medicines</i>	<i>Drugs whose levels are <u>DECREASED</u> by Rifampicin</i>	<i>Comments</i>
<i>Anti-infectives</i>	<u>NNRTIs</u> Nevirapine, efavirenz	Efavirenz is preferred. See table TB/HIV section on page 7 & 8
	<u>protease inhibitors</u> Saquinavir, lopinavir/ritonavir, ritonavir, indinavir, nelfinavir, amprenavir	Change to lopinavir/ritonavir or saquinavir/ritonavir with dose modifications and monitoring. See TB/HIV section on page 7 & 8
	<u>macrolides</u> Erythromycin, clarithromycin	Azithromycin or roxithromycin (if available) can be used as an alternative
	<u>azole antifungals</u> Ketoconazole, itraconazole, voriconazole	Fluconazole may be used, although levels are slightly reduced. Avoid other azole antifungals due to loss of effectiveness.
	Chloramphenicol	Consider an alternative antibiotic
	Doxycycline	Consider an alternative antibiotic
	Mefloquine	Consider alternative malaria prophylaxis / treatment
	Praziquantel	Consider alternative anthelmintic
	Quinine	Avoid combination or increase quinine dose, seek specialist advice.
<i>Hormone Therapy</i>	Hormone contraceptive (oral, implants)	Use non-hormonal contraceptive method until one month after rifampicin treatment finishes
	Thyroxine, levothyroxine	Monitoring of thyroid function is recommended, may require increased dose of thyroxine
<i>Analgesics</i>	Codeine, morphine	Monitor for adequate pain control, increase opioid dose if needed.
<i>Anti-coagulants</i>	Warfarin	Monitor prothrombin time or INR (international normalized ratio). May require significant dose increase
<i>Immuno-suppressants</i>	Cyclosporin, tacrolimus	Avoid combination or monitor concentrations. May require significant dose increase
	<u>Corticosteroids</u> Hydrocortisone, fludrocortisone, methylprednisolone, prednisolone	Monitor clinically. May require significant dose increase
<i>Anti-convulsants</i>	carbamazepine, diazepam, phenytoin, valproate,	Monitoring of levels or clinical effect required. May require anticonvulsant dose increase
<i>Cardio-vascular medicines</i>	<u>Calcium-Channel Blockers</u> Diltiazem, verapamil, nifedipine, felodipine	Clinical monitoring required. May require dose increase or change to an alternative medicine
	Propranolol, metoprolol	Clinical monitoring required. May require dose increase or change to an alternative beta-blocker (atenolol preferred)
	Enalapril, losartan	Clinical monitoring required. May require dose increase or change to an alternative medicine
	Digoxin	Monitoring of levels or clinical effect required. May require digoxin dose increase
<i>Broncho-dilators</i>	Theophylline	Monitoring of levels or clinical effect required. May require theophylline dose increase
<i>Hypo-glycaemics</i>	<u>Sulfonylureas</u> Glibenclamide, gliclazide, glimepiride	Rifampicin may increase metabolism of glibenclamide and decrease its hypoglycaemic effect; monitor blood glucose and increase glibenclamide dosage if necessary
<i>Psychotropics</i>	Amitriptyline, nortriptyline	Clinical monitoring required. May require dose increase or change to an alternative medicine
	Haloperidol, quetiapine	Clinical monitoring required. May require dose increase or change to an alternative medicine
<i>Hypnotics</i>	Diazepam, triazolam, zolpidem, buspirone	Clinical monitoring required. May require dose increase or change to an alternative medicine

Adapted from *Treatment of Tuberculosis, ATS, CDC, IDSA. MMWR 2003;52 (No. RR-11): [p47]*

Table 6: Interacting Medicines

<i>Interacting Medicines</i>	<i>Effect</i>	<i>Recommended Management</i>
Isoniazid		
Note that isoniazid interacts with many of the same medicines as rifampicin (see list below). For these medicines, rifampicin has an opposite (and greater) effect to that of isoniazid, so that the overall effect of rifampicin / isoniazid combination therapy is usually a <u>decrease</u> in the levels of: <i>carbamazepine, diazepam, phenytoin, valproate, itraconazole, ketoconazole, theophylline, aminophylline and warfarin</i>		
Didanosine, stavudine (NRTIs)	Increase risk of peripheral neuropathy (burning or tingling of feet)	Pyridoxine (vitamin B6) 10-30mg daily should be offered. Patient should be counseled and monitored for signs of peripheral neuropathy
Pyrazinamide (PZA)		
Zidovudine (NRTI)	Reduced PZA levels	Avoid combination if possible. If used together, consider possibility of low PZA levels
Streptomycin (an aminoglycoside medicine)		
Medicines which are potentially <i>nephrotoxic</i> (toxic to the kidney) or <i>ototoxic</i> (toxic to the ear) (eg. the other aminoglycosides, amphotericin, cephalosporins, furosemide, ethacrynic acid, cyclosporin, vancomycin)	Increase/additive risk of nephrotoxicity or ototoxicity	Avoid combination if possible. If used together, monitor very carefully for potential nephrotoxicity or ototoxicity
Neuromuscular blockers (atracurium, pancuronium, vecuronium)	Increase effect of neuromuscular blockers	Avoid combination if possible. If used concurrently, monitor very carefully
Magnesium	Possible neuromuscular weakness	Avoid combination

Management of side-effects

- Pyridoxine (Vitamin B6) 10-30mg daily should routinely accompany isoniazid, to prevent peripheral neuropathy.

Table 7: Side effects of TB medicines

Side effect	Medicines most probably responsible	Recommended management
<i>Minor side effects → Continue TB medicines, check doses, reassure patient</i>		
Gastrointestinal (nausea, belly pain, no appetite)	Rifampicin, pyrazinamide	Give medicines with small meals or last thing at night before sleeping
Joint pains, gout	Pyrazinamide	Anti-inflammatories (e.g. ibuprofen) as required
Burning, numbness, or tingling sensation in feet (peripheral neuropathy)	Isoniazid	Pyridoxine 100mg daily
Orange / red urine	Rifampicin	Give reassurance. When starting treatment, patients should be told that this commonly happens, is normal, and is not dangerous.
<i>Major side effects → Stop responsible medicine(s)</i>		
Itching, skin rash	Most TB medicines	If a patient experiences any of these major side effects and other causes have been excluded, the medicine(s) considered responsible should be immediately stopped and the patient urgently referred to their TB doctor
Jaundice, confusion, vomiting	Most TB medicines (especially H,R, Z)	
Visual changes	Ethambutol	
Generalised reaction, including shock or red / purple skin lesions	Rifampicin	
Deafness or dizziness (with other causes excluded)	Streptomycin	

Adapted from WHO TB Guidelines 2003

Drug Resistant Tuberculosis

Multi-Drug Resistant TB

WHO estimates that there are currently up to 1.5 million Multi-Drug Resistant TB (MDR-TB) cases worldwide, with reported cases in every region of the world. This means that a proportion of your patients probably have MDR-TB.

QUICK TIP!
MDR-TB is defined as a form of tuberculosis which is resistant to at least isoniazid and rifampicin (the two most powerful TB drugs).

Resistance to TB medicines can occur when the medicines are misused or mismanaged. Examples include:

- When patients do not complete their full course of treatment;
- When healthcare providers prescribe the wrong treatment, the wrong dose, length of time for taking the medicines;
- When the supply of medicines is not always available; or
- When the medicines are of poor quality.

It should not be assumed that a patient has been non-adherent, although any adherence problems must be overcome before considering further treatment.

Healthcare staff need to help to prevent the spread of MDR-TB by quickly diagnosing cases, following treatment guidelines, monitoring patients' responses to treatment, checking adherence, and ensuring their health facility has infection control measures in place.

Identification and treatment of MDR-TB can only be carried out by specially-trained staff where culture and drug-susceptibility testing (DST) is available. Patients must be referred to a centre equipped to manage MDR-TB.

Treatment

Treating MDR-TB takes longer (a minimum of 18 months) and requires medicines that are more toxic, more expensive, often of limited availability, and generally less effective – particularly in persons with HIV infection. However, it is generally treatable, and programs have to be scaled-up to stop the progress of MDR-TB.

WHO has established the *Green Light Committee* to promote access to and rational use of these second-line TB medicines, with eligibility based on a national TB program being able to guarantee appropriate use of these second-line medicines, such that further resistance is not caused.

Country specific drug-resistant TB treatment guidelines are designed based on local resistance patterns and available resources. For more information on the management of MDR-TB, refer to your national guidelines and the WHO Drug-Resistant TB Management Guidelines (2006).

Extensively Drug Resistant TB (XDR-TB)

XDR-TB is defined as TB which is resistant to isoniazid, rifampicin, any fluoroquinolone and at least one of the injectable second-line medicines (e.g. amikacin, kanamycin, or capreomycin).

XDR-TB can develop when both the first-line and the second-line medicines are mismanaged and misused. This extensive resistance means that treatment options become seriously limited.

The emergence of XDR-TB poses a very large threat to TB control efforts, particularly in areas with high HIV prevalence. It emphasizes the need to strengthen basic TB control, and for countries to adopt MDR-TB management guidelines very carefully.

Tuberculosis and HIV

Background

TB and HIV are closely interlinked, and represent a deadly combination. Each disease rapidly speeds up the progression of the other: HIV infection is the most potent risk factor for converting latent TB into active TB, while TB accelerates the progress of the HIV infection in a patient.

TB in HIV positive people is harder to diagnose, but if left untreated it is almost certain to be fatal. Furthermore, HIV co-infection has been shown to greatly increase the incidence of MDR-TB. This highlights the need to treat both diseases as aggressively and as carefully as possible.

Treatment

It is critical for all people with active TB to be treated immediately to prevent their health from rapidly getting worse. This is especially the case for people living with HIV.

Treatment of co-infection requires great care. When to start ARVs still depends on a patient's CD4 count. Choosing which ARV regimen to use is complicated by significant medicines interactions, and if co-treatment is started, the patient experiences a high pill burden and a higher risk of side-effects. In some cases *continued on page 8...*

QUICK TIPS!

- TB is the most common opportunistic infection and a leading cause of death in people with HIV infection.
- HIV is the most powerful factor known to increase the risk of TB. It is said to “fuel the TB epidemic” in HIV-prevalent areas.
- People who are HIV positive and infected with TB are up to 50 times more likely to develop active TB in a given year than people who are HIV-negative.
- Diagnosis of active TB infection should ring alarm bells to make sure the patient is HIV tested.

a patient's TB can temporarily get worse after starting ARVs as their immune system essentially reactivates and discovers that it also has to fight TB infection. This event is called Immune Reconstitution Inflammatory Syndrome (IRIS) and should be kept in mind when assessing a patient's health after starting ARVs.

All patients with HIV-TB co-infection should receive cotrimoxazole prophylaxis. *Practical Pharmacy* Issue 17 details cotrimoxazole prophylaxis doses, and provides a basic guide on timing of ARV therapy in patients receiving TB treatment.

Medicines interactions

Medicines interactions **MUST** be considered when treating TB and HIV concurrently. In particular, rifampicin increases the production of metabolising liver enzymes, which reduces the blood levels of all Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs).

Rifampicin levels are not significantly affected by ARVs and it can be used in standard doses. Note that rifabutin, if available, has more manageable interactions than rifampicin, and may be used as an alternative (see http://www.cdc.gov/nchstp/tb/tb_hiv_drugs/Rifabutin.htm).

The treatment options for these ARV classes are summarised below:

NNRTIs

- Efavirenz is only slightly reduced and may be used without dose modifications. It is by far the preferred option.
- Nevirapine (NVP) may be considered if necessary, however patients should be monitored closely due to a significant decrease in NVP levels and increased risk of liver toxicity.

PIs

- Rifampicin causes significant decreases in all PIs, even when boosted by Ritonavir – no PI should be used in standard doses.
- Lopinavir/ritonavir and Saquinavir/ritonavir are the only recommended combinations but require dose-modification (see table below) and very careful monitoring of liver enzymes
- Modified PI doses should be reverted back to standard doses one month after completion of Rifampicin therapy.

Table 8: Dose modifications of PIs when using rifampicin

Protease Inhibitors	Recommended change in dose of PI	Comments
Lopinavir/ritonavir (Kaletra®) <i>Note: Additional ritonavir required</i>	Lopinavir/ritonavir (Kaletra®) 400/100mg (3 soft-gel capsules or 2 heat-stable tablets) + ritonavir 300 mg twice-daily	Both combinations have limited clinical experience. Increased liver toxicity is likely - monitor very carefully
Saquinavir and ritonavir	saquinavir 400 mg + ritonavir 400 mg twice-daily	

Adapted from CDC guidelines: http://www.cdc.gov/nchstp/tb/tb_hiv_drugs/Table1.htm

Tuberculosis in children

TB remains one of the major diseases afflicting children throughout the world, with approximately 1 million new cases and 400,000 deaths per year. Many of these cases go undiagnosed and untreated. Improvements in diagnostics and treatments are urgently needed.

The source of infection of most children is an infectious adult in their close environment, which highlights the need for holistic national TB treatment and prevention programs.

There are a few key differences regarding TB between adults and children:

- Identification and diagnosis is more difficult in children;
- In children, extra-pulmonary TB (including disseminated TB) is more common than pulmonary TB;
- Children are usually not as infectious;
- Some TB medicines have limited experience in children (particularly second line medicines).

Children who are most at risk are those who:

- have had household contact with a newly diagnosed smear-positive case,
- are aged less than five years,
- are living with HIV,
- are severely malnourished.

Treatment

The support of a child's family is vital to ensure a good outcome from treatment, and they should be provided with education and support. FDC medicines should be used whenever possible to improve simplicity and adherence, along with regular checks that doses are administered correctly.

The treatment regimens and dosages in mg/kg are generally the same for children as for adults. (See table 2, page 3) Many guidelines have omitted ethambutol due to lack of experience in

continued on page 9...

QUICK TIP!
The two key indicators which should alert you to TB in children are

- history of close contact with TB
- symptoms suggestive of TB (chronic cough, fever, and weight loss or failure to thrive)



DOTS drugs being administered to an infant at a hospital in Addis Ababa-Ethiopia

children, and a young child's inability to report visual side effects. However, it is now agreed that ethambutol is safe in children at a dose of 20mg/kg (range 15-25mg/kg).

Children usually tolerate TB medicines very well and serious side effects are uncommon. As with adults, thioacetazone should not be given to children living with HIV. Streptomycin should also be used with caution to avoid permanent hearing damage.



Tuberculosis in Pregnancy

Untreated TB is the biggest threat to a pregnant woman and her foetus, and therefore treatment should not be delayed. Fortunately, the standard four first-line medications are all safe for use in pregnancy. Pyrazinamide had previously been omitted from regimens due to unknown effects on the foetus, however it is now considered safe to use. On the other hand, streptomycin and many second-line agents (including fluoroquinolones, thioamides, and the other aminoglycosides) can have harmful effects and must not be used. Treatment of MDR-TB must be undertaken with specialist advice and careful consideration of the risks and benefits. Note also that

pyridoxine supplementation (25mg daily) is recommended to all women taking isoniazid during pregnancy and breastfeeding.

Breastfeeding

A breastfeeding woman who has TB can safely be given a normal course of TB treatment, as it is the surest way to prevent TB transmission to her baby. The levels of TB medicines found in the breast milk are too small to produce toxicity in the newborn. Pyridoxine should also be provided to mothers taking INH.

How healthcare workers can protect themselves

(Reference: WHO TB Infection Control for staff 2007)

Healthcare workers and other staff are at a particularly high risk of infection with TB because of frequent exposure to patients with infectious TB disease. If they are immunosuppressed due to HIV the risk of developing TB disease once infected is much higher.

One of the most effective means to reduce the risk of transmission of tuberculosis in hospital settings is to manage TB patients in the outpatient setting whenever possible.

How to handle suspected TB cases

1. Give face masks or tissues.
2. Instruct on cough hygiene
3. Direct to a separate waiting area.
4. Provide whatever services they are accessing quickly (ahead of the queue).
5. Refer to a TB diagnostic and treatment facility.

Reducing the risk of transmission

There are two main ways to reduce the risk of TB transmission in the outpatient facility:

1. Work practice and administrative control measures – These include:

- Promptly detecting patients who may have infectious TB disease,
- Placing these patients in an area away from other patients,
- Instructing patients on cough hygiene,
- Making sure patients get a diagnostic evaluation, and then treatment if they have TB disease.

2. Environmental control measures

These are the second line of defense for preventing the spread of TB in out-patient HIV care facilities. The main environmental control is natural and mechanical ventilation.

Protecting others

There are several ways that a person living with TB can prevent infecting others. An important step is to take regular treatment to become cured. Another measure to prevent infecting others is to cover to noses and mouths when coughing or sneezing. Finally, infected persons should open windows and doors to allow fresh air into their homes.

The most infectious cases are those with a positive smear by microscopy (smear positive cases). Those in whom micro-organisms cannot be seen directly under the microscope (smear negative cases) are much less infectious. Extra-pulmonary cases are almost never infectious, unless they have pulmonary tuberculosis as well.

REFERENCES

Guidelines

1. WHO Treatment of tuberculosis: guidelines for national programmes (2003) http://www.who.int/tb/publications/cds_tb_2003_313/en/index.html
2. Centers for Disease Control and Prevention. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR 2003;52(No. RR-11) Available: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm>
3. WHO Guidance for national TB programs on the management of TB in children (2006) http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf
4. WHO Guidelines for the programmatic management of drug-resistant tuberculosis (2006) http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf
5. WHO TB/HIV: A Clinical Manual (2004) http://www.who.int/tb/publications/who_htm_tb_2004_329/en/index.html
6. WHO Tuberculosis infection control in the era of expanding HIV care and treatment (2007) http://whqlibdoc.who.int/hq/1999/WHO_TB_99.269_ADD_eng.pdf
7. CDC Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nucleoside Reverse Transcriptase Inhibitors (January 20, 2004): http://www.cdc.gov/nchstp/tb/hiv_drugs/TOC.htm
8. IUATLD Best practice for the care of patients with TB: a guide for low income countries (2007) http://www.iuatld.org/index_en.phtml

Websites

1. WHO TB site <http://www.who.int/tb/en/>
2. CDC TB <http://www.cdc.gov/nchstp/tb>
3. <http://www.findtbresources.org/>
4. Stop TB Partnership www.stoptb.org
5. International Union Against Tuberculosis and Lung Disease http://www.iuatld.org/index_en.phtml
6. Green Light Committee

Factsheets

1. DR-TB Factsheet <http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/mdrib.htm>
2. treatment <http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/250112.htm>
3. <http://www.who.int/mediacentre/factsheets/fs104/en/>

Other

1. Micromedex

***Special Acknowledgement:** Jason Bower, a volunteer pharmacist with HAI Africa during 4 weeks in 2007 researched and drafted the contents of Practical Pharmacy 18