National Tuberculosis Management Guidelines

2009

health

Department:
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PREFACE

Tracking epidemiological trends and the extent to which TB targets have been reached provides an indication of progress in TB control. Two key targets had been set by the World Health Assembly in 1991: to detect 70% and to cure 85% of smear-positive clients by the year 2000. These targets were based on epidemiological modelling which suggested that this would reduce the prevalence of infectious TB cases, the number of infected contacts, and the incidence of infectious cases. It was estimated that in the absence of HIV co-infection, the annual incidence of TB could be reduced by 7-12%. The DOTS strategy was in support of these goals.

The Millennium Development Goals (MDG) set by the United Nations frames TB control within the developmental context of reducing poverty and improving the health of the poor. The Millennium Development Goal 6 - "To combat HIV and AIDS, malaria and other diseases" has a target to "have halted by 2015 and begun to reverse the incidence of malaria and other major diseases". The Stop TB Partnership has endorsed two targets linked to the MDG:

- To detect at least 70% of new sputum smear-positive TB cases and cure at least 85% of these cases
- By 2015, to reduce TB prevalence and death rates by 50% relative to 1990 levels

The new Stop TB Strategy builds on current achievements of the DOTS strategy, but calls for additional strategies to effectively address constraints and challenges in TB control including efforts to strengthen health systems, alleviate poverty and advance human rights. Specific local aspects include ensuring equitable access to services, improving continuity of care and improving the care of those co-infected with TB and HIV.

The National TB Strategic Plan for 2007-2011 aims to intensify TB activities towards the attainment of the MDG TB targets. This plan aims to ensure that everyone has access to good quality TB services whilst also providing an environment that is conducive to health, free of infection. It highlights the need for availability of skilled human resources, sustained adequate funding, partnership building, mobilising communities and fighting poverty to accelerate economic and social growth is critical for the success of this plan. The targets set in plan for 2011 are:

Case detection rate	70%
Cure Rate	85%
Treatment Success rate	>85%

The basis for this being that it is with sustained high case detection and cure rates over time that an impact on the prevalence of TB can be made.

These guidelines therefore aim to provide guidance to primary health care personnel and managers in addressing the challenges of TB control and successfully managing all clients presenting with TB, including those co-infected with HIV as well as early detection of drug resistant TB.

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List of abbreviations

AFB	Acid-Alcohol Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BCG	Bacille Calmette - Guerin
CBO	Community Based Organisation
CHW	Community Health Worker
DOH	Department of Health
DOT	Directly-Observed Treatment
DOTS	Directly-Observed Treatment, Short course
E	Ethambutol
ETR	Electronic TB Register
H	Isoniazid
HIV	Human Immunodeficiency Virus
HR	Isoniazid/ Rifampicin
MDG	Millennium Development Goals
MDR-TB	Multidrug-Resistant Tuberculosis
NGO	Non-Governmental Organisation
TB PROGRAMME	National Tuberculosis Control Programme
PHC	Primary Health Care
PN	Professional Nurse
PMTCT	Prevention of Mother-to-Child HIV Transmission
QA	Quality Assurance
R	Rifampicin
RSA	Republic of South Africa
S	Streptomycin
SHR	Streptomycin/ Isoniazid/ Rifampicin
SHRZE	Streptomycin/ Isoniazid/ Rifampicin/ Pyrazinamide/ Ethambutol
STI	Sexually Transmitted Infections
TB	Tuberculosis
VCT	Voluntary Counselling and Testing
WHO	World Health Organisation
XDR-TB	Extensively drug-resistant TB
Z	Pyrazinamide

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1 Introduction

1.1 Global epidemiology and burden of disease

TB is still a major cause of death and disease worldwide with estimates[1] of 9.2 million new TB cases in 2006 and 1.7 million deaths, including 200,000 in clients co-infected with HIV. Even though the global epidemic is in decline with decreasing global TB prevalence and death rates, the total number of new TB cases is still rising due to population growth.

Africa is the only region to show huge increases in TB, from an estimated 162 per 100,000 population in 1990 to 363 per 100,000 population in 2006. Factors contributing to the increasing TB burden include:

- Poverty and rapid urbanisation.
- The impact of the HIV-pandemic.
- Poor health infrastructure.
- Poor programme management with inadequate case detection, diagnosis and cure.

Amongst the 202 countries that report to the World Health Organisation (WHO), the 22 high burden countries accounted for 80% of TB cases. The average estimated incidence[1] of TB in the high burden countries in 2006 was 177 cases per 100,000 population compared to a global figure of 139 cases per 100,000 population. The TB incidence in Africa was higher, at 363 cases per 100,000 population and in South Africa it was a massive 940 per 100,000 population.

1.2 TB control in South Africa

According to the WHO Global Tuberculosis Report 2008[1], South Africa had the highest TB incidence in the world, at over 5 times the average incidence rate found in the 22 high-burden countries. It had the 4th highest estimated total burden of TB for 2006, behind only India, China and Indonesia, countries with much larger populations. In 2006, South Africa with only 0.7% of the world's population had an estimated 28% of HIV positive adult TB cases reported globally. On a more positive note, revised estimates suggest that the 70% case detection rate target was reached in 2006.

National TB Control Programme data shows that over the last five years TB case notification has increased by a massive 81%, from 188,695 cases in 2001 to 341,165 in 2006. In 2006, Kwa-Zulu Natal had the highest total TB caseload accounting for 31% of all TB cases nationally.

Table 1.1: TB Case Finding 2006

	All TB Cases	PTB Cases	New Smear Positive PTB Cases	Retreatment Smear Positive PTB Cases	Smear Negative PTB Cases	No Smear PTB Cases	Children 0-7 years	EPTB Cases	*Incidence All TB cases per 100,000*	*Incidence PTB cases per 100,000*
Eastern Cape	48,512	41,558	19,527	8,473	3,615	9,943	2,805	6,954	*687*	589
Free State	23,374	19,058	9,553	2,840	2,479	4,186	2,295	4,316	*789*	643
Gauteng	46,093	34,290	20,609	4,188	2,915	6,578	4,155	11,803	*501*	372
KZN	104,705	88,271	32,855	9,527	20,547	25,342	8,593	16,434	*1076*	907
Limpopo	17,301	14,118	7,574	1,323	1,305	3,916	1,069	3,183	*305*	249
Mpumalanga	15,035	13,496	7,216	1,081	859	4,340	7,55	1,539	*463*	416
North West	28,421	24,519	12,539	2,954	1,764	7,262	2,156	3,902	*738*	637
Northern Cape	8,631	7,951	3,583	1,482	901	1,986	1,018	680	*950*	875
Western Cape	49,093	43,296	17,644	8,563	8,366	8,723	6,955	5,797	*1,033*	911
South Africa	**341,165**	**286,557**	**131,100**	**40,431**	**42,751**	**72,276**	**29,801**	54,608	***720***	605

Source: TB Management and Control, National Department of Health

[1] WHO figures are epidemiological estimates based on case notification and other surveillance data. TB Management and Control data is based on case notification.

PTB cases accounted for 84% of the total TB caseload and EPTB for 16%. Considering the high levels of TB and HIV co-infection, this ratio is low and may reflect missed TB diagnosis, particularly in late stage HIV-infection. Amongst PTB cases, 60% are smear-positive, 15% smear-negative and 25% had no smear taken, 10% of these being accounted for as children under 8-years of age. The implication is that 15% of PTB cases (children under 8 excluded) had the diagnosis made without laboratory confirmation (no smear or culture). This probably reflects a combination of very ill clients, poor diagnostic practices and poor availability of laboratory services in some areas. It should be emphasised that bacteriological confirmation of disease is the standard required for the diagnosis of pulmonary TB in adults.

Treatment outcomes have improved with new smear positive cure rates of 58% and treatment success rates of 71% in 2005 compared to rates of 51% and 66% respectively in 2004. The poor documentation of cure (high completion rates), defaulter rates over 10% and large numbers of cases not evaluated are indicative of poor systems at health facilities, and contribute to the failure to reach programme targets.

Table 1.2: New Smear Positive Treatment Outcomes 2005

	Registered	Cured	Completed	Treatment Success	Died	Failed	Default	Transfer	Not evaluated
Eastern Cape	20,551	54.7%	20.0%	74.7%	7.0%	1.2%	9.0%	3.6%	4.5%
Free State	9,731	67.5%	9.3%	76.9%	10.1%	2.0%	5.9%	4.8%	0.3%
Gauteng	23,921	66.7%	5.0%	71.7%	9.6%	1.5%	6.9%	8.1%	2.2%
KZN	36,511	45.2%	19.1%	64.2%	6.1%	1.2%	14.7%	5.8%	7.9%
Mpumalanga	7,642	51.8%	13.9%	65.7%	9.0%	1.0%	10.8%	4.3%	9.2%
North West	13,771	57.6%	12.3%	70.0%	7.3%	2.9%	9.5%	6.5%	3.8%
Northern Cape	3,888	50.1%	21.3%	71.4%	6.8%	3.2%	13.1%	2.8%	2.6%
Limpopo	6,807	60.8%	9.2%	70.0%	9.5%	2.0%	7.4%	8.5%	2.5%
Western Cape	18,845	71.9%	7.8%	79.7%	3.7%	1.9%	11.1%	3.2%	0.4%
South Africa	**141,667**	**57.7%**	**13.3%**	**71.1%**	**7.2%**	**1.7%**	**10.4%**	**5.5%**	**4.2%**

Source: TB Management and Control, National Department of Health

1.3 Challenges to TB control

We face several challenges to improving TB control:

- Inadequate financial and human resources for the TB Control Programme.
- Poor community participation in TB control, characterised by low levels of awareness of TB, poor health seeking behaviour amongst symptomatic people resulting in late presentation to health facilities and inadequate community support for those on TB treatment.
- Inadequate health systems that result in low case detection, poor continuity of care and high levels of treatment interruption (the latter compounded by high levels of client mobility and poor referral systems).
- Poorly trained or supervised health care personnel, low levels of accountability of health care personnel, non-adherence to protocols, poor record keeping and poor relationships with clients.
- Low levels of integration of TB and HIV services at patient management level.
- The numbers of MDR-TB and XDR TB cases have been increasing. The management of drug resistant TB at facility level is sub-optimal, with inadequate early pick-up of resistance and poor follow-up of MDR-TB clients discharged from in-patient facilities.
- Programme management, particularly at the facility level, is often inadequate. Poor quality data is collected and data is not analysed or used to improve current practices.

2 The National Tuberculosis Programme

2.1 Mission, strategic objectives and targets for TB control

The mission of the Department of Health is to prevent TB and to ensure that those who do contract TB have easy access to effective, efficient and high quality diagnosis, treatment and care that reduces suffering.

The TB control targets for 2011 are:
Case detection rate: 70%
Cure rate: 85%
Treatment success rate: >85%

For the period 2007-2011, the strategic objectives are:

1 **To strengthen the implementation of the DOTS strategy which has 5 components namely;**
   a) **Political commitment with increased and sustained financing:** The commitment is to increase human and financial resources and make TB control a nation-wide priority, integral to the national health system. Emphasis is placed on adequate planning and promoting accountability for programme results at all levels in the health system.
   b) **Case detection through quality-assured bacteriology**: Bacteriology remains the recommended method of TB case detection using sputum smear microscopy, culture and drug susceptibility testing (DST). This requires an expanded laboratory network with culture and DST services introduced in a phased manner to assist in the diagnosis of sputum smear-negative TB and diagnosis and monitoring the response to MDR-TB treatment. Special attention is necessary for case detection amongst HIV infected people and other high-risk groups, such as household and other close contacts of infectious cases and people in institutions. A well functioning microscopy service needs to meet the programme goal of a 48-hour turn-around time for smear results.
   c) **Standardized treatment, with supervision and patient support**: Standardised treatment should be provided to all categories of adult and paediatric TB clients as per treatment protocol, using the most effective drugs in fixed-dose combination tablets to facilitate adherence and reduce the risk of drug resistance. Adequate supervision, including directly observed therapy, and support mechanisms need to be established to ensure good adherence to treatment. Amongst TB clients, barriers to treatment adherence including social support needs, substance abuse and knowledge about TB need to be addressed. The training, supervision and attitude of health care personnel need to be improved.
   d) **An effective drug supply and management system** with reliable drug procurement and distribution systems that ensure an uninterrupted supply need to be maintained.
   e) **A monitoring and evaluation system, and impact measurement**: Standardised recording of individual patient data and treatment outcomes has been established, with an electronic system to assist systematic data collation and analysis. This is used to compile quarterly cohort reports that are submitted to district, provincial and national levels to help monitor and evaluate progress in achieving programme goals. Key areas for improvement include data analysis at facility level and the use of data to drive programme improvement, supported through closer facility supervision. Additional information on TB AND HIV co-infected clients is being standardised to monitor the provision of HIV care.

2 **To address TB, HIV, MDR-TB and XDR-TB**
   a) **Implement collaborative TB and HIV activities**: Accelerated HIV prevention efforts will, in the long-term, play a role in reducing TB. Fundamental shifts are required within TB services in increasing HIV testing among all TB clients and TB suspects. Integrated management of co-infected TB clients such as provision of cotrimoxazole preventive therapy, management of other opportunistic infections, provision of antiretroviral therapy and general HIV support services must be included in TB services. Equally, routine TB screening should to ensure early TB diagnosis and treatment of TB; provision of isoniazid preventive therapy to HIV positive patient in whom TB has been excluded must be included in HIV services.
   b) **Prevent and control MDR and XDR-TB**: The increase in multidrug-resistant and extensively drug resistant TB presents a threat to TB control. The approach first and foremost requires effective implementation of TB programme policies aimed at curing cases of tuberculosis at the first attempt. Prevention is the key to effective MDR-TB control. Other measures to improve the management of

existing MDR-TB cases include early detection of MDR-TB and treatment thereof, contact screening and testing and good case management.

3 To contribute to health system strengthening

a) Improving the health system includes strengthening policies, human resources, finance, and service delivery and information systems.
b) Rapid progress in TB control will not occur unless TB control is integrated into the PHC-system, therefore PHC must ensure early TB case detection and case holding.
c) Improving health management and service delivery requires the provision of quality, client-centred services that ensure good continuity of care. This requires motivated, well-trained staff and management being held accountable for the services they deliver.
d) Innovations in service delivery models, such as the syndromic approach to respiratory disease described in Practical Approach to Lung Health South Africa (PALSA – PLUS), can help integrate TB and HIV services within primary health care and improve case detection.
e) Other service delivery innovations adapted from HIV and other programmes should be explored to find ways in which to improve TB treatment outcomes and use limited resources, including human resources, more effectively.

4 To work collaboratively with all care providers

Collaboration between public, private sectors is essential to ensure accessible and quality-assured TB diagnosis and treatment, including the development of community-based support mechanisms under the guidance of provincial health authorities, All service providers, including those within the private sector and other government departments need to adhere to the standards established for TB diagnosis and treatment.

5 To empower people with TB as well as communities

a) Advocacy, communication and social mobilization – Advocacy is important in influencing policy and ensuring that commitment to financial and human resources are sustained. High visibility social mobilisation provides an opportunity to engage with communities and to communicate key messages about TB to help improve knowledge levels, modify health seeking behaviour, improve access and utilisation of health services and encourage communities to become active in contributing towards TB control efforts.
b) Community participation in TB care can be formalised through identifying specific roles and responsibilities for community members and community based organisations in supporting TB diagnosis and treatment. It is essential that expectations, such as the payment of incentives for assisting in providing community-based DOT, be clarified at the outset. Community involvement in TB care is not a matter of devolving the responsibility for TB care; it requires training, supervision, good communication and ensuring lines of accountability between heath services and community organisations.
c) Respecting the rights of TB clients to free and equitable services, empowering clients with knowledge about their disease, respecting their dignity and fostering partnerships in which these rights are balanced with responsibilities to adhere to treatment, all contribute towards TB control.

6 To coordinate and implement TB research

a) Programme-based operational research
b) Research to develop new diagnostics, drugs and vaccines

7 To strengthen infection control

a) Strengthen infection control in all health facilities
b) Increase awareness on community infection control

2.2 The structure of The National TB Programme

The National TB Programme consists of four levels within the general health services:

- The National level functions through the National Department of Health to coordinate facilitate and evaluate tuberculosis services countrywide.
- The Provincial level is responsible for implementation and budgeting.
- The District level is the key level for the management of primary health care and is the most peripheral unit of the health services administration.
- The Facility level functions within a district to provide primary health care services. This level consists of rural hospitals, health centres, dispensaries and clinics.

The structure varies to some extent; for example, in some provinces a regional level has been established between the provincial and district levels. In others, districts are further divided into sub-districts.

2.2.1 Core activities at the national level

The main function of the national unit is to provide support and technical guidance to the provinces on the following key activities:

- Countrywide implementation of the DOTS strategy
- Collaborate with provincial management teams in planning TB activities so that the national work plan is an aggregation of the provincial work plans
- Training of provincial and district TB coordinators on all elements of the DOTS strategy
- Establish and update the national technical policies and guidelines on TB case detection and treatment for health facilities and laboratories.
- Conduct quarterly supervisory visits and advise on planning, monitoring and evaluation of TB control activities.
- Develop and update training materials on case management, programme monitoring and supervision for TB and Drug Resistant TB
- Collaborate with the pharmaceutical and laboratory services to ensure programme needs are met.
- Ensuring an efficient recording and reporting system for monitoring TB and DR TB clients and programme performance.
- Strengthening collaboration between TB, HIV programmes to ensure better management of co-infected clients.
- Enhance and support communication, coordination and collaboration between all stakeholders in tuberculosis control.
- Support implementation of the Advocacy and social mobilization plan.
- Promote, coordinate and support operational and epidemiological research activities

2.2.2 Core activities at the provincial level

The key functions at provincial level are to:

- Monitor the implementation of TB control policies and strategies.
- Collaborate with district management teams in planning TB activities so that the provincial work plan is the consolidation of district work plans.
- Plan training and conduct supervisory/support visits including laboratory and pharmacy personnel who perform activities related to TB control.
- Ensure that a district's needs for TB stationery and laboratory materials are supplied as required.
- Facilitate procurement of TB dugs, advise on rational distribution and ensure accountable drug management with uninterrupted supply of drugs throughout the province.
- Supervise record keeping of the TB case registers and laboratory registers.
- Review quarterly reports provided by the districts for accuracy and completeness and provide feedback to the district officers.
- Collaborate with staff working in the HIV and AIDS programme to ensure better management of clients.
- Collaborate with other agencies and NGO's as well as private doctors, who provide care for TB clients.
- Coordinate the advocacy and social mobilization activities.
- Monitor and evaluate electronic TB register data from districts and laboratory data.
- Submit consolidated provincial quarterly reports on case finding and treatment outcomes to the national level.

2.2.3 Core activities at the district level

The district and sub-district is the implementation level and the key functions at this level are to:

- Implement TB programme policies and procedures.
- Plan and budget for TB activities
- Coordinate training activities at district level
- Develop an efficient referral system of clients to ensure continuity of care for TB clients
- Coordinate and establish community based DOT programmes
- Ensure sufficient drug supply at all facilities
- Coordinate laboratory services and communication with laboratories

- Conduct support visits to health facilities including NGO's, laboratories and pharmacies
- Collate and validate facility data and submit quarterly reports on case finding, case holding and treatment outcomes
- Ensure adequate supplies of diagnostics and drugs at all times
- Ensure functional integration of TB and HIV activities at facility level
- Plan and conduct social mobilisation and awareness campaigns, health promotion and educational campaigns.
- Adapt, develop and distribute relevant IEC (information, education and communication) material in local language.
- Collaborate with all stakeholders in the district.
- Submit quarterly reports on case finding and treatment outcomes to the provincial level.

2.2.4 Core activities at the PHC facility level

PHC facilities are the responsible for the provision of care:

- Early case-detection and treatment
- Patient education and counseling
- HIV testing, treatment for opportunistic infections, psychosocial support for co-infected clients
- Establish and implement community based DOT programmes
- Maintain updated patient records and TB registers
- Prepare quarterly reports on case detection, sputum conversion and treatment outcome and submit to the sub-district and district
- To maintain an adequate supply of drugs, laboratory supplies and TB clinic/ patient card and registers
- Provide appropriate health education materials (IEC materials) and conduct group health education activities.
- Ensure tracing, screening of all contacts of clients with infectious TB.
- Ensure continuity of care for all TB clients until treatment completion
- Establish proper referral systems for tertiary care

2.2.5 Core activities at the community level

- Verify address of all new clients and educate them and their families on TB and treatment.
- Identify any social issues in household that may affect treatment compliance and report to health care provider
- Ensure clients take their treatment daily throughout the treatment period.
- Retrieval of treatment interrupters and initial defaulters
- Contact tracing.
- Establish psych-social support systems for TB clients and their families
- Establish poverty alleviation projects for TB clients and their families

Transmission and Pathogenesis of TB

3.1 Transmission of tuberculosis

There are five closely related mycobacteria responsible for tuberculosis: M. tuberculosis, M. bovis, M. africanum, M. microti and M. canetti. Mycobacterium tuberculosis, by far the commonest, is transmitted between humans through the airborne route. There are no known animal reservoirs of M. tuberculosis. Mycobacterium bovis may penetrate the gastrointestinal mucosa or invade the lymphatic tissue of the oropharynx when ingested in milk from diseased cows. Human infection with M bovis has decreased significantly in developed countries as a result of the pasteurisation of milk and effective tuberculosis control amongst cattle. Infection with the other organisms is relatively rare.

Tuberculosis is usually spread from person-to-person through the air by droplet nuclei that are produced when a person with pulmonary or laryngeal tuberculosis coughs, sneezes or sings. Droplet nuclei may also be produced by aerosol-producing investigations such as sputum induction, bronchoscopy and through manipulation of lesions or processing of tissue or secretions in the laboratory.

People with active tuberculosis generate droplets of different sizes. The larger droplets containing higher numbers of bacteria do not serve as effective vehicles for TB-transmission as they do not remain airborne for long periods. If they are inhaled, they do not reach the alveoli because they deposit in the upper airways where they are trapped in the mucous blanket, carried by mucociliary action to the oro-pharynx and swallowed or expectorated.

Micro-droplets, which are small particles 1 to 5 µm in diameter containing 1-5 bacilli, are highly infectious. They are so small that air currents normally present in any indoor space can keep them airborne for long periods of time. These droplets are small enough to reach the alveolar spaces within the lungs, where the organisms replicate.

Three factors determine the likelihood of transmission of M. tuberculosis:
- The number of organisms expelled into the air
- The concentration of organisms in the air, determined by the volume of the space and its ventilation
- The length of time an exposed person breathes the contaminated air

One cough can produce 3,000 droplet nuclei and a sneeze up to a million droplets. Between 10-200 droplets can cause infection. The most infectious cases are those with smear positive pulmonary TB, particularly with lung cavities. Smear negative pulmonary TB cases are much less infectious. Extra-pulmonary cases are almost never infectious, unless they have pulmonary tuberculosis as well. Individuals with latent tuberculosis infection are not infectious, as they do not have replicating bacteria and cannot transmit the organism.

Transmission generally occurs indoors, in dark, damp spaces where droplet nuclei can stay airborne for a long time. Direct sunlight quickly kills tubercle bacilli, but they can survive in the dark for several hours. Close contact and prolonged exposure increases the risk of transmission.

Once infected, the progression to active disease is dependent on the immune status of the individual. In those with normal immunity, 90% will not progress and only 10% will develop active disease (half of these now and half later on in life). The risk is highest in the first two years after infection, when half the cases will occur. Those most at risk include children <5 years of age and the elderly.

People with suppressed immunity are more likely to develop active TB than those with normal immunity; 50-60% of HIV positive people infected with TB will go on to develop active disease. The annual risk of TB in an HIV positive person is 10% compared to a lifetime risk of 10% in a healthy individual. Other immunosuppressive conditions with such as silicosis, diabetes mellitus, and where corticosteroids and other immunosuppressive drugs are used, also increase the risk of progression to active TB.

BCG immunisation gives variable protection against the progression of TB from infection to disease. The main benefit of BCG is the protection against the development of the serious forms of TB in children, such as TB meningitis and miliary TB.

3.2 Pathogenesis of tuberculosis

After inhalation, the droplet nuclei are carried down the bronchial tree and deposit in a respiratory bronchiole or alveolus where they are ingested by alveolar macrophages that produce a non-specific response to the bacillus. Whether or not an inhaled tubercle bacillus establishes an infection in the lung depends both on the bacterial virulence and the inherent microbicidal ability of the alveolar macrophage that ingests it. If the bacillus is able to survive initial defences, it can multiply within the alveolar macrophage.

The tubercle bacillus grows slowly, dividing approximately every 25 to 32 hours within the macrophage. The mycobacterium has no known endotoxins or exotoxins, so there is no immediate host response to the infection. The organisms grow for 2 - 12 weeks and reach 10^3 to 10^4 in number, which is sufficient to elicit a cellular immune response that can be detected by a reaction to the tuberculin skin test. The destruction of macrophages and release of tubercle bacilli products and chemokines stimulates an immune response.

Before the development of cellular immunity, tubercle bacilli spread via the lymphatics to the hilar lymph nodes and from there through the bloodstream to more distant sites. Certain organs and tissues are notably resistant to multiplication of these bacilli. The bone marrow, liver and spleen are almost always seeded with mycobacteria, but uncontrolled multiplication of the bacteria in these sites is unusual. Organisms deposited in the upper lung zones, kidneys, bones and brain find environments that favour their growth. Numerous bacterial divisions may occur before specific cellular immunity develops, limiting multiplication.

3.3 Primary infection

Primary infection occurs on first exposure to tubercle bacilli. This usually occurs in childhood so primary TB is often thought of as childhood TB. However, it can occur at any age in a previously unexposed individual. Inhaled droplet nuclei containing bacilli lodge in the terminal alveoli of the lungs, usually just below the pleura in the lower part of the upper lobe or upper part of the lower lobe. Bacilli are phagocytosed by the alveolar macrophages; mycobacterial products inhibit the bactericidal activities of the alveolar macrophages, allowing the bacilli to replicate within the macrophages. Other macrophages and monocytes are attracted to the area and produce an immune response. This inflammatory area is known as the Ghon focus.

Bacilli and antigens drain from the Ghon focus via the lymphatics to the hilar lymph nodes and together these form the primary complex. The inflammatory response produces the typical picture of caseous necrosis. Within the lymph node, the T-lymphocytes mount a specific immune response and activated macrophages inhibit the growth of the phagocytosed bacilli. This primary focus contains 1,000–10,000 bacilli that gradually lose their viability and multiply more and more slowly. The inflammatory area in the primary focus is replaced by fibrous scar tissue, sometimes with calcification, in which the macrophages containing bacilli are isolated and die. Some dormant bacilli in the primary focus can survive for months or years: these are known as “latent bacilli”.

Primary infection is usually asymptomatic and a positive tuberculin skin test 4-6 weeks after infection is the only evidence of infection. In a few cases, the immune response is not strong enough to prevent multiplication of bacilli and bacilli may spread from the lymphatics into the bloodstream and throughout the body causing disease within a few months. Primary progressive TB in the lungs leads to enlargement of the primary focus with spread throughout the airways or lymphatics. Multiple areas of caseation and cavitation are found, producing a clinical picture similar to post-primary TB.

Table 3.1: Possible Outcomes of Primary Infection

No clinical disease Positive tuberculin skin test (Usual "outcome" in 90% of cases)	**Hypersensitivity reactions** e.g. erythema nodosum phlyctenular cojunctivitis dactylitis
Pulmonary and pleural complications e.g. tuberculous pneumonia lobar collapse (bronchial compression) pleural effusion	**Disseminated disease** e.g. lymphadenopathy (usually cervical) meningitis pericarditis miliary disease

3.4 Post-primary TB / Secondary TB

Post-primary TB is the pattern of disease that occurs in a previously sensitised host. It occurs after a latent period of months or years after primary infection. It may occur either by reactivation of latent bacilli or by re-infection.

Reactivation occurs when dormant bacilli, persisting in tissues for months or years after primary infection, start to multiply. This may be in response to a trigger such as weakening of the immune system by HIV infection. Re-infection occurs when a person who previously had a primary infection is exposed to an infectious contact.

In a small number of cases it occurs as a progression of primary infection. Following primary infection, rapid progression to intra-thoracic disease is more common in children than in adults. Chest X-rays may show intra-thoracic lymphadenopathy and lung infiltrates.

Post-primary TB usually affects the lungs but can involve any part of the body. The characteristic features of post-primary PTB include upper lobe involvement with cavitation and extensive lung destruction. Sputum smears are usually positive and there is usually no intrathoracic lymphadenopathy.

Pulmonary tuberculosis is the infectious and most common form of the disease, occurring in over 80% of cases. Tuberculosis may, however, affect any part of the body. Extra-pulmonary tuberculosis is a result of the spread of mycobacteria to other organs, most commonly pleura, lymph nodes, spine, joints, genito-urinary tract, nervous system or abdomen.

4 Diagnosis of TB

4.1 Symptoms and signs of TB

Symptoms of pulmonary TB include:
- Persistent cough for more than 2 weeks
- Sputum production (which may occasionally be blood-stained)
- Fever for more than 2 weeks
- Drenching night sweats
- Loss of appetite
- Unexplained weight loss (more than 5 kg in a month)
- A general feeling of illness (malaise) and tiredness
- Shortness of breath, chest pain

A productive cough, often accompanied by systemic symptoms, is the commonest presentation of pulmonary tuberculosis. Every client who presents to a health facility with a cough for more than 2 weeks should be regarded as a "tuberculosis suspect" and investigated appropriately. Not all those with TB have a cough; a high index of suspicion is required, particularly with HIV, and symptoms such as weight loss need to be investigated. A history of contact with a person with PTB increases the l kelihood of a TB diagnosis.

TB case finding depends on clients presenting to the health facility with these symptoms and having the appropriate TB tests done (known as passive case finding). Intensified TB case finding is essential for HIV positive clients in view of their susceptibility to TB. HIV positive clients should be screened for TB at each clinical visits: clients should be asked specifically if they have each of the TB symptoms listed and weight should be monitored; if signs or symptoms are present, the appropriate TB tests should be done.

Symptoms of extra-pulmonary tuberculosis depend on the organ involved. Chest pain from tuberculosis pleurisy, enlarged lymph nodes in the neck and armpit and sharp angular deformity of the spine are frequent signs of extra-pulmonary tuberculosis. .

4.2 How is the diagnosis of tuberculosis confirmed?

- All individuals suspected of having tuberculosis should have at least two sputum specimens examined for bacteriological confirmation of disease.
- The client's HIV status influences the diagnostic algorithm. Hence, the standard of care is to provide HIV counselling to all TB suspects. Clients should be given enough information to help make an informed choice about the test. All clients should be strongly advised to have an HIV test and consent sought for testing.

4.2.1 Smear and culture evaluation of a TB suspect pre-treatment

- **No previous TB or less than 4 weeks previous TB treatment:** Send 2 specimens on consecutive days for TB smear microscopy. The first specimen is a spot specimen and the second an early morning specimen.
  If these are negative:
  - And the client is HIV positive: send a 3rd specimen for smear and culture and commence 5 days of Amoxicillin.
  - And the client is HIV-negative or HIV status is unknown: commence 5 days of Amoxicillin. Send a 3rd specimen for smear and culture if there is no response to antibiotics.

- **Previous TB treated for 4 or more weeks or a high-risk TB suspect (MDR contact, health care personnel and prisoners):** Send a spot specimen for smear microscopy and an early morning specimen for smear microscopy, culture and susceptibility.
  If these are negative:
  - And the client is HIV positive: send a 3rd specimen for smear and commence 5 days of Amoxicillin.
  - And the client is HIV-negative or HIV status is unknown: commence 5 days of Amoxicillin. Send a 3rd specimen for smear if there is no response to antibiotics.

4.2.2 Sputum smears

Microscopic examination of stained sputum is the most rapid method for confirming a TB diagnosis. Smears may be prepared directly from clinical specimens or from concentrated preparations. Two methods can be used to detect acid-fast bacilli: Ziel-Neelsen (carbol fuchsin) staining or fluorescent auramine staining. The acid fast staining procedure depends on the ability of mycobacteria to retain these dyes when treated with acid and alcohol solutions.

Two specimens are to be taken from the TB suspect for sputum smears as follows:

- **First specimen:** At the first visit a "spot" (i.e. on the spot or immediate) specimen is collected. This specimen should be collected at the health facility under supervision of a health worker.
- **Second specimen:** The client is given a sputum container for the collection of an early morning specimen at home, usually the following day. If the first specimen is collected on a Friday, the second specimen should be collected on the following Monday morning. The jar should be brought back to the clinic on the day that the specimen is collected, as soon after collection as possible.

A spot specimen followed by an early morning specimen gives the best yield in the diagnosis of TB. However, there are many situations where clients are unable to return to facilities with an early morning specimen. In these situations, it is recommended that two spot specimens be collected at least 1-hour apart. It is important that convenience does not compromise the efficacy of the diagnostic algorithm and that two spot specimens is the exception rather than the rule.

Finding acid-fast bacilli (AFB) is highly specific in confirming the diagnosis of smear positive tuberculosis. Sending sputa for smear microscopy is important because it correctly and efficiently identifies cases that are most infectious, most likely to die from TB and thus those that have the highest priority for care.

4.2.2.1 Sputum labelling

Correct labelling of sputum samples is essential as it will save time and prevent errors. Label the container first very clearly with:

- Name of clinic / hospital.
- Name of client
- Clinic/ hospital number.
- Date of specimen collection (check that the date is correct for early morning specimens brought in by the client)
- Indicate whether the specimen is pre-treatment (suspect), follow-up (2 or 3 months) or end-of-treatment specimen (5 or 7 months).
- Attach the bar code from the TB laboratory request form to the specimen jar.

The container should always be labelled and not the lid as lids may get mixed up.

4.2.2.2 Sputum collection

It is important that sputum collection occurs in a well-ventilated area or outside, but in private and without others watching. Supervise the collection, but do not stand in front of the client. Carefully explain the steps to the client:

- Ask the client to rinse out their mouth with water.
- Advise the client to be very careful and direct the sputum into the container so as not to contaminate the outside of the container.
- Give the client the container, without the lid.
- Demonstrate a deep cough from the bottom of the chest, beginning with deep breathing.
- Be ready to replace the lid on the container immediately.
- Once the specimen is in the container, securely close the lid by pressing down on the centre of the lid until a click is heard.
- Wash your hands after handling the sputum specimen.

The person must be encouraged to produce a specimen even if this resembles saliva.

4.2.2.3 Completion of the laboratory form

Complete the standard National Health Laboratory TB Investigation Form.

- Name of clinic / hospital.
- Name of client
- Clinic / hospital number.
- Date and time of specimen collection (check that the date is correct for early morning specimens brought in by the client)
- Indicate whether it is a new or re-treatment client
- Indicate whether the specimen is pre-treatment (suspect), follow-up (2 or 3 months) or end-of-treatment specimen (5 or 7 months).
- Write clear instructions regarding what investigations are required.
- Note the appearance of the sputum (e.g. mucoid, lumpy, green, offensive, etc).

4.2.2.4 Sputum storage

- Place the sputum bottle in the plastic bag provided by NHLS to prevent contamination. The laboratory form goes into a separate sleeve in this bag.
- Send the specimen to the laboratory as soon as possible
- Store sputum specimen in a fridge (not a freezer) if transport is not immediately available.

4.2.2.5 Transportation of sputum specimens

- Specimens should be transported to the laboratory in a cooler bag.
- High temperatures during transit will kill bacilli.
- Specimens should be kept out of direct sunlight.
- Explain to the driver the need for specimens to go directly to the laboratory.

4.2.2.6 Completion of the Case Identification and Follow-Up Register

- Record the clients' details and the date on which the specimen was collected in the Case Identification and Follow-Up Register.
- The register should be updated on a daily basis (with clients results and treatment commencement dates)

Each workday, the person responsible should check the register to see which results are outstanding and contact the laboratory to follow-up on these results. Close cooperation with the laboratory will help ensure that smear-positive clients are started on treatment as soon as possible.

4.2.2.7 Sputum turnaround time

The sputum turnaround time (TAT) is the duration of time from taking a smear specimen from the client (or receiving it at the facility if it is an early morning sputum) to receiving the result at the health facility, including weekends and holidays. The sputum TAT is monitored as one of the factors that can contribute to delays in the initiation of treatment

The target of the TB programme is to have 80% of smear results back at the health facility within 48 hours. The 80% target makes allowances for specimens collected on Fridays.

4.2.2.8 Sputum results

The results of laboratory reports are subject to various sources of error including: poor quality of specimens, clerical errors, handling errors, process errors and poor quality control. A laboratory result that does not tie up with other clinical information must be interpreted with care.

The number of bacilli (AFB) seen in a smear reflects the client's infectivity. The laboratory records the number of bacilli seen on each smear as follows:

Table 4.1: Smear Reporting		
Number of bacilli seen on a smear		**Results reported**
No AFB	Per 100 oil immersion field	0
1-9 AFB	Per 100 oil immersion field	Scanty
10-99 AFB	Per 100 oil immersion field	1+
1-10 AFB	Per 1 oil immersion field (min 50 fields)	2++
>10 AFB	Per 1 oil immersion field (min 20 fields)	3+++

4.2.3 Sputum culture and drug susceptibility testing

Culture is more sensitive than smear microscopy, detecting a higher proportion of cases among clients with symptoms. The specificity is also higher as each live bacillus forms a colony on culture. However, it is an expensive and slow diagnostic technique, not accessible to some clients and takes at least 4 weeks to provide a definitive result.

Culture is however an important diagnostic tool in clients with paucibacillary tuberculosis, such as HIV positive clients with smear-negative pulmonary tuberculosis.

Indications for the use of sputum culture include:

- To diagnose paucibacillary disease in TB suspects who have two negative smears, including those who may be HIV positive.
- For drug susceptibility testing in TB suspects with a history of previous TB treatment (interruption, failure, relapse)
- For drug susceptibility testing in high-risk TB suspects such as MDR and XDR-TB contacts, health care personnel and prisoners.

In other cases where drug susceptibility testing is necessary, including clients who remain smear-positive at the end of the intensive phase of treatment and who fail to improve clinically or bacteriologically or who are smear-positive at the end of treatment.

4.2.3.1 Culture methods

Traditional culture uses a solid medium such as coagulated egg (e.g. Löwenstein-Jensen) or agar (e.g. Middlebrook 7H10) as a base. Solid media are simple and cost effective to use. Disadvantages include slow bacterial growth (3-4 weeks) and errors due to manual reading of results.

These drawbacks have led to the development of faster, more sensitive liquid medium culture techniques including:

- Semi-automated radiometric systems such as BACTEC 460, which uses radiation technology
- Automated non-radiometric systems, such as MGIT, which uses fluorometric technology is the new standard used.

The liquid medium is most commonly used in conjunction with solid medium as back up. The detection of bacilli occurs within 7 to 14 days in liquid medium.

4.2.3.2 Drug susceptibility testing

Susceptibility tests are used to determine the susceptibility or resistance of a client's bacillary strain to the different anti-tuberculosis drugs. There are two types of susceptibility testing:

- Direct tests are performed directly on a sample that is rich in bacilli with results available in 4-6 weeks.
- Indirect tests are performed on cultures that have to be grown and tested in the exponential phase of growth.

Results are only available 2 to 3 months after sampling if grown in solid media or in 1 month if grown on liquid media.

4.2.4 Chest x-rays

The primary method of TB diagnosis is smear microscopy and culture. Whilst chest x-rays are quick and convenient, reliance on them as the only diagnostic test results both in over-diagnosis of TB and missed diagnosis of TB. Many diseases mimic TB on chest x-rays and this may lead to an incorrect diagnosis. Chest x-rays may also show lung fibrosis or destruction due to old TB, leading to over diagnosing pulmonary TB.

Chest x-rays are necessary in TB suspects who cannot produce sputum or who have negative smears, and where extrapulmonary TB (such as pleural effusions and pericardial TB) is suspected. They must be interpreted in the light of the client's history and clinical findings.

4.2.4.1 Indications for the use of chest x-rays

- To assist in the diagnosis of TB:
  - In an HIV positive client, when both pre-treatment smears are negative
  - In an HIV-negative or status unknown client, when both pre-treatment smears are negative and there is no response to antibiotics.
  - Where EPTB or miliary TB is suspected
  - For primary TB in children
- During or at the end of treatment: for specific clinical reasons or where response to treatment is not satisfactory.
- To assist in the diagnosis of suspected complications:
  - In a breathless client to exclude a pneumothorax or pleural effusion.
  - For frequent or severe haemoptysis.
- To help in diagnosing other lung diseases such as lung cancer, bronchiectasis, lung abscess and pneumoconiosis.

4.2.5 Tuberculin skin test

The tuberculin test has limited value in clinical work, especially where TB is common. The test shows hypersensitivity to proteins of the TB bacillus, as a result either of infection with M. tuberculosis or induced by Bacille Calmette-Guérin (BCG) vaccination. Infection is one of the criteria used in the diagnosis of TB in children. A positive TST does not indicate TB disease, only infection. A negative result does not rule out the diagnosis of TB disease as various conditions, including HIV, may suppress the reaction.

4.3 The seriously ill TB-suspect

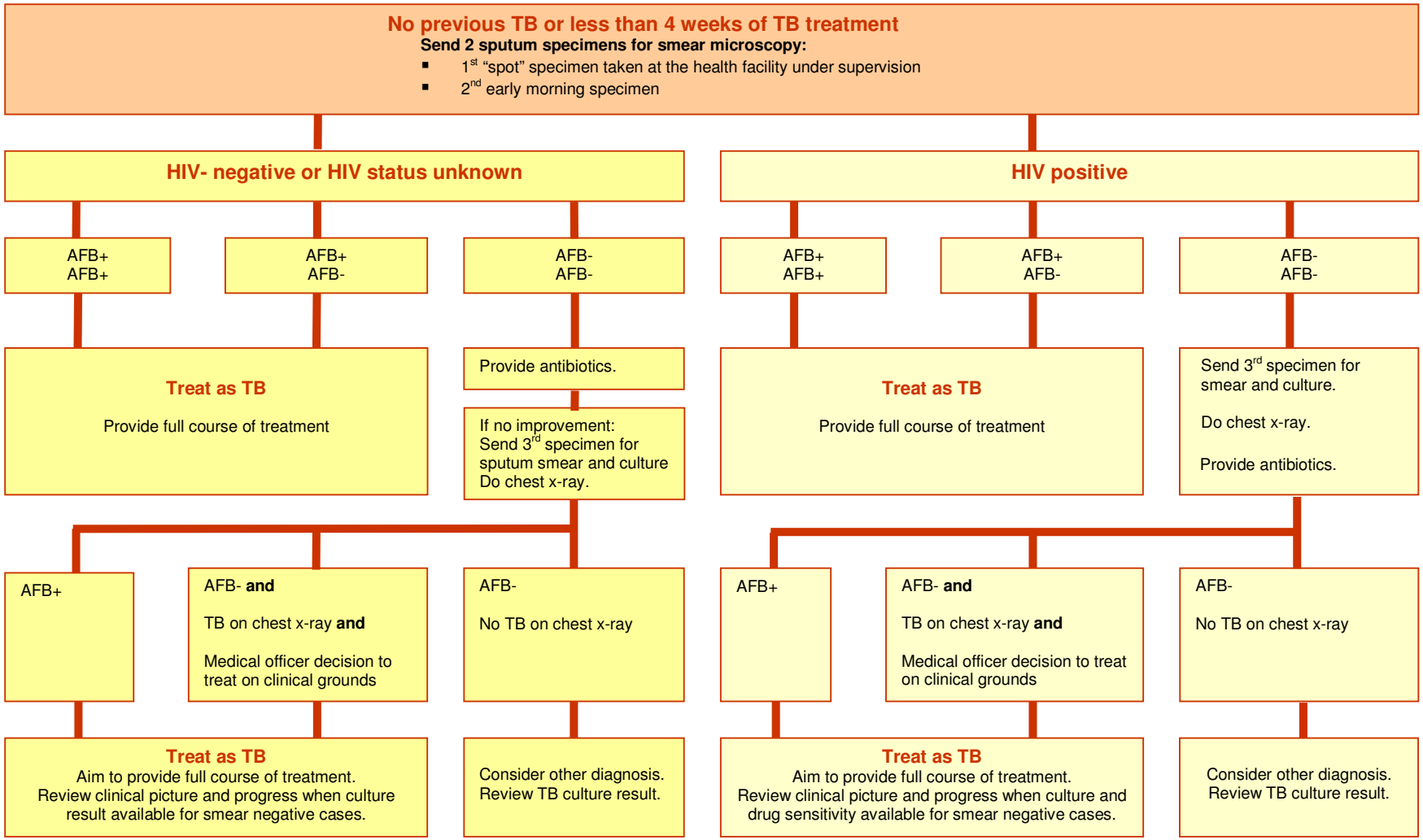
An adult TB suspect is classified as seriously ill if they have one or more of the following features:
- Unable to walk unaided
- Respiratory rate equal to or more than 30 per minute
- Fever of more than 39°C
- Pulse rate of more than 120 per minute

Management of the seriously ill client is as follows:
- Take 3 sputa: 2 for AFB and 1 for culture as promptly as possible
- Commence parenteral antibiotics: Ceftriaxone 1g IM stat
- Refer to secondary level of care for hospitalisation

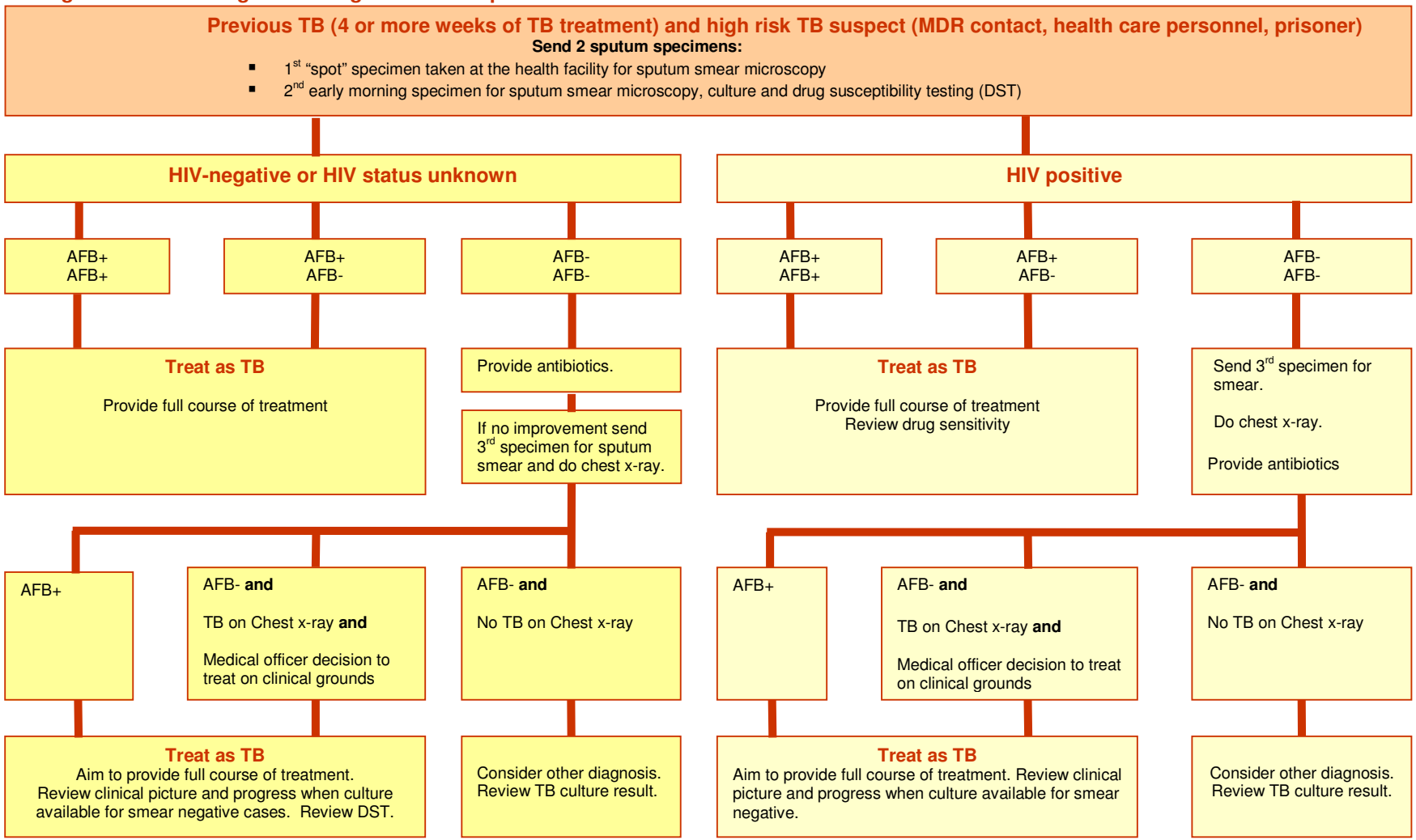
If unable to immediately refer:
- Do a chest x-ray
- Provide HIV counselling and testing
- If HIV positive:
  - Consider treating for PCP[2]
  - TB treatment can be started on clinical grounds if client does not improve within 3-5 days on antibiotics, microscopy results are negative and no other diagnosis is confirmed.
  - Once started TB treatment should be continued unless an alternative diagnosis is confirmed

[2] Pneumocystis Carinii Pneumonia

4.4 Algorithm for TB diagnosis in a new case



4.5 Algorithm for TB diagnosis in high risk TB suspects and re- treatment cases



5 TB Case Definitions

The diagnosis of TB refers to the recognition of an active TB case, that is, a client with symptomatic disease due to Mycobacterium tuberculosis. Beyond making the diagnosis of TB, it is also necessary to define the type of TB case for appropriate treatment to be provided and for the outcome of treatment to be evaluated in a standardised way.

5.1 Why case definitions?

- For proper client registration and case notification.
- To provide standardised treatment to different categories of TB cases.
- To prioritise the treatment of smear-positive TB as the main source of infection in communities.
- To evaluate the trends in TB notification such as the proportions of new smear-positive cases, smear-negative TB and retreatment smear-positive cases.
- For cohort analysis of treatment outcomes.

5.2 Why match treatment to standardised category?

- The correct use of standardized treatment regimens for new and retreatment cases reduces bacillary load and prevents the survival of resistant bacteria. It is the best way to prevent the emergence of multi-drug resistant tuberculosis.
- For the most cost-effective use of resources.
- To minimise side effects for clients by avoiding over-treatment.

5.3 What determines case definitions?

- Site of TB disease (pulmonary or extrapulmonary).
- Bacteriology (sputum smear and culture result).
- Severity of TB disease (determined by bacillary load, anatomical site of EPTB and extent of disease).
- History of previous treatment of TB.

5.3.1 Site of TB disease - pulmonary or extra-pulmonary

- Pulmonary TB refers to disease involving the lung parenchyma.
- Extra-pulmonary TB refers to TB of organs other than the lungs: e.g. pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints and bones and meninges
- Intrathoracic TB such as mediastinal or hilar lymphadenopathy or pleural effusion without a parenchymal lesion in the lungs, constitutes a case of extra-pulmonary TB.
- A client with both a parenchymal lesion in the lungs (pulmonary TB) and extra-pulmonary TB constitutes a case of pulmonary TB.
- Where several sites are affected, the site representing the most severe form of disease determines the case definition of extra-pulmonary TB.
- Recommended treatment regimens are similar, irrespective of the site of disease. Defining the site is of importance for reporting purposes.

5.3.2 Bacteriology - sputum smear and culture result

- **Definition of a smear-positive PTB case:**

The new case definition for sputum smear-positive tuberculosis is “a tuberculosis suspect with at least 1+ acid-fast bacilli in at least 1 sputum smear examination”

- A laboratory result of 1+ indicates 10-99 AFB per 100 oil immersion fields
- A single positive result confirms the diagnosis of TB and these clients should be started on treatment.
- The specificity of smear microscopy is high and placing these clients on treatment will help ensure that cases of TB are placed on treatment as quickly as possible; the numbers that die or are lost to follow-up whilst their diagnosis is being confirmed will be reduced.

- Identifying smear positive TB is important:
  - These are the most infectious cases
  - They have the highest mortality
  - Reporting on treatment outcomes is most feasible in this group.

- **Definition of a smear-negative PTB case:**
  - One sputum smear negative for AFBs **and**
    - Sputum culture is positive for mycobacterium TB **or**
    - Chest x-ray abnormalities are consistent with active TB, there has been no response to broad-spectrum antibiotics and a clinician has taken the decision to treat with a full course of TB treatment.

Pulmonary TB diagnosed without smear results should be classified as "smear not done"
Patients suspected to have extra-pulmonary TB should have specimens obtained from the suspected site and histopathological or culture and DST conducted. This is important in the early diagnosis of drug resistant TB particularly in high risk groups.

5.3.3 Severity of disease

The extent of disease and anatomical site determine the severity of disease and appropriate treatment. Disease is considered to be severe if there is a significant, acute threat to life and / or risk of serious long-term consequences.

Table 5.1: Severity of EPTB

Severe extra-pulmonary disease	Less severe extra-pulmonary disease
Meningitis	Lymph node
Miliary	Bone (excluding spine)
Pericarditis	Peripheral joint
Peritonitis	Adrenal gland
Bilateral or extensive pleural effusions	Pleural effusion (unilateral)
Spinal	
Intestinal	

5.3.4 History of previous treatment

It is important to define a case according to whether or not the client has previously received TB treatment in order to identify those clients at increased risk of acquired drug resistance and to prescribe appropriate treatment.

- **New:** A client who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than 4 weeks.
- **Previously treated (Re-treatment):** A client who has taken treatment for TB before for 4 weeks or more and either relapsed, defaulted or had treatment failure.
  - **Relapse:** A sputum smear or culture-positive pulmonary TB client who received treatment and was declared cured or treatment completed at the end of the treatment period and has now developed sputum smear or culture positive pulmonary TB again
  - **Treatment after failure:** A pulmonary TB client who is still sputum smear or culture positive at the end of the treatment period and is started on a retreatment regimen.
  - **Treatment after default:** A client who completed at least one month of treatment and returns after having interrupted treatment for two months or more, and is still smear or culture positive or has signs of active TB on clinical and radiological assessment.
- **Transfer in:** A client already registered for treatment in one district that has been transferred to another district to continue treatment is recorded as a "transfer in" at the referral site.
- **Other:** All cases that do not fit the above definitions, including
  - **Chronic case:** Client who remains sputum smear positive after completing a supervised re-treatment regimen.

5.4 Recording treatment outcomes with smear-positive TB

- **Cure[3]:** Client who is smear-negative in the last month of treatment and on at least one previous occasion at least 30 days prior.
- **Treatment completed:** Client who has completed treatment but who does not meet the criteria to be classified as cure or treatment failure.
- **Treatment success:** Client who is cured or treatment completed
- **Treatment failure:** Smear positive client who remains or is again smear-positive at 5 months (for new) or 7 months (for retreatment) after treatment start date or whose DST shows MDR-TB at 2 or 3 months.
- **Died:** Client who dies for any reason during the course of TB treatment.
- **Treatment default:** Client whose treatment was interrupted for more than two consecutive months before the end of the treatment period.
- **Transfer out:** Client who has been transferred to another reporting unit (e.g. district) and for whom the treatment outcome is not known.
- **Moved:** Client who moves to another facility within the same district.

Monitoring and evaluation of programme performance focuses on new smear-positive TB cases. The priority given to this category is appropriate as this is the largest group, containing the most infectious clients and therefore important from a public health perspective.

Whilst the main stated goal of the TB programme is to cure at least 85% of new smear-positive TB cases, the intention is also to cure at least 85% of retreatment smear–positive cases and to ensure the successful treatment of all other categories of TB. The outcomes of other categories of clients, such as smear-negative, culture-positive TB and EPTB may also be analysed as separate cohorts.

[3] New case cure: Negative smear at 120 days or later **and** at least 1 negative smear 30 days prior **and** treatment end date at least 150 days after treatment start date.
Retreatment case cure: Negative smear at 180 days or later **and** at least 1 negative smear 30 days prior **and** treatment end date at least 210 days after treatment start date.

6 Extra-Pulmonary Tuberculosis

Although most commonly affecting the lungs, tuberculosis can involve any organ in the body. Extra-pulmonary tuberculosis covers all forms of tuberculosis in which the disease process occurs outside the lung parenchyma. It accounts for about 20-25% of tuberculosis cases. Many forms of extra-pulmonary tuberculosis originate from direct, lymphatic or haematogenous spread of mycobacteria from a primary focus in the lung. Disseminated tuberculosis affects many parts of the body simultaneously.

The most common types of extra-pulmonary tuberculosis are:
- TB lymphadenitis
- Tuberculous pleural effusion (usually single-sided)
- TB of the bones and joints
- Tuberculous pericardial effusion
- TB meningitis
- Disseminated / miliary tuberculosis
- Tuberculous empyema
- TB peritoneal effusion

Diagnosis of extra-pulmonary TB is often difficult and requires invasive procedures to obtain diagnostic specimens. For this reason, many clients with extra-pulmonary TB have to be managed without bacteriological or histological confirmation of diagnosis, based on a presumptive clinical diagnosis. Prompt diagnosis and management of extra-pulmonary TB is important, as disseminated TB is a common cause of death, particularly amongst those with HIV.

Extra-pulmonary TB can present with non-specific symptoms such as unintentional weight loss (more than 5 kg in a month), night sweats and fever for more than 2 weeks. Other signs and symptoms depend on the site involved:
- Enlarged glands in the neck of armpits due to TB lymphadenitis.
- Non-productive cough for 2 weeks or more and chest pain due to pleural effusions.
- Breathlessness due to pleural or pericardial effusions.
- Chronic headache or altered mental state due to meningitis.

Disseminated tuberculosis and tuberculous meningitis are acute, severe forms of TB, often occurring soon after primary infection. They occur most commonly in children and young adults. These acute forms of TB are highly fatal. When this form of disease is suspected, treatment should be commenced immediately without waiting for bacteriological proof of diagnosis.

The basic principles of treatment for pulmonary tuberculosis also apply to extra-pulmonary forms of the disease. Six months treatment is as effective in extra-pulmonary as in pulmonary disease. In some instances of severe disease, treatment may need to be extended to nine months. The use of corticosteroids is also more commonly required in extra-pulmonary tuberculosis, particularly for TB meningitis and TB pericarditis. Only a specialist may make decisions on extended treatment and the use of steroids.

HIV testing should be offered to all clients suspected of extra-pulmonary TB. HIV positive adults with extra-pulmonary TB are categorised as WHO Clinical Stage 4 and require referral for antiretroviral therapy, in addition to receiving standard HIV care such as cotrimoxazole prophylaxis.

Bacteriologic evaluation of extra-pulmonary tuberculosis is often limited and the response to treatment must be judged on the basis of clinical and x-ray findings. If after 1 month, there is no response to treatment, an alternative diagnosis should be sought.

6.1 TB meningitis

Before the advent of effective anti-tuberculosis chemotherapy, TB meningitis was uniformly fatal. TB meningitis remains a potentially devastating disease that is associated with a high morbidity and mortality. HIV positive clients appear to be at increased risk for developing TB meningitis but the clinical features and outcome of the disease are similar to that in HIV-negative clients.

6.1.1 Clinical presentation and management

- Clients present with gradual onset of headache, malaise, confusion, decreased consciousness and sometimes vomiting.
- Examination reveals neck stiffness and a positive Kernig's sign (flex one of the client's legs at hip and knee with the client lying on back, and then straighten the knee; resistance to straightening the knee and pain in the low back and posterior thigh suggest meningeal inflammation).
- Diagnosis rests on clinical presentation and a lumbar puncture examination of cerebrospinal fluid (CSF). The following CSF features are highly suggestive of TB meningitis:
  - Clear CSF
  - Elevated pressure
  - High levels of protein (>1g/ l)
  - High lymphocyte count (30-300/mm^3)
  - Low glucose
  - Negative Indian ink stain for cryptococcus
- Clients with suspected TB meningitis should be referred to hospital without delay as TB meningitis is life threatening, with serious complications if not treated promptly.
- Those presenting with more severe neurological impairment such as drowsiness or coma have a greater risk of neurological sequelae and a higher mortality.

Table 6.1: CSF Differential Diagnosis for TB Meningitis

Disease	White Cell count	Protein	Glucose	Microscopy
Tuberculous meningitis	Elevated L > PMN	Increased	Decreased	Presence of AFB (rare)
Bacterial meningitis	Elevated PMN > L (L increases with partial treatment)	Increased	Decreased	Presence of bacteria after gram staining (rare)
Viral meningitis	Elevated L > PMN	Moderately increased	Normal	Negative
Cryptococcal meningitis	Elevated L > PMN	Increased	Decreased	Presence of parasites shown by Indian ink stain

L-lymphocytes PMN-polymorphonuclear leucocytes

6.2 Disseminated / miliary TB

Disseminated or miliary TB results from widespread blood borne dissemination of TB bacilli. This is either the consequence of a recent primary infection or the erosion of a tuberculous lesion into a blood vessel. It occurs most often in children and young adults. Unlike pulmonary tuberculosis, acute disseminated TB is highly fatal. Disseminated TB is an under-diagnosed cause of end-stage wasting in HIV positive individuals and should be considered in all febrile clients presenting with HIV wasting syndrome.

When disseminated TB is suspected, treatment should be commenced immediately without waiting for bacteriological proof of diagnosis.

6.2.1 Clinical features

- The client presents with a general deterioration in health and constitutional symptoms such as high fever, night sweats, weight loss and shortness of breath.
- Clinical signs may reflect the involvement of other organs: pleural effusion, digestive problems, hepatosplenomegaly and meningeal signs.
- There may be choroidal tubercles on fundoscopy.
- Other conditions that may present in a similar way need to be excluded, including: acute viral infections, staphylococcus, salmonella, crytococcus and malaria.

6.2.2 Diagnosis

- Chest X-ray shows diffuse, uniformly distributed, small miliary ("like small millet seeds") nodules.
- Full blood count may show pancytopenia (this may also be seen as a result of HIV) or anaemia.

- Liver function tests may be abnormal.
- Bacteriological confirmation is sometimes possible from sputum, C.S.F., or bone marrow.
- Smear microscopy of sputum from cases with disseminated (miliary) tuberculosis is usually negative, as the disease is paucibacillary.

6.3 Tuberculous lymphadenopathy

TB lymphadenopathy, caused by lymphatic spread of the organism, is one of the commonest forms of extra-pulmonary TB. Involvement of the lymph nodes is usually a complication of primary TB and is commoner in children. It tends to also be found in the later stages of HIV infection.

6.3.1 Clinical features

- Large mediastinal lymph nodes can compress the airways leading to an audible wheeze or typical brassy cough.
- Peripheral TB lymphadenopathy most commonly occurs in the neck and armpits. Typically lymph nodes are large (>2 cm), tender, non-symmetrical, matted, firm to fluctuant and rapidly growing.
- Associated systemic features include fever, night sweats and weight loss.
- As nodes increase in size and become fluctuant, they may suppurate and drain via a chronic fistula, resulting ultimately in scarring.
- TB lympahadenopathy needs to be differentiated from persistent generalized lymphadenopathy (PGL). PGL develops in up to 80% of HIV-infected individuals during the early stages of infection. These lymph nodes are typically non-tender, <2 cm in size and symmetrical. PGL requires no treatment.
- TB infected lymph nodes decrease extremely slowly in size (over weeks or months) on treatment, and in a few cases, are still the same size after the treatment has finished. This does not mean that the treatment was not successful.

6.3.2 Diagnosis

- If a lymph node is exuding caseous material through a fistula, this can sent to the laboratory for microscopy.
- Otherwise, refer the client to a doctor to do a needle (18G or 19G) aspirate of the lymph node. TB is diagnosed if a smear of the aspirated material reveals acid-fast bacilli.
- If no diagnosis is made after a needle aspirate, a lymph node biopsy should be done.
- Mediastinal lymph nodes can be diagnosed through chest x-rays.
- Intra-abdominal lymphadenopathy is more readily detected by ultrasound or computerised axial tomography (CT scan). These cases are treated empirically, unless the nodes can be readily aspirated at a tertiary health facility.

6.4 Tuberculous serous effusions

Inflammatory tuberculous effusions may occur in any of the serous cavities of the body, i.e. pleural, pericardial or peritoneal cavities. They are a common form of TB in HIV positive clients. In populations with a high prevalence of HIV, TB is the commonest cause of a serous exudate.

Clients usually have systemic and local features. Microscopic examination of the aspirate rarely shows AFBs because the fluid forms as an inflammatory reaction to TB lesions in the serous membrane. TB culture is of no immediate help because a culture result takes up to six weeks or more. The aspirate is an exudate with a protein content of more than 30g/l. A biochemical test is not required to diagnose an exudate: let the aspirated fluid stand for a while - if it clots, it is an exudate. However, failure of the aspirate to clot does not exclude TB as it may indicate a low protein content, found for example in wasted clients.

6.4.1 Tuberculous pleural effusion

Tuberculous pleural effusion is the commonest cause of a unilateral pleural effusion in countries with a high TB burden. It is also the commonest form of HIV-related extra-pulmonary disease, with a mortality of about 20% in the first 2 months on treatment. Management of tuberculous pleural effusion should aim at starting TB treatment promptly and determining the HIV-status of the client.

6.4.1.1 Clinical features

- Presentation is most often acute with a non-productive cough, chest pain, shortness of breath and high temperature.
- The chronic form is found predominantly in the elderly and presents with systemic symptoms such as weakness, anorexia, weight loss, slight fever, cough, and chest pain.
- Clinical examination shows:
    - Tracheal and mediastinal shift away from the side of the effusion
    - Decreased chest movement
    - Stony dullness on percussion on the side of the effusion.

6.4.1.2 Diagnosis

- Suspected pleural effusions should be confirmed by immediate chest x-ray. This will show unilateral, uniform white opacity, often with a concave upper border.
- Pleural aspiration should be undertaken wherever possible: the fluid is a straw coloured exudate and has a protein content >30g/l. The white cell count is high (1000-2500 per mm^3) with predominantly lymphocytes. The adenosine deaminase (ADA), which is a measure of the lymphocyte count, is raised >30 IU.
- Failure of the aspirate to clot does not exclude TB as it may indicate lower protein content in wasted clients; the predominance of lymphocytes (>50%) confirms a TB diagnosis.
- Since the number of bacilli present is relatively small, AFB are not usually seen on microscopy of centrifuged specimens of pleural fluid, however, culture may be positive.
- If aspiration is not possible, commence TB treatment unless the chest x-ray suggests a different diagnosis.
- Differential diagnosis of a pleural exudate includes malignancy, a post-pneumonia effusion and pulmonary embolism.
- Bilateral effusions or those with cloudy or bloody aspirates should be investigated further.
- Pleural biopsy is not recommended, as it is unnecessarily invasive.

6.4.2 Tuberculous pericardial effusion

Tuberculosis accounts for about 90% of pericardial effusions in HIV positive clients and for about half of those who are HIV-negative.

6.4.2.1 Clinical features

- Cardiovascular symptoms include: chest pain, shortness of breath, cough, dizziness and weakness due to low cardiac output.
- Symptoms of right-sided heart failure include leg swelling, right hypochondrial pain (liver congestion), abdominal swelling (ascites).
- Signs include: tachycardia, low blood pressure, pulsus paradoxus (fall in systolic pressure >10mHg on inspiration), raised jugular venous pressure, impalpable apex beat, distant heart sounds and a pericardial friction rub.
- Signs of right-sided heart failure include hepatosplenomegaly, ascites, and peripheral oedema.

6.4.2.2 Diagnosis

Diagnosis usually rests on suggestive systemic features and ultrasound:
- Chest X-ray may show a large globular heart, clear lung fields and bilateral pleural effusions.
- ECG may show tachycardia, flattening of ST and T waves, low voltage QRS complexes.
- In cases of cardiac tamponade the client should be referred to a specialist for aspiration of the effusion.
- Treatment without pericardiocentesis usually results in resolution of a tuberculous pericardial effusion.

In high TB and HIV prevalent populations, TB is the most likely treatable cause of a pericardial effusion. It may be safer for the client to start presumptive TB treatment than to undergo diagnostic pericardiocentesis. Treatment is the same as for all types of TB, but a specialist may decide to add corticosteroids if required. If not properly treated, TB pericarditis may evolve towards constriction over the following months.

6.4.3 Peritoneal Tuberculosis

Peritoneal TB is the commonest type of abdominal TB.

6.4.3.1 Clinical features

- Clinical features include systemic features and ascites with no signs of portal hypertension.
- There may be palpable abdominal masses (mesenteric lymph nodes).
- Bowel obstruction may develop from adhesion of caseous nodules to bowel.

6.4.3.2 Diagnosis

- Always do a diagnostic ascitic tap - the aspirated fluid is usually straw coloured, but is occasionally turbid or blood stained. The fluid is an exudate, usually with more than 300 white cells per mm^3 with lymphocytes predominating (in spontaneous bacterial peritonitis which is a common complication of cirrhosis, polymorphonuclear leucocytes predominate).
- Investigate for pulmonary TB
- Abdominal ultrasound may show retroperitoneal or mesenteric lymph node enlargement ·
- Diagnosis is usually presumptive - in doubtful cases, a macroscopic examination and bacteriological or histological examination of the samples may be considered in a hospital where exploratory surgery or laparoscopy can be performed.

6.5 Tuberculous empyema

- This usually arises when a tuberculous cavity in the lung ruptures into the pleural space.
- The physical signs are similar to a pleural effusion, but aspiration reveals thick pus. Send the pus to the laboratory for examination for TB, gram stain and bacterial culture. The main differential diagnosis is bacterial empyema.
- A succussion splash is a splashing sound heard with the stethoscope while shaking the client's chest. It indicates a pyopneumothorax (pus and air in the pleural space). After chest x-ray confirmation of a pyopneumothorax, insert a chest drain with underwater seal to remove fluid and air.

6.6 Tuberculosis of the spine

TB can affect any bone but most commonly affects the verterbral column. It is seen both in children and adults and can be severe, with neurological sequelae.

Involvement of the intervertebral disc occurs by spread of a lesion from the vertebral body. In many cases more than one intervertebral disc is involved. It is characterised by loss of bone density and slow bone erosion, with the disc space being maintained for a long time (differentiating it from pyogenic infections). In children, an acute form may develop with vertebral osteomyelitis, collapse of the vertebral body and neurological involvement. Collapse of adjacent vertebral bodies may lead to angulated kyphosis. Thrombosis of the anterior spinal artery caused by the inflammation causes transverse myelitis and paralysis.

Spread may occur into the soft paravertebral tissue to form a so-called “cold abscess”. These form symmetrical masses; they may spread further and end up calcifying.

6.6.1 Clinical features

- Features include back pain, stiff back, reluctance to bend the back
- There may be referred pain radiating out from the site of origin
- Localised swelling, sometimes with an obvious lump or abnormal curvature of the spine
- A child that refuses to walk or has weakness or paralysis of the lower limbs.
- Involvement of cervical vertebrae may cause pain in the neck and shoulders and rigidity of the neck. A cold abscess can develop behind the sternocleidomastiod muscle. More rarely, neurological involvement leads to progressive tetraplegia.
- Involvement of the thoracic vertebrae causes localized back pain, deformity of the spine, and in extreme cases an angulated kyphosis (gibbus). The chief risk is spinal cord compression and paraplegia.

- Involvement of the lumbar vertebrae results in lower back pain. A “cold abscess” from here can drain along the psoas muscle towards the inguinal area.
- In the early stages the physical examination can be non-specific.
- Clients with weakness or paraplegia should be referred to a specialist urgently.

6.6.2 Diagnosis

- X-rays of the spine show disc space narrowing and erosion of the adjacent vertebral bodies, wedge shaped collapse and angulation.
- Biopsy of cold abscess for microscopy and culture if possible, can confirm the diagnosis.
- Differential diagnosis includes degenerative disc disease, infectious spondylitis and cancerous vertebral metastases.

The principles of treatment for clients with EPTB are the same as for PTB:

- Regimen 1 for new cases
- Regimen 2 for retreatment cases
- A specialist may decide to extend the treatment of severe forms of extra-pulmonary TB from 6 to 9 months and to provide corticosteroids.

The response to treatment is assessed clinically. Weight loss may occur as large effusions / ascites resolves and does not necessarily indicate failure to respond.

7 Principles of TB Treatment

The aims of TB treatment are to:

1. Cure the client of TB
2. Decrease transmission of TB to others
3. Prevent the development of acquired drug resistance
4. Prevent relapse
5. Prevent death from TB or its complications

The key to stopping the spread of TB in a community is to start treating clients who are coughing up live TB bacilli (smear or culture positive) as soon as poss ble. Apart from the public health imperative, effective treatment reduces individual morbidity and mortality. For treatment to be effective, it is crucial that the correct drugs are given for the correct period of time. PTB and EPTB are both treated in the same way: regimen 1 for new cases and regimen 2 for retreatment cases.

7.1 The essential TB drugs

TB drugs have varying properties:

- They may be bactericidal, bacteriostatic (sterilising) or have the ability to prevent resistance.
- They differ in the ability to act against the various populations of bacilli found in a tuberculosis lesion:
  - Metabolically active bacilli, intermediately active bacilli, semi-dormant bacilli (persisters), which undergo occasional spurts of metabolism and dormant bacilli (that may become active).
- Some TB drugs act best in an acid environment; others better at a more alkaline pH
  - Bacilli occur both in extracellular spaces where the pH is usually neutral or alkaline and in intracellular spaces where it is acid.

Table 7.1: Properties of TB Drugs

Drug	Drug Property	Target Bacilli	ph	Site of Action
Isoniazid (H)	Bactericidal after 24 hours. High potency: kills >90% bacilli in first few days of treatment.	Rapid and intermediate growing bacilli	Alkaline and acid media.	Intracellular and extracellular.
Rifampicin (R)	Bactericidal within 1 hour. High potency. Most effective sterilising agent.	All populations including dormant bacilli.	Alkaline and acid media.	Intracellular and extracellular.
Pyrazinamide (Z)	Bactericidal with a low potency. Achieves its sterilising action within 2-3 months.	Slow growing bacilli.	Acid medium.	Intracellular bacilli only (macrophages).
Ethambutol (E)	Bacteriostatic. Low potency. Minimises the emergence of drug resistance.	All bacterial populations.	Alkaline and acid media.	Intracellular and extracellular.
Streptomycin (S)	Bactericidal with a low potency.	Rapidly growing bacilli.	Alkaline medium.	Extracellular bacilli

7.2 Fixed dose combination tablets

The use of fixed dose combinations (FDCs) has several advantages over individual drugs:

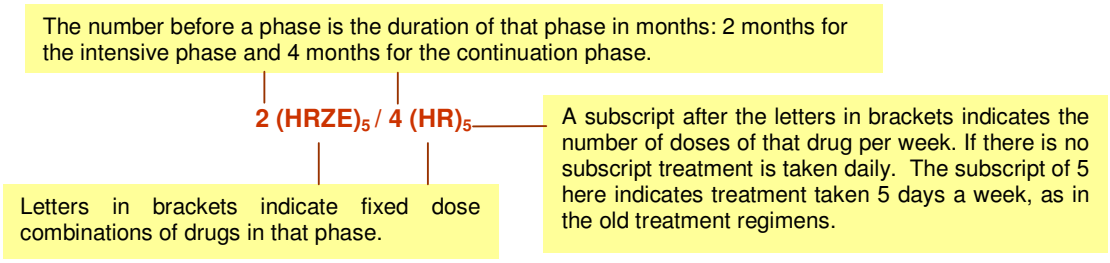
- Prescription errors are less likely as dosage recommendations are more straightforward and adjustment of doses according to client weight is easier.
- The number of tablets to be ingested is fewer and this may encourage client adherence.
- If treatment is not observed, clients cannot be selective in the choice of drugs ingested.

7.3 Standard treatment regimens for adults (8 years and older)

Standardised treatment regimens have several advantages over individualised treatment:
- Reducing prescription errors
- Facilitating estimates of drug requirements and procurement
- Reducing cost
- Facilitating regular drug supply when clients move from one facility to another
- Simplifying training

A standard code is used to describe treatment regimens. It describes the duration of both the intensive and continuation phases, the fixed drug combinations used in each of the phases and the number of doses of the drugs per week.

Each antituberculosis drug has an abbreviation: R (Rifampicin), H (Isoniazid), Z (Pyrazinamide), E (Ethambutol) and S (Streptomycin).



New recommendations are that treatment is given <u>daily</u>. The exception is where Streptomycin injections may be given a minimum of 5 times per week where health services are unavailable on weekends and no alternative plan for daily injections is possible.

7.3.1 New Cases

A new case is a client who has never been treated for TB in the past or who has taken TB treatment for less than four weeks.

The standard treatment regimen for new cases has an initial (or intensive) phase lasting 2 months and a continuation phase lasting 4 months. Treatment with 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) in the intensive phase results in rapid killing of tubercle bacilli. Infectious clients become non-infectious within approximately 2 weeks. Symptoms abate. The vast majority of clients with sputum smear-positive TB become smear-negative within 2 months. In the continuation phase, 2 drugs (isoniazid, rifampicin) are used, but for a longer period of time. The sterilizing effect of the drugs eliminates the remaining bacilli and prevents subsequent relapse.

The standard treatment regimen for new cases is regimen 1: 2(HRZE) / 4(HR)
- The intensive phase is 2(HRZE). Treatment is with isoniazid, rifampicin, pyrazinamide and ethambutol in fixed dose combinations given 7 days a week for 2 months.
- The continuation phase is 4(HR). Treatment is with isoniazid and rifampicin in fixed dose combinations given 7 days a week for 4 months.

7.3.2 Retreatment cases

Retreatment clients include all TB clients who were treated for 4 weeks or more in the past and who are now smear or culture positive or who have clinically been diagnosed with TB (failure, relapse, return after default).

These cases have a higher likelihood of resistance that may have been acquired through inadequate prior chemotherapy. The retreatment regimen has an intensive phase lasting 3 months. For the first 2 months, treatment includes 5 drugs: isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. In the 3rd month, treatment is with 4 drugs: isoniazid, rifampicin, pyrazinamide, ethambutol. The continuation phase with 3 drugs (isoniazid, rifampicin, ethambutol) lasts 5 months.

This regimen can cure clients excreting bacilli still fully sensitive to the drugs as well as those excreting bacilli resistant to isoniazid and or streptomycin. Under proper case management conditions, MDR-TB cases are those most at risk of failure on the retreatment regimen.

The standard regimen for retreatment cases is regimen 2: 2(HRZES) / 1(HRZE) / 5(HRE)

- The intensive phase is 2(HRZES) / 1(HRZE). It lasts 3 months in total. For the first two months treatment is with isoniazid, rifampicin, pyrazinamide and ethambutol in fixed dose combinations given 7 days a week and streptomycin injections given 7 days a week (or a minimum of 5 times a week if daily injections are not possible). In the third month only isoniazid, rifampicin, pyrazinamide and ethambutol in fixed dose combinations is given 7 days a week.
- The continuation phase is 5(HRE). It lasts 5 months. Treatment is with isoniazid, rifampicin and ethambutol in fixed dose combinations given 7 days a week.

7.4 Standard treatment regimen dosages

Table 7.2: Adult TB Drug Dosages

Essential TB drug (abbreviation)	Dose mg/kg	Dose range mg/kg
Rifampicin (R)	10	8 - 12
Isoniazid (H)	5	4 – 6
Pyrazinamide (Z)	25	20 – 30
Ethambutol	15	15 – 20
Streptomycin	15	12 – 18

Daily doses of TB drugs are given in Table 7.2. The following fixed-dose combination tablets are available for adults:

Table 7.3: Fixed dose combination tablets available for adults

Intensive Phase	Continuation Phase
RHZE (150,75,400,275mg)	RH(150,75mg) RH(300,150mg)

To further facilitate standardisation, the daily dosage is standardised in 4 weight bands.

Table 7.4: Regimen 1 (New Cases) For adults and children < 8 years

Pre-treatment body weight	Intensive Phase 7 days a week for 2 months	Continuation phase 7 days a week for 4 months	
	RHZE (150,75, 400,275)	RH (150,75)	RH (300,150)
30-37 kg	2 tabs	2 tabs	
38-54 kg	3 tabs	3 tabs	
55-70 kg	4 tabs		2 tabs
>70kg	5 tabs		2 tabs

R-Rifampicin, H-Isoniazid, Z-Pyrazinamide, E-Ethambutol

Table 7.5: Regimen 2 (Retreatment Cases) for adults and children < 8 years							
Pre-treatment body weight	**Intensive Phase** 7 days a week for 2 months.		**Intensive Phase** 7 days a week for 1 month	**Continuation phase** 7 days a week for 5 months			
	RHZE (150,75, 400,275)	Streptomycin (g) *	RHZE (150,75,400,275)	RH (150,75)	E (400)	RH (300,150)	E (400)
30-37 kg	2 tabs	0.5	2 tabs	2 tabs	2 tabs		
38-54 kg	3 tabs	0.75	3 tabs	3 tabs	2 tabs		
55-70 kg	4 tabs	1.0	4 tabs			2 tabs	3 tabs
>71 kg	5 tabs	1.0	5 tabs			2 tabs	3 tabs

R-Rifampicin, H-Isoniazid, Z-Pyrazinamide, E-Ethambutol, S-Streptomycin
* Streptomycin should NOT be given during pregnancy and to those over 65 years.

Effective treatment of TB requires adherence to the TB treatment short-course. Keep strictly to the correct dose and duration of treatment:
- Cure of the new TB clients depends on taking regimen 1 for 6 months.
- Cure of retreatment TB clients depends on taking regimen 2 for 8 months.

No trials of therapy should be given. A client either has TB and should be treated, or does not have TB. In a client in whom the diagnosis was not based on bacteriological confirmation, TB treatment should be continued until completion, unless an alternative diagnosis is confirmed. Treatment regimens have to be modified under special circumstances (see Chapter 10).

7.5 Side-effects of TB drugs and their management

7.5.1 Isoniazid (H)

Adverse effects:
- Peripheral neuropathy (tingling and numbness of the hands and feet)
- Hepatitis, more often in clients older than 35 years (rare)
- Generalised skin rash (rare)
- Fever
- Joint pains

Management:
- **Mild itching:** Continue drug treatment; reassure the client; give calamine lotion and if necessary antihistamine.
- **Fever and generalised skin rash:** Stop all drugs and give antihistamine.
- **Neuropathy:** Give 10 mg -25 mg of pyridoxine, daily.
- **Drug induced hepatitis:** Stop TB treatment; do liver function tests. If there is a loss of appetite, jaundice and liver enlargement, do not give treatment for at least 1 week or until the liver functions have returned to normal. In most clients INH can usually be given later without the return of hepatitis.

Drug interactions:
- Isoniazid inhibits the breakdown of epileptic drugs such as phenytoin and carbamazepine. Dosages of these drugs may need to be reduced during the treatment period.

7.5.2 Rifampicin (R)

Adverse effects:
- Gastro-intestinal: nausea, anorexia and mild abdominal pain; diarrhoea occurs less frequently.
- Cutaneous reactions: mild flushing and itchiness of the skin.
- Hepatitis: This is uncommon unless the client has a history of liver disease or alcoholism.
- Serious side effects like influenza syndrome and shock may occur in clients who take the medicine

intermittently instead of daily. Stop the treatment and refer the client.
- The client should be warned that rifampicin colours the urine, sweat and tears pink (urine looks orange-pink).

Drug interactions:
- Rifampicin stimulates liver enzymes, which may break down other drugs more rapidly than normal e.g. oral anticoagulants (warfarin), oral diabetic drugs, digoxin, phenobarbitone and other anti-epileptics.
- Contraception: The dose of contraceptives should be increased in clients on rifampicin. Depo provera 150mg should be given 8 weekly instead of 12 weekly. Nur-Isterate 200mg should be given 6 weekly instead of 8 weekly. Combined oral contraceptives with at least 0.05mg of ethinyloestradiol should be prescribed. The pill free interval should be shortened from 7 to 4 days. Intra Uterine Contraceptive Devices (IUCDs) may be recommended. Warn the client that the effect of rifampicin may last up to 2 months after the treatment is stopped.

7.5.3 Streptomycin (S)

Adverse effects:
- Cutaneous hypersensitivity, rash and fever.
- Ototoxicity (damage to eighth cranial nerve). Damage to the vestibular (balancing) apparatus causes dizziness, sometimes with vomiting. Unsteadiness is more marked in the dark. Can cause deafness.
- Deafness in unborn children. Streptomycin should be avoided during pregnancy because it crosses the placenta.
- Anaphylaxis: Streptomycin injection may be followed by tingling around the mouth, nausea and occasionally by sudden collapse. Treat as for any anaphylactic reaction and do not give streptomycin again.

Management:
- Skin reactions: treat as for allergic skin reactions.
- Damage to vestibular apparatus: treatment must be stopped immediately.
- Ringing in the ears or loss of hearing: if the drug is stopped immediately, the symptoms will usually clear over weeks. If not, the damage will be permanent.

Contra-indications:
- Do not give streptomycin to pregnant women (it crosses the placenta and can cause ototoxicity and nephrotoxicity in the foetus).
- Should be avoided where possible in children because injections are painful and it can cause irreversible auditory nerve damage.
- Do not give to clients with existing renal disease, as it will further impair renal function.
- Do not give to clients with myasthenia gravis.
- Older people (>65 years) have reduced renal function and the dosage may need to be reduced.

7.5.4 Ethambutol (E)

Adverse effects:
- Progressive loss of vision caused by retrobulbar neuritis, usually manifests first as loss of colour vision and usually presents after the client has been on treatment for at least two months. This is usually caused by excessive doses of ethambutol.
- Skin rash.
- Joint pains.
- Peripheral neuropathy.

Management:
- If the client complains about visual disturbance, stop treatment immediately.
- Skin rashes and joint pains usually respond to symptomatic treatment.

Contra-indication:
- Ethambutol should not be given if there is pre-existing optic neuritis or creatinine clearance is less than 50ml/min

7.5.5 Pyrazinamide (Z)

Adverse effects:
- Liver damage: Anorexia, mild fever, tender enlargement of the liver and spleen may be followed by jaundice.
- Arthralgia: This is common and mild. The pain affects both large and small joints, the level of uric acid is increased and gout may occur.
- Skin rash on sun exposed areas.

Management:
- Hepatotoxicity: Do not give the drug again if severe hepatitis occurs.
- Arthralgia: Treatment with aspirin is usually sufficient. Allopurinol may be required for the treatment of gout.

Contra-indication:
- Should not be given with severe hepatic impairment.

7.5.6 Pyridoxine

- It is unnecessary to give pyridoxine routinely.
- The use of alcohol during drug therapy should be discouraged or restricted.
- However, pyridoxine should be added for TB clients who are alcohol abusers, pregnant, diabetic or epileptic. The protective dose is 10-25 mg daily. This dose should never be exceeded in pregnancy.

7.6 Symptom-based approach to the management of side-effects

Minor Symptoms	**Drug(s) responsible**	**Management**
Anorexia, nausea, abdominal pain	Rifampicin	Continue TB drugs. Give tablets last thing at night.
Joint pains	Pyrazinamide	Continue TB drugs. Aspirin.
Burning sensation in feet	Isoniazid	Continue TB drugs. Pyridoxine 25mg daily.
Orange / red urine	Rifampicin	Continue TB drugs. Reassurance.
Major Symptoms	**Drug(s) responsible**	**Management**
Skin itching / rash (anaphylactic reaction)	Streptomycin	Stop streptomycin. Treat as for hypersensitivity reaction.
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin.
Dizziness (vertigo and nystamus)	Streptomycin	Stop streptomycin if severe.
Jaundice (other causes excluded)	Most TB drugs	Stop TB drugs until jaundice resolves, then re-introduce one by one
Vomiting and confusion (suspected drug-induced pre-icteric hepatitis)	Most TB drugs	Stop TB drugs, urgent liver function tests.
Visual impairment	Ethambutol	Stop ethambutol.
Generalised reaction, including shock and purpura	Rifampicin	Stop rifampicin.

8 Monitoring the Response to Treatment

Appropriately monitoring the response to treatment is important for the clinical care of all categories of TB clients. Clients with bacteriological confirmation of pulmonary tuberculosis should have bacteriological as well clinical monitoring to assess their response to treatment:

- Clients with smear-positive PTB are monitored by sputum smear examination
- Clients with smear-negative, culture-positive PTB are monitored by sputum smear and culture examination

Clients with EPTB and those in whom there has been no confirmed bacteriological diagnosis are assessed through clinical monitoring.

Smear-positive treatment outcomes are the focus of cohort reports for TB programme evaluation as these are the cases that pose the highest risk of TB transmission. It should be remembered however that smear-negative, culture-positive cases are also able to transmit TB, although at a reduced rate.

A minimum of two sputum specimens is taken on two separate occasions during the course of PTB treatment to evaluate the bacteriological response to treatment. It is important that the dates on which these sputa are due are clearly indicated in the client's blue clinic folder and client-held green card to serve as a prompt to both staff and clients. From the programme perspective, timely collection of sputa from smear-positive cases helps to improve the facility's smear conversion and cure rates.

8.1 Monitoring the response of new cases

8.1.1 New smear-positive cases

Response to treatment should be monitored by sputum smear examination. Two sputum specimens should be collected for smear examination at each time point:

- One week before the end of the 2 month intensive phase of treatment (i.e. at 7 weeks), to evaluate smear conversion
- At the end of 5 months of treatment, to evaluate treatment outcome.

There should be no interruption to treatment whilst smears are evaluated. Negative sputum smears indicate good treatment progress. At the end of the second month of treatment, most clients will have negative sputum smears and be able to start the continuation phase of treatment. If a client has a positive smear at this time, it indicates one of the following:

- Most frequently, that the initial phase of therapy was poorly supervised and that client's adherence to treatment was poor.
- Sometimes, that there is a slow rate of progress with smear conversion. For example, when a client has extensive cavitations and a heavy initial bacillary load.
- Rarely, that the client may have drug resistant TB that does not respond to first line drugs.

Whatever the reason, if either of the sputum smears are positive at the end of the second month, the intensive phase with four drugs is prolonged for one month, after which the smears are repeated and the continuation phase of treatment with two drugs is started.

- If smears are positive at 2 months and there is no bacteriological improvement (e.g. 2+ smears becoming 1+) or no clinical improvement, a sputum culture should be done for drug susceptibility testing.
- In clients in whom the continuation phase has been extended for a 3rd month, two sputum smears are repeated at the end of 3 months.
- If the client is still positive at the end of the third month, a sputum culture should be done for drug susceptibility testing.
- **If the 2 or 3-month drug susceptibility test shows MDR-TB, the client should be recorded as a treatment failure and referred immediately for MDR treatment.**

Treatment outcome:
- If the client has negative smears at 5 months (120 days or later) and had negative smears on at least one previous occasion at least 30 days prior, the client is discharged as cured after 6 months of treatment (treatment end date at least 150 days after treatment start date).
- If client has shown susceptibility to the first line drugs and the sputum is still positive at 5 months, the client is categorised as a treatment failure and started on the retreatment regimen afresh.
    - Culture and susceptibility tests should be done: if cultures are sensitive use the standard retreatment regimen and if MDR refer for MDR treatment.
- If client had a negative smear at 2-months but a positive smear at 5-months:
    - The client should be registered as a treatment failure
    - Start the client on the intensive phase of regimen 2 and provide a full course of treatment.

8.1.2 New smear-negative, culture-positive cases

Response to treatment should be monitored both clinically and by sputum smear and culture examination:
- Two sputum specimens should be evaluated one week before the end of the 2 month intensive phase of treatment (i.e. at 7 weeks), to evaluate non-response to treatment (disease progression)
- Two sputum samples should be evaluated at the end of 5 months of treatment – 1 for smear and 1 for smear and culture, to evaluate treatment outcome.

Although the client was diagnosed initially as smear-negative, smears should be done for the following reasons:
- To monitor drug resistance and non-response to treatment resulting in disease progression.
- To monitor non-adherence to treatment resulting is disease progression.

When the client has completed the 2-month intensive phase:
- If both sputum smears are negative, start the continuation phase of treatment.
- If both the sputum smears have become positive at the end of the 2 months:
    - Register the client as a treatment failure
    - Start client on the intensive phase of regimen 2 and provide with a full course of treatment; check drug susceptibility.
- If only one smear is positive, a third smear should be taken as two positive smears are required to confirm diagnosis of treatment failure to avoid errors

Treatment outcome:
- If the client has negative smears and culture at 5 months, the client is discharged as cured after 6 months of treatment
- If client has shown susceptibility to the first line drugs and the sputum smear or culture is still or becomes positive at 5 months, the client is registered as a treatment failure and started on regimen 2 afresh.

8.2 Monitoring the response of retreatment cases

All clients with previous TB (treated for 4 weeks or more) have a higher likelihood of drug resistance that may have been acquired as a result of inadequate treatment. Drug susceptibility test (DST) results are usually not available when a client commences the retreatment regimen. It is essential that the DST results be evaluated as soon as they are available. The retreatment regimen can cure clients with sensitive bacilli and bacilli that are resistant to isoniazid and / or streptomycin. If the tests show resistance to isoniazid and rifampicin (in addition to resistance to any other drugs) the client should be re-classified as MDR-TB and referred appropriately.

8.2.1 Retreatment smear-positive cases

Response to treatment should be monitored by sputum smear examination. Two sputum specimens should be collected for smear examination at each time point:
- One week before the end of the 3 month intensive phase of treatment (i.e. at 11 weeks), to evaluate smear conversion
- At the end of 7 months of treatment, to evaluate treatment outcome.

There should be no interruption to treatment whilst smears are evaluated. Negative sputum smears indicate

good treatment progress. If the smears are negative at the end of the intensive phase, the client is started on the continuation phase of treatment.

If the client is smear-positive at the end of the 3rd month, the four drugs used in the 3rd month of treatment are extended by another month and sputum culture and DST is repeated:
- If sensitive, commence the continuation phase of treatment and repeat smears at the end of the 4th month.
- If resistant to two of the three drugs used in the continuation phase (RHE), record as treatment failure and refer to MDR unit for evaluation and treatment.

Treatment outcome:
- If the client has negative smears at 7 months (180 days or later) and had negative smears on at least one previous occasion 30 days prior, the client is discharged as cured after 8 months of treatment (treatment end date at least 210 days after treatment started).
- If the client has shown susceptibility to the first line drugs and the sputum smear is still or becomes positive at 7 months, the client is categorised as a treatment failure and referred for the management of chronic TB.

8.2.2 Retreatment smear-negative, culture-positive cases

Response to treatment should be monitored both clinically and by sputum smear and culture examination:
- Two sputum smears should be evaluated one week before the end of the 3 month intensive phase of treatment (i.e. at 11 weeks), to evaluate non-response to treatment (disease progression)
- Two sputum samples should be evaluated at the end of 7 months of treatment – 1 for smear and 1 for smear and culture, to evaluate treatment outcome.

When the client has completed the 3-month intensive phase:
- If both sputum smears are negative, start the continuation phase of treatment.
- If both the sputum smears have become positive at the end of the 3 months:
  - Register the client as a treatment failure and refer for management of chronic TB.
- If only one smear is positive, a third smear should be taken as two positive smears are required to confirm diagnosis of treatment failure to avoid errors

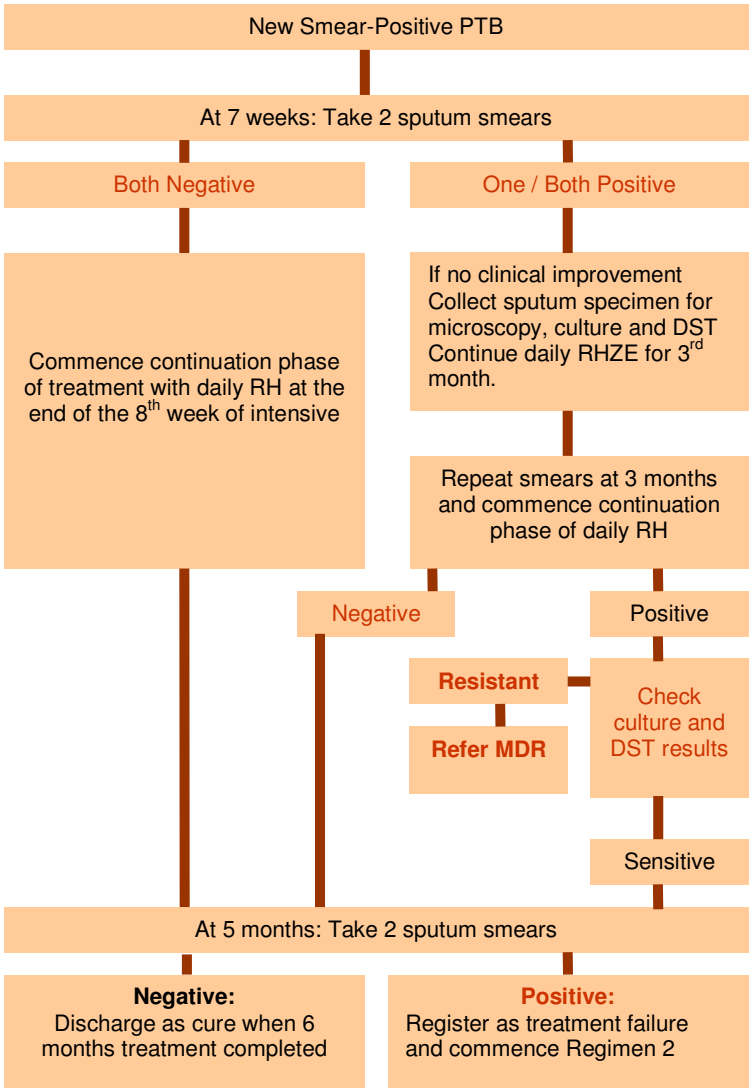
Treatment outcome:
- If the client has negative smears and culture at 7 months, the client is discharged as cured after 8 months of treatment
- If client has shown susceptibility to the first line drugs and the sputum smear or culture is positive at 7 months, the client is registered as a treatment failure and referred for management of chronic TB.

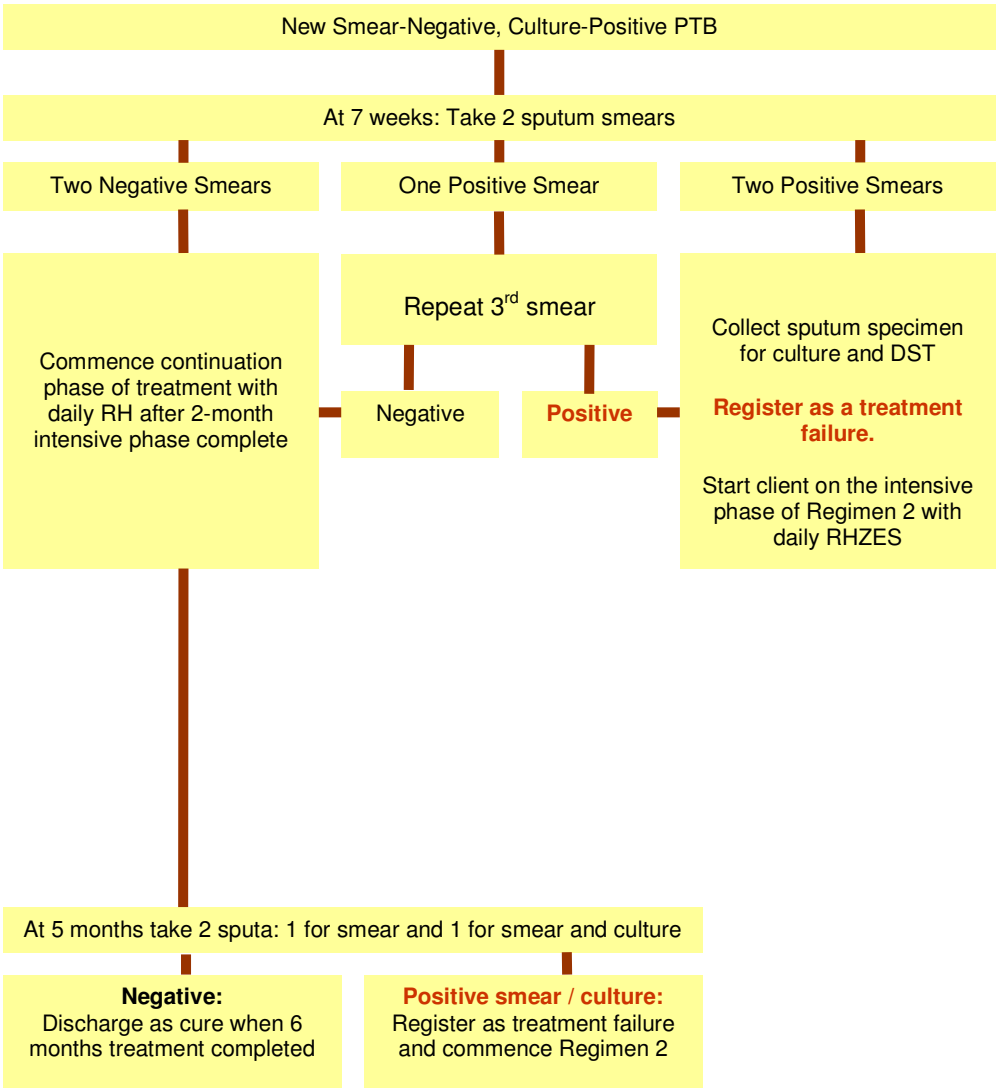
8.3 Monitoring the response of EPTB and smear-negative, culture-negative cases

Extra-pulmonary TB or cases that have been diagnosed on clinical grounds without bacteriological confirmation of TB should be monitored clinically over the duration of treatment.

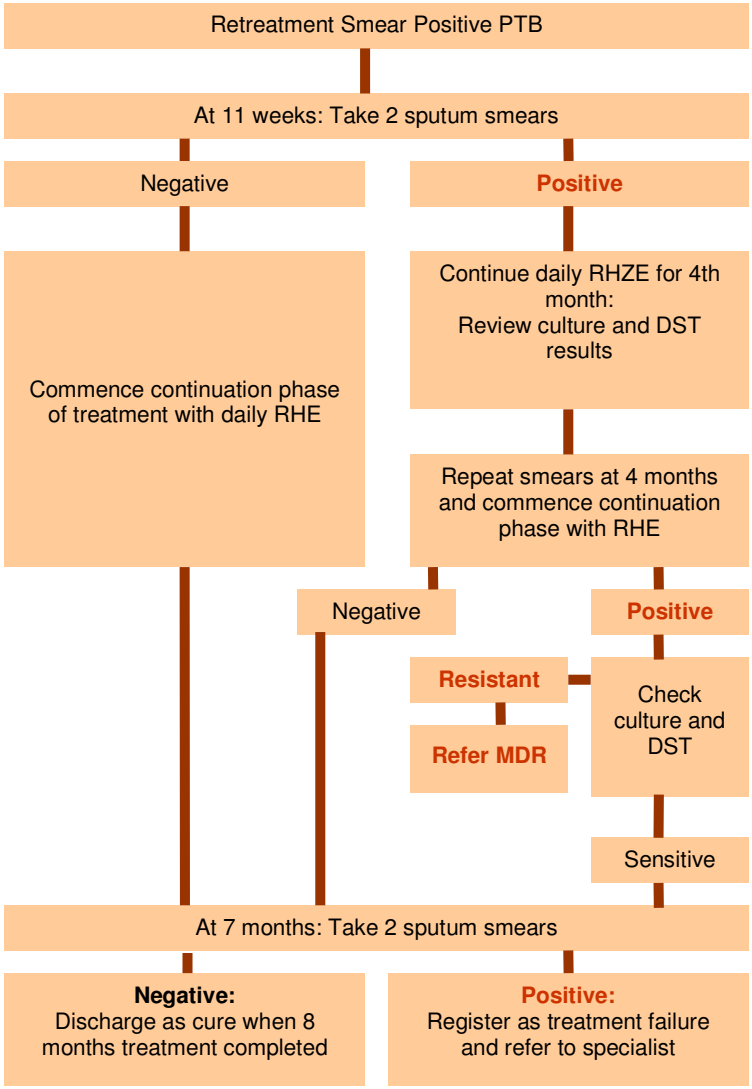
Weight is a useful indicator of clinical improvement. X-ray changes are a poor indication of clinical response and should not be used. If there is poor response to treatment consider alternative diagnoses and the possibility of drug resistance. The latter should be excluded through culture and drug susceptibility testing where specimens can be collected.

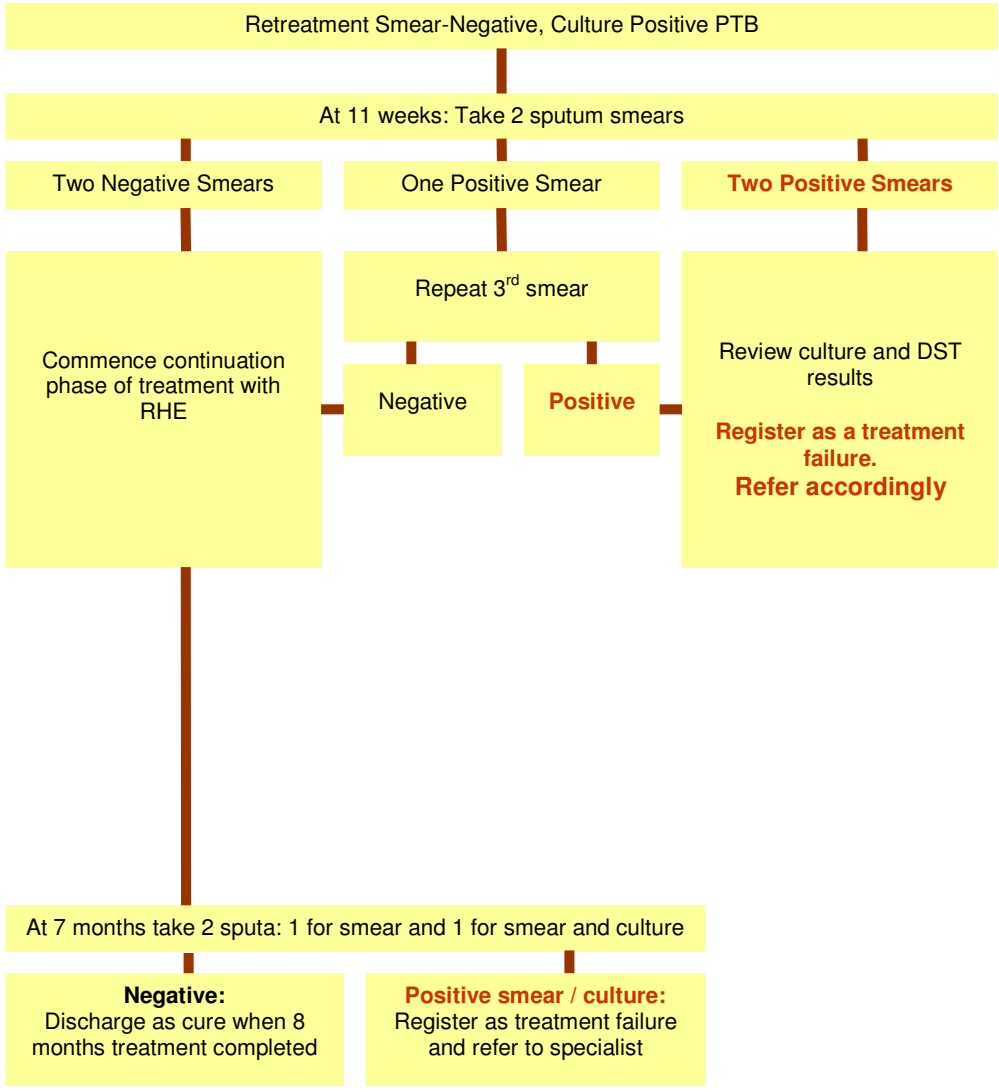
8.4 Monitoring algorithm for new PTB adults





8.5 Monitoring algorithm for retreatment PTB adults





9 Adherence to Treatment

The public health priority of the TB PROGRAMME is to cure smear-positive cases, while preventing the emergence of drug resistance. This can only be achieved by ensuring good adherence to treatment. TB is curable if clients take a complete and uninterrupted course of the appropriate drug therapy. However, poor adherence to TB medication is a common problem. Treatment interruption presents a problem for clients, for their family and community and for the health care personnel caring for them. The consequences of inadequate and incomplete treatment are serious:

- Prolonged illness and disability for the client.
- Infectiousness of the client causing continued TB transmission in the community.
- Development of drug resistant TB.
- The possibility of death.

TB is a complex disease that has biological, social, economic and cultural implications for the client. Health care providers should be mindful of the strong impact that TB can have on all aspects of the client's life. Due consideration should be given to the many factors that can adversely influence treatment outcomes.

Table 9.1 Factors that Influence Treatment Outcomes

Social and Economic Factors ▪ Extreme poverty ▪ Poor support networks ▪ Unstable living circumstances ▪ Substance abuse ▪ Beliefs about TB and its treatment	**Health System Factors** ▪ Poor health infrastructure ▪ Poorly trained or supervised health care personnel ▪ Low levels of accountability of health staff ▪ Poor relationships with clients ▪ Inadequate development of community based support for clients
Client related factors ▪ Stigma ▪ Depression ▪ Disempowerment ▪ Poor knowledge about TB and the efficacy of treatment	**Therapy related factors** ▪ Complex treatment regimens ▪ Large pill burden ▪ Adverse effects of medication ▪ Long treatment duration.

A comprehensive approach needs to be adopted, that addresses all these issues. Particular attention should be paid to factors within the health care system, such as access to services and the attitude and behaviour of health care providers as these lie within our sphere of influence.

9.1 Adherence

Adherence to treatment means following the recommended course of treatment by taking all the medication, as prescribed, for the entire length of time necessary. Adherence is a key factor in treatment success.

Promoting good adherence is more effective than spending time and resources on defaulter tracing. The basic approach to supporting adherence is to facilitate access to treatment, to simplify treatment, to ensure that services are client-centred and as convenient for the client as possible and to ensure that the client understands the treatment regimen and is motivated to comply with it. This can be achieved by:

- Providing laboratory tests for diagnosis and TB drugs free of charge.
- Reducing the time and cost to the client to obtain treatment.
- The use of fixed dose combination tablets and blister packs to simplify treatment.
- Being attentive to the client's needs and providing other social and medical services as required.
- Providing quality, efficient attention.
- Choosing with the client the most convenient time and place for the direct observation of treatment.
- Providing adequate counselling about TB treatment and the need to adhere to treatment and motivating and supporting the client to do so.

Convenience to the client must be balanced with the assurance of regular drug intake. Close monitoring of adherence gives the client the best chances of cure.

9.2 What is directly observed treatment (DOT)?

Directly observed treatment is an important element in the WHO recommended policy package for TB control. Directly observed treatment means that an observer (treatment supporter) watches the client swallowing the tablets, in a way that is sensitive and supportive to the client's needs. Close supervision and monitoring of clients allows good monitoring of adherence and early pick up of non-adherence and adverse drug effects.

DOT is recommended for all clients for the entire period of treatment.

It is impossible to predict who will or will not adhere to treatment and appropriate support mechanisms should be put in place for all clients. This helps ensure that a TB client takes the right drugs, in the right doses, at the right times. In practice, it means providing a treatment supporter that is both acceptable to the client and able to ensure completion of the treatment regime. DOT may occur in the clinic, at workplaces or in the community. The treatment supporter may be a health worker or a trained workplace or community member. In limited circumstances, the treatment supporter could be a family member.

The role of the treatment supporter is to help ensure treatment adherence, to reinforce client's motivation to continue treatment and to counter the tendency of some to interrupt treatment, particularly as they start to feel better. If a TB client misses one attendance for directly observed treatment, close contact with the client makes it possible to trace the client and re-institute treatment immediately.

When clients self-administer treatment there is the risk that they may take drugs irregularly. There is usually a much longer period between the interruption and re-initiation of treatment as there is no immediate way of identifying the interruption. Tracing unsupervised clients can also be difficult and often unproductive.

9.3 Applying DOT to fit clients' needs

One of the aims of the TB programme is to organize TB services so that the client has treatment as close to home (or the workplace) as possible. Implementation of directly observed treatment depends on the setting, facilities, resources and environment. The approach to applying directly observed treatment should be flexible, with local adaptation to suit different districts and provinces.

For any chosen method of supervision and administration of treatment, the programme must show high sputum smear conversion and cure rates under routine conditions, in both rural and urban areas. Within a province, a district that demonstrates a successful method of implementing directly observed treatment could be a model for other districts.

9.3.1 Clinic DOT

Clients who live close to a clinic should be encouraged to take treatment at the clinic if this is convenient for the client. During the first two months of Regimen 2, all clients require intra-muscular streptomycin and should therefore receive DOT at the clinic.

The following measures are required to ensure effective clinic DOT:

- Daily medication collected through fast-tracks that reduce waiting times.
- Recording of daily doses taken on client-held green cards.
- Regular updating of blue clinic folders.
- Systems to identify clients who did not present for DOT on that day and to trace and recall them rapidly.
- Pill containers with tablets or blister pack cut-outs provided on Fridays for medication required on the week-end.
- Responsibility allocated to a family member to observe and sign the green card for doses taken on weekends.
- A system to identify clients presenting for DOT who are also due for sputum collection.

The reality is that for many clients, clinic DOT is inaccessible, inconvenient, costly and causes loss of income; alternative methods of treatment supervision are necessary.

9.3.2 Workplace DOT

Workplace DOT is beneficial to both employees and employers. TB clients usually require about 2-weeks sick leave at the start of treatment. After this period, clients are non-infectious and most are able to return to work. For the employee, workplace DOT enables them to continue employment, if fit to do so, and ensures a continued income. For the employer it shows a commitment to social and corporate responsibility. Trained / skilled staff are retained and productivity is maintained at higher levels than would be possible with high employee turnover or long periods of absenteeism. It conveys the message that the employer cares about the health and welfare of its employees, fostering good relationships.

A workplace programme provides an opportunity to create an environment in which stigma can be addressed and anxieties such as workplace transmission of TB tackled. It enables ill employees to come forward more readily and early diagnosis reduces the likelihood of TB transmission in the workplace.

The treatment supporter in the workplace could be an occupational health nurse, manager, supervisor, shop steward or other employee. Establishing workplace DOT requires:

- Training of workplace treatment supporters.
- Establishing systems that allow treatment to be taken and monitored in privacy.
- Confidentiality to be ensured.
- Good communication with the clinic where the client is registered.
- Allocating time for clinic visits so that medication can be collected, sputa provided for monitoring the response to treatment and clinical evaluation undertaken.

9.3.3 Community DOT

Community DOT can contribute substantially to local TB Control Programmes. It has the advantage of being more accessible and convenient to clients. A TB client who has far to travel for treatment is less likely to adhere to treatment and community based DOT can be a viable alternative. In some areas, limited resources and high TB caseloads overwhelm clinics; using community-based DOT may contribute to a more rational use of limited resources in these settings.

The treatment supporter can be an existing community health care worker or a community member trained to provide DOT. Collaboration with other programmes (e.g. home-based care) allows the identification of health care workers that, with suitable training and supervision, can support TB clients.

The approach to establishing community DOT should include:

- Contacting existing community groups and organisations to determine how they might be able to contribute to community TB care (rather than setting up new systems, groups and organisations).
- Involving community representatives in the selection of community treatment supporters and ensuring an appropriate geographic spread of treatment supporters.
- Establishing a written contract with the community organisation and between the community organisation and the treatment supporter, defining roles and responsibilities and the standards required. The contracts should clarify whether incentives will be made available and under what terms.
- Providing adequate initial training to DOTS supporters on TB: transmission; signs and symptoms; diagnosis; treatment; side effects; monitoring response to treatment; link to HIV; goals of the TB Control Programme; programme monitoring and evaluation; record-keeping; process for supervision of DOTS supporter. Additional training may vary from "on the job instruction" by TB Control Programme staff to more formal short courses.
- Working with the community organisation to provide regular supervision, support, feedback and motivation of treatment supporters to ensure that quality outcomes are maintained.
- Addressing ethics and confidentiality.
- Establishing standard operating procedures and systems for:
    - Administering daily medication.
    - Monitoring adherence, including completion of the client-held green card when doses are taken and methods for identifying those interrupting treatment.
    - Follow-up and recall of treatment interrupters.
    - Communication and feedback to clinic.
    - Reminding clients about sputa that are due during the course of treatment.
- Keeping records at the clinic indicating the location of treatment supporters and clients allocated to them.
- Providing regular feedback to the organisation on TB Control Programme results and audits; addressing problems through joint problem-solving; acknowledging the community contribution to TB care.

If Community DOT is to succeed, resources are required for training, supporting and supervising community treatment supporters. The district coordinator is responsible for coordinating training and for monitoring the performance of the community treatment supporters. There must be a clearly defined line of accountability for community DOT.

It should be emphasised that community DOT is not simply a matter of devolving responsibility for clients to another agency and washing one's hands off them. Responsibility for the programme still rests with the clinic and the local TB Control Programme.

9.3.4 The role of family / friends

Members of the client's family should be encouraged to provide support and encouragement to the client to complete treatment. Where possible, at initiation of treatment, a family member or friend should be counselled about TB with the client, so that they have all the information necessary to help the client complete treatment.

In situations where a child or an elderly or infirm person is receiving TB treatment, family members have a far greater role to play and may be required to provide DOT. It is essential that these family members are adequately equipped through counselling and that they agree to monitor and record daily treatment and to contact the clinic if difficulties are experienced. Having a community health worker visit the family at regular intervals provides an opportunity to reinforce key messages and to review the record of treatment taken.

In any situation where clinic, workplace or community DOT is not feasible, it is essential that a family member or friend living close to the client is formally co-opted to assist with treatment. One of the difficulties with involving family is that underlying family dynamics can adversely influence treatment. When selecting a family member or friend to assist with treatment, it should be someone whom the client trusts, respects and has a good mutual relationship with.

On weekends, clients will be provided with medication to take at home. Specifically identified family members will need to be involved in supporting clients to take their medication and recording medication taken on the client-held green card.

9.4 Strategies for good adherence

Achieving good adherence to TB treatment is an objective that has to be specifically planned for and should include the following aspects:

- Education and counselling of clients.
- Adherence planning.
- Developing and monitoring a treatment plan that is client specific.
- Ensuring treatment availability at points most accessible to clients.
- Adopting a caring, client-centred approach to treatment.
- Involvement of family members, friends and community based organisations as part of the team supporting clients.

At the initiation of TB treatment, it is important to set aside enough time to meet with the client and family. This is an opportunity to counsel the client, identify potential problems that the client may face during treatment and plan for optimal adherence. It is essential to record the client's correct contact details. In addition to the name already provided, note other names that the client is known by in the community (for example nick names and clan names). The correct physical address should be noted as well as other contact addresses (e.g. partner, spouse, parents, close friend, work place, place of study) so that clients can be readily located.

Clear instructions should be provided about how to take the medication, possible side effects and what to do about these. A discussion about the difficulty in remaining motivated to continue with TB treatment once the client starts to feel better can help pre-empt treatment interruption.

Once counselling is complete, a clear treatment plan needs to be developed for each client. Highlight important steps in the treatment plan such as dates when sputa are due, medication changed and treatment completed. These dates should be clearly documented in the treatment section of the blue clinic card and green client-held card as a reminder to both clients and staff. Interactions with the client should be used to

emphasise the importance of taking tablets regularly, providing sputa to monitor progress and completing treatment.

Ask clients to consult staff ahead of any temporary or permanent change of address to facilitate continuation of treatment. Check the client's movements over the treatment period to plan treatment during visits that may take place away from the area. If clients unexpectedly find themselves having to go away, advise them to take their client-held green card with them and to present it to the nearest clinic for treatment.

Where resources permit, it is helpful for clinic staff or a community health worker to accompany the client to their home. This allows verification of the client's exact address. It provides an opportunity to arrange for screening of all household contacts, including other symptomatic household members and children under the age of 5 years and those who are HIV positive who require TB prophylaxis. It also presents an opportunity to identify social problems that could impact on adherence to treatment.

Ensuring good adherence requires careful monitoring. Unless adequate records are kept of daily treatment, it is difficult to identify when treatment interruption occurs and to take remedial action. Keeping track of daily medication is a challenge, particularly in busy facilities. If client-held green cards are used for this purpose it is difficult to identify clients who do not present for daily DOT, as there is nothing to prompt staff about a no-show. The blue folders also need to be updated from the client-held green cards on a regular basis to ensure that the clinic has a record of treatment taken. It is recommended that both blue clinic folders and green client-held cards be used to ensure up-to-date records in both. A system should be established to prompt staff about a missed dose and any missed dose or appointment should be followed up rapidly.

9.4.1 Education and adherence counselling

Client education and adherence counselling has three main purposes:
- To provide information on TB to clients and their families.
- To prepare the client to complete TB treatment.
- To help the client plan for good adherence to TB treatment by anticipating difficulties that may be experienced and dealing with these proactively.

The desired outcome of adherence counselling is a change in knowledge, attitude and behaviour of the client. To be effective, counselling needs to be a mutual process between clients and counsellors. Active participation of clients should be encouraged. Clients should be treated with respect and their beliefs accepted in a non-judgemental way. Counsellors who are reliable, dependable, consistent, and have good listening skills are more likely to establish a trusting relationship with the client.

It is important that the information provided to clients and their families on TB and its treatment is appropriately structured and emphasises key messages:
- Do not overload the client with too much information at one time.
- Always check the clients understanding of information given.
- Use educational materials that are culturally and linguistically appropriate for the client.
- Assess the client's beliefs about TB and if possible integrate the beliefs into the treatment plan.
- Clarify client's questions and respond to these clearly.

Appropriately trained nurses, lay counsellors or community health workers can do adherence counselling. It is important that adherence counselling is structured and includes the following aspects:
- What TB is; how it is transmitted and how to protect those around you.
- Medication used to treat TB; when and how to take it; side effects
- The duration of treatment; important milestones during treatment such as sputum testing to monitor the response to treatment and changes in medication; the importance of completing treatment
- Developing an adherence plan to identify barriers to treatment and address these to ensure treatment completion
- The link to HIV and the need for an HIV test
- General health issues including choosing the best foods available, stopping smoking and reducing alcohol intake.

Table 9.2: Roles and Responsibilities of the TB Support Team

TB Client
- Take their tablets as prescribed
- Report side-effects to the treatment supporter or clinic nurse
- Return to the clinic for scheduled visits
- Bring sputum specimens to the clinic for testing at the required times
- Provide feedback to the team of any problems that they experience
- Inform treatment supporter and clinic staff if they are going away and make plans for taking medication whilst away
- Take responsibility for completing their treatment

Family / Friend:
- Provide emotional support to the client
- Encourage/remind client to take their tablets daily
- Supervise treatment on the weekends, or daily if required, and record doses in the client-held green card
- Remind client to bring sputum specimens to the clinic for testing at the required times
- Motivate client to complete the full course of treatment
- Report problems to the clinic

Nurse:
- Provide basic information on TB
- Initiate TB treatment and explain how to take the tablets
- In consultation with client, allocate to DOT that is most suitable for them
- Provide daily treatment at the clinic for all clients for a minimum of 2-3 weeks and for those clients receiving Clinic DOT thereafter
- Keep a record of where all clients registered at the facility are receiving DOT
- Complete clinical records: clearly indicate when sputa are due; maintain daily records in blue clinic and green client-held cards
- Update the TB register
- Assess clients on a scheduled basis, monitor response to treatment, encourage treatment completion
- Provide monthly treatment to the client receiving DOT in the community or worklplace
- Get feedback from treatment supporters on clients receiving community DOT
- Arrange transfer of clients moving to another area
- Arrange tracing of clients who have defaulted treatment

Treatment supporter
- If possible, visit clients commencing treatment at their homes: assess and refer other suspects and contacts to the clinic; identify problems in the household that might affect adherence and report these to the clinic; confirm the clients address
- Meet with clients on a daily basis (including over weekends if possible) and supervise their treatment
- Complete the client-held green card to record doses taken
- Ensure that clients have collected their monthly medication
- Provide support to TB clients and their families
- Motivate TB clients to complete their treatment
- Remind TB clients to bring their sputa to the clinic for testing at the appropriate times
- Provide regular feedback to the clinic on their clients
- Trace clients who have interrupted treatment
- Create awareness in the community about TB and HIV

Adherence Counsellor
- Provide structured education and counselling to client
- Prepare client for completing their TB treatment
- Assist the TB client in anticipating problems with adherence and planning ways to overcome these
- Offer additional counselling to clients having problems with adherence

9.4.2 The TB support team

Completing treatment and documenting a cure for all smear-positive cases is the joint responsibility of health care personnel, TB clients and communities. In sharing responsibility for treatment outcomes, the roles and responsibilities of the TB support team need to be clarified (see Table 9.2).

Building a good relationship between members of the team and the client can help improve adherence. This can be achieved through:

- Creating a sense of partnership between the TB support team, the client and their family
- Emphasising the importance of the client (and family) taking responsibility for treatment, supported by health care personnel
- Giving the client adequate time at each visit
- Treating clients with respect and consideration
- Being positive; not intimidating or frightening the client
- Addressing any anxieties the client may have
- Understanding the client's cultural beliefs and values.

9.4.3 Special considerations for children and adolescents

Children with TB present specific problems for adherence. There is very little information about the rates of adherence among children or methods for improving it. Many children with TB have few or no symptoms of the disease. For those who do, many do not experience dramatic improvement in symptoms when given appropriate treatment. Because of the characteristics of the disease in children, it may be difficult to convince parents that their children are ill and need treatment and that the treatment needs to given as prescribed.

To improve adherence amongst children, work with the parents or caregivers who will administer medication to the children. You cannot assume that parents will give the medication as prescribed, as some parents are non-adherent.

Provide anticipatory guidance:

- Talk with parents about the potential problems they might experience once treatment is initiated. For example, that children may resist taking medication, experience adverse reactions to the medication or have difficulty in swallowing medication
- When parents are aware of potential problems they may be better equipped to deal with them and assist with the treatment.

Ensure DOT:

- Direct observation of treatment must be ensured either by a facility healthcare provider, community health worker, parent or caregiver with proper documentation of every dose taken.
- If a parent or caregiver assumes this role, a community health worker should visit on a regular basis to assess adherence to treatment.
- Adolescents are at high risk of poor adherence because of concerns about stigma; they may not take their TB seriously; they may feel embarrassed about having to take TB treatment and concerned about what their friends think.

9.5 Interruption of treatment

Directly observed treatment adapted to clients' needs and accommodating the working conditions of health care personnel is certainly the best method of avoiding treatment interruption. However, even with directly observed treatment, there may be treatment interruptions that need to be addressed.

9.5.1 Minimise the duration of treatment interruption

When a client doesn't keep an arranged appointment to receive treatment, it is necessary to inquire after the client using the contact addresses previously obtained and appropriate means of tracing the client. It is important to find out the cause of the client's absence in order to take appropriate action and continue treatment. If treatment interruption does occur, early identification and follow-up is essential.

9.5.2 Managing treatment interruption

The management of clients who have interrupted treatment is complex and takes into consideration multiple variables including their immune status, degree of remission of the disease with the previous treatment and drug susceptibility. A simplified decision tree is suggested in table 9.3.

Table 9.3: Management of Treatment Interruption

I. Interruption for less than one month

- Trace client
- Address the cause of interruption

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- Continue treatment and prolong it to compensate for missed doses:
  - Days of treatment missed in both the intensive and continuation phase

II. Interruption for one to two months

- Trace client
- Address the cause of interruption
- Do 3 sputum smears
- Continue treatment while waiting for results

Smears negative or EPTB	One or more smears positive: Send sputum for culture and DST	
	Treatment received: Less than 5 months	Treatment received: More than 5 months
Continue treatment and prolong it to compensate for missed doses as above.	Continue treatment and prolong it to compensate for missed doses as above. Review DST	Regimen 1: Start Regimen 2 Review DST
		Regimen 2: Refer (may evolve to chronic TB)

III. Interruption for two months or more (defaulter)

- Trace client
- Address the cause of interruption
- Do 3 sputum smears
- No treatment while waiting for results

Smears negative or EPTB	One or more smears positive: Send sputum for culture and DST	
Clinical decision on whether to: continue or restart or have no further treatment.	Regimen 1: Start Regimen 2 Review DST	Regimen 2: Refer (may evolve to chronic TB)

10 Treatment Regimens in Special Circumstances

10.1 Pregnant women

Untreated tuberculosis represents a far greater hazard to a pregnant woman and the foetus than does treatment of the disease. It is important to ask a woman if she is pregnant before starting TB treatment. Most TB drugs, except for streptomycin, are safe for use in pregnant women.

Streptomycin is ototoxic to the foetus and should not be used in pregnancy.

10.2 Breastfeeding women

A woman who is breastfeeding and has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby. All the TB drugs are compatible with breastfeeding and a woman taking them can safely continue to breastfeed her baby.

If the mother is infectious (both smear-positive and smear-negative PTB) the child should be given prophylactic isoniazid (10mg/kg/day) for six months and continue breastfeeding. BCG vaccination should be postponed until the end of isoniazid prophylaxis as the TB treatment and INH can destroy the vaccine.

10.3 Women using contraceptives

Rifampicin interacts with the oral contraceptive pill and decreases the protective efficacy against pregnancy. A woman on oral contraception receiving rifampicin requires combined oral contraceptives with at least 0.05mg of ethinyloestradiol to be prescribed. The pill free interval should be shortened from 7 to 4 days. Alternatively, another form of contraception could be considered.

The dose of injectable contraceptives should also be increased in clients on rifampicin. Depo provera 150mg should be given 8 weekly instead of 12 weekly. Nur-Isterate 200mg should be given 6 weekly instead of 8 weekly. Alternatively, an Intra-Uterine Contraceptive Device (IUCD) may be recommended.

Warn the client that the effect of rifampicin may last up to 2 months after the treatment is stopped.

10.4 Liver disorders

Isoniazid, rifampicin and pyrazinamide are all associated with hepatitis. Of the three, rifampicin is least likely to cause hepatocellular damage, although the drug is associated with cholestatic jaundice; pyrazinamide is the most hepatotoxic.

Clients who are hepatitis virus carriers, have a past history of acute hepatitis or excessive alcohol consumption can receive the usual short-course chemotherapy regimen provided there is no clinical evidence of chronic liver disease. However, hepatotoxic reactions to TB drugs may be more common in these clients and should be anticipated.

10.5 Established chronic liver disease

Clients with chronic liver disease should not receive pyrazinamide. Isoniazid and rifampicin plus one or two non-hepatoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of eight months. Alternative regimens are 9RE in the initial phase followed by 3HE in the continuation phase or 2 SHE in the initial phase followed by 10HE in the continuation phase, giving a total treatment duration of 12 months. Therefore recommended regimens are 2SHRE/6HR, 9RE/3HE or 2SHE/10HE. Liver function should be monitored.

It is better to use rifampicin than isoniazid if necrosis is present or the liver pathology is undefined and isoniazid containing regimens if cholestasis is present.

10.6 Acute hepatitis

Uncommonly a client has TB and concurrent acute hepatitis (e.g. acute viral hepatitis) unrelated to TB or TB treatment. Clinical judgment is necessary in making treatment decisions. In some cases it is possible to defer TB treatment until the acute hepatitis has resolved. In cases where it is necessary to treat TB during acute hepatitis, the combination of SE for the first 3 months is the safest option. If the hepatitis has resolved the client can then receive a continuation phase of isoniazid and rifampicin for six months. If not resolved, SE should be continued for a total of 12 months. The treatment alternatives are therefore 3SE/6HR or 12SE.

10.7 Renal failure

Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can therefore be given in normal dosages to clients with renal failure. In severe renal failure, clients should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy.

Streptomycin and ethambutol are both excreted by the kidney. Where facilities are available to monitor renal function closely it may be possible to give streptomycin and ethambutol in reduced doses. The safest regimen to be administered in clients with renal failure is 2HRZ/4HR.

11 TB in Children

The main aims of TB management in children are to:
- Identify children with TB infection at risk of developing disease (young children and HIV infected children) and provide them with prophylaxis to prevent TB disease.
- Diagnose and treat children with TB disease to prevent the development of more serious TB or death.

More broadly, children can be protected from developing tuberculosis, especially the serious forms of tuberculosis, by implementing a combination of three strategies:
- The early detection and treatment of adult infectious cases
- Universal use of BCG
- TB preventive therapy to children under 5 years of age and HIV infected children in contact with cases of infectious tuberculosis.

BCG vaccination provides children with a degree of protection against serious forms of TB (TB meningitis and miliary TB). Many children get TB despite BCG vaccination. In the Expanded Programme of Immunization (EPI), BCG is given soon after birth. There is no value in revaccinating with BCG and this is discouraged.

BCG vaccination can lead to serious vaccine-associated adverse effects in HIV-infected children. However, due to the high TB burden in South Africa, **it is recommended that routine BCG vaccination continue at birth**.

11.1 Tuberculous infection

Tuberculosis infection should be differentiated from disease:
- TB infection – A child becomes infected when the child inhales the TB organism. TB infection is diagnosed when the child is asymptomatic and the Tuberculin Skin Test (TST) is positive. Not all children exposed to an infectious adult case of TB will become infected.
- TB disease – About 10% of children who have been infected with TB develop active disease. TB disease may manifest in many different ways but is indicated by the presence of well-defined symptoms.

The source of TB infection in a child is usually an adult (often a family member or care giver) with pulmonary TB. When the infectious person coughs, bacilli are expelled in droplets into the air, inhaled by the child, and cause infection. The proportion of children infected will depend on the duration of exposure (time), the closeness of the contact and the number of organisms in the sputum of the source case.

The risk of infection is increased with:
- Long duration of exposure to an infectious case.
- High intensity of exposure – smear-positive cases are the most infectious, smear-negative, culture-positive cases are less infectious while extrapulmonary TB cases are normally not infectious.
- Close exposure – where the mother or caregiver has active TB.
- Young children.
- HIV positive children

Drug resistant TB is as infectious as drug susceptible TB. Children exposed to drug resistant TB therefore have the same risk of being infected as children exposed to drug susceptible TB.

11.1.1 Diagnosis of tuberculous infection

A child that has been infected by TB develops a positive tuberculin skin test (TST). It takes between 6 weeks and 3 months after exposure for a positive TST to develop. Children with tuberculous infection are asymptomatic. Most children have an immune system that is strong enough to prevent the infection from progressing to disease.

The TST measures the hypersensitivity to tuberculin purified protein derivative (PPD). A positive tuberculin test does not indicate the presence or extent of tuberculosis disease; it only indicates TB infection.

There are different types of TSTs but the Mantoux is the best test. The test is read after 48-72 hours. The Mantoux skin test is positive when the transverse diameter of skin induration is 10mm or greater. In HIV infected children the TST is less likely to be positive and an induration of 5 mm or greater is regarded as positive. See Annexure 1 for information on how to do the Mantoux test.

Any child, under 5 years of age or HIV infected (irrespective of age), with a **positive Mantoux skin test**, has been infected with TB and should be screened for TB disease. After disease has been excluded, the child should receive **INH prophylaxis** to prevent the development of TB disease (whether there is known contact with an index case or not).

A negative TST does not exclude TB infection. The TST can be negative in a TB infected child due to:
- Severe malnutrition
- HIV infection
- Disseminated TB such as miliary TB or TB meningitis
- Immunosuppressive drugs e.g. high dose steroids

11.1.2 Contact screening

All children in close contact (same household) with an infectious case of TB (smear and/or culture positive) must be screened to exclude TB disease. Screening should include a thorough history and clinical examination. Children who have symptoms suspicious of TB disease require a Mantoux test and chest x-ray, if available, to aid the diagnosis of TB.

All children under 5 years of age in close **contact** with an infectious case of TB who are asymptomatic for TB, should receive **INH prophylaxis** to prevent developing TB disease. The likelihood of TB infection in these children is high. A chest x-ray and a Mantoux skin test is not required prior to commencing INH prophylaxis in asymptomatic children. Symptomatic children must have TB disease excluded.

Close child contacts of MDR-TB cases should be rapidly identified and screened. These children should ideally be referred to the expert MDR centre in the Province for evaluation. Asymptomatic contacts should receive careful clinical follow-up for a period of at least two years. If active MDR-TB develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is essential.

11.1.3 Management of children with tuberculous infection

After exclusion of TB disease, INH prophylaxis should be given to:
- All children under 5 years of age and HIV-infected children (irrespective of age) in contact with an infectious case of TB (drug susceptible TB and MDR-TB)
- All children under 5 years of age with a positive Mantoux (10 mm in diameter or greater)
- All HIV-infected children, irrespective of their age, with a positive Mantoux (5 mm in diameter or greater)

The rationale for providing INH prophylaxis to asymptomatic MDR child contacts is that in areas of high TB prevalence, it is likely that there has also been exposure to drug susceptible TB strains as well. On the basis of the currently available evidence, WHO does not recommend second-line drugs for chemoprophylaxis in MDR-TB contacts.

Children older than 5 years who are well do not require prophylaxis but only clinical follow-up as they have the lowest risk of serious or disseminated disease.

Previous treatment or prophylaxis does not protect the child therefore all children younger than 5 years or HIV-infected should receive prophylaxis with each exposure, after excluding TB disease.

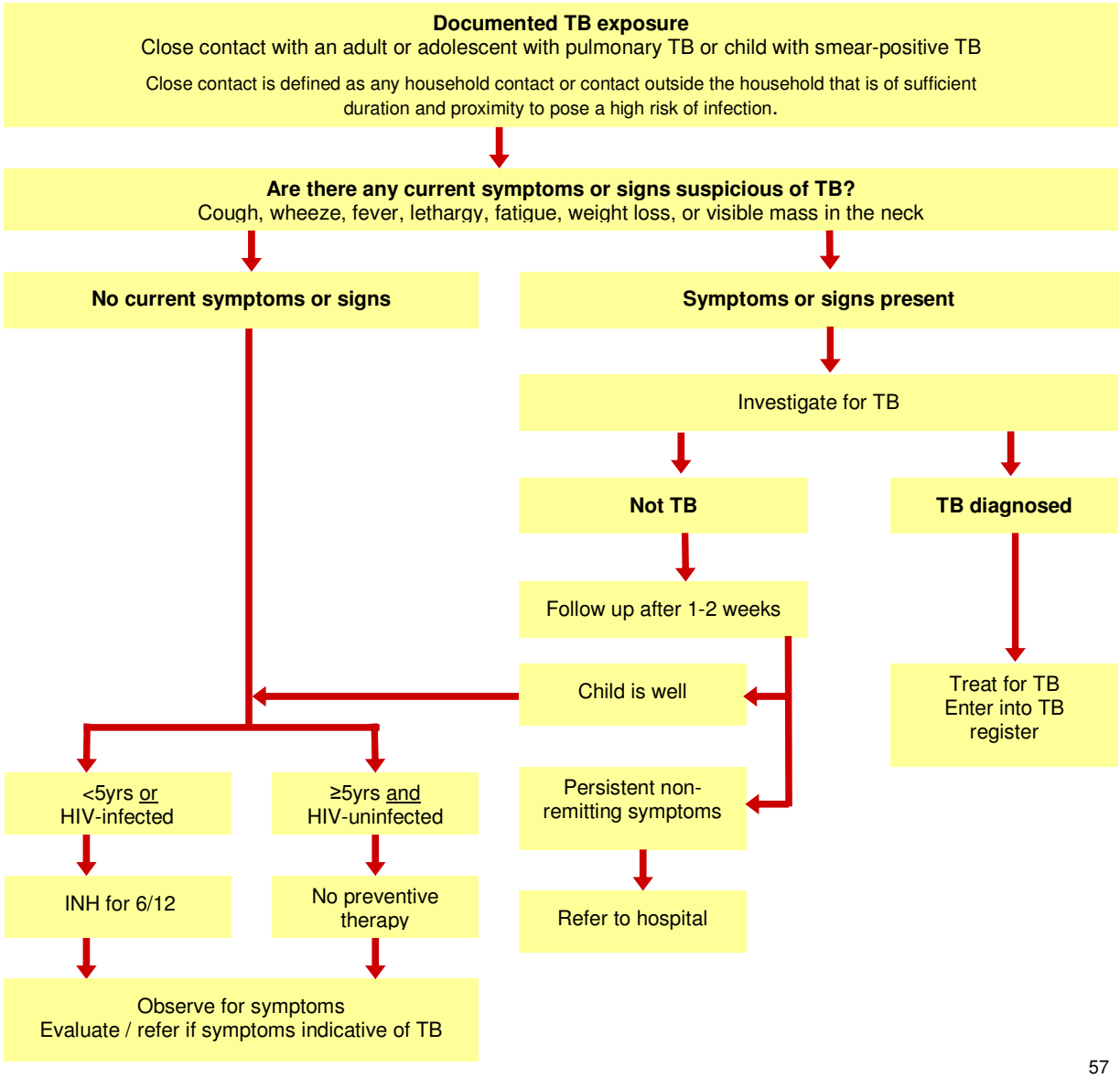
If the index case is an HIV positive parent, it is important to also check the HIV status of the child and to offer HIV testing.

The recommended regimen for TB prophylaxis is isoniazid (INH) 10 (10-15) mg/kg/day for 6 months. Caregivers should be advised to crush the appropriate fraction of the 100mg INH tablet and to dissolve it in water or multi-vitamin syrup before giving it to the child.

Table 11.1 Dosage recommendations for INH preventive therapy in children

Body weight	Daily isoniazid (INH) 100mg tablet
2 - 3.4 kg	1/4 tab
3.5 - 6.9 kg	½ tab
7 - 9.9 kg	1 tab
10 –14.9 kg	1 1/4 tabs
15 – 19.9 kg	1 ½ tabs
20 – 24.9 kg	2 tabs
25 – 29.9 kg	2 ½ tabs
≥ 30 kg	3 tabs

11.1.4 Algorithm for screening a child with documented TB exposure



11.1.5 A baby born to a mother with tuberculosis

A baby born to a mother diagnosed with TB in the last two months of pregnancy or who has no documented smear conversion needs to be carefully managed.

- The baby should not receive BCG at birth. The baby requires either full TB treatment if TB disease is diagnosed or INH prophylaxis if asymptomatic.
- If the baby is symptomatic:
  - The baby should be referred to a hospital for evaluation to exclude TB
  - If the baby has TB, the baby should receive a full course of TB treatment with regimen 3.
  - TB treatment should be started in a referral centre to ensure correct dosages.
- If the baby is asymptomatic:
  - The baby needs preventive therapy (isoniazid 10 mg/kg/day) for 6 months.
  - The baby should not initially receive BCG vaccination.
  - If the baby continues to be asymptomatic the BCG is administered after completion of the preventive treatment (unless the child is HIV infected or has symptoms suggestive of HIV infection).
  - If tuberculin is available, the child can be tested after 3 months of INH treatment. If the TST is negative and the mother has become sputum smear-negative, the INH can be stopped and the child given BCG vaccination (unless the child is HIV infected or has symptoms suggestive of HIV infection).

An HIV-uninfected mother on TB treatment should be encouraged to breastfeed. An HIV-infected mother she should be counselled about sole feeding options (sole breast feeding or sole formula feeding). Although anti-tuberculosis drugs are secreted in breast milk, the concentrations are very low and do not affect the baby. These low concentrations are too low to protect the baby.

11.2 TB disease

Risk factors for the progression from infection to TB disease include:

- Age of the child: Young children especially those under 2 years of age have the highest risk of developing disease. Another high-risk age group is adolescents who get infected for the first time during adolescence. Children going to primary school have the lowest risk.
- Immune suppression: HIV infected children, severely malnourished children, especially those with kwashiorkor, and following a bout of measles.
- Recent infection: most children who progress to disease do so within 12 months of being infected.

Children who are infected with drug resistant TB are at the same risk of developing disease as children infected with drug susceptible TB.

Young children (under 5 years of age), HIV-infected children and malnourished children have both an increased risk of infection as well as an increased risk of developing serious forms of TB like TB meningitis and disseminated or miliary TB.

Unlike tuberculous infection, which is asymptomatic, TB disease manifests with symptoms or physical signs of disease. The most common type of disease is pulmonary TB, characterised by hilar and/or mediastinal lymph gland enlargement.

11.3 Clinical presentation of TB

Children can present with TB at any age but it is commonest in the under-5 age group and during adolescence. The symptoms are those of a chronic disease, most of which are non-specific and overlap with other chronic diseases, especially HIV.

History and symptoms of TB disease:

- Contact with a smear and/or culture positive pulmonary TB case, especially if there is close contact (family member, person living in the same household, care-giver and in congregate settings such as crèches and pre-schools). Other information about the source case that is important is their response to treatment, as failure to respond might indicate exposure to a drug resistant source case.

- The commonest symptoms are chronic unremitting cough, fever, weight loss and unusual fatigue.
  - Chronic cough is a cough that has been present for more than 14 days and that is not improving, especially if the child fails to respond to a course of antibiotics (amoxycillin).
  - Fever of greater than 38^0C for 14 days after common causes like malaria or pneumonia have been excluded.
  - Children with weight loss, especially when documented on the "Road to Health" card should be investigated for TB. A child in a nutrition programme who fails to gain weight should also be investigated for TB.
  - Unusual fatigue: The child becomes less playful or complains of feeling tired.

Signs suggestive of TB disease:
- Fever, especially if present for more than 14 days without an obvious cause (such as malaria).
- Painless enlarged lymph glands, most commonly in the neck, that do not respond to a course of antibiotics.
- Other non-specific signs including night sweats, breathlessness (due to pleural effusion), peripheral oedema (due to pericardial effusion) or painful limbs and joints (due to erythema nodosum or dactylitis/inflammation of digits).

Although TB in children is a chronic disease, there are **danger signs** that require immediate referral to hospital as they indicate serious, life-threatening forms of TB:
- Headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (signs of TB meningitis)
- Meningitis not responding to treatment, with a sub-acute onset or raised intracranial pressure
- Big liver and spleen (signs of disseminated TB)
- Distended abdomen with ascites
- Breathlessness and peripheral oedema (signs of pericardial effusion)
- Severe wheezing not responding to bronchodilators (signs of severe bronchial compression)
- Acute onset of angulation (bending) of the spine.

11.4 Diagnosis of TB

The diagnosis of TB is based on a combination of history of exposure, clinical presentation, Mantoux test and chest x-ray. The approach to the diagnosis of TB in children depends on the resources that are available. In areas where Mantoux skin test and chest x-ray are limited, the diagnosis can still be made through taking a good history and doing a thorough clinical examination.

Indications for the evaluation of children as TB suspects include:
- Exposure to a smear or culture positive case of PTB.
- Indication of TB infection (Mantoux 10mm or more in HIV-negative or 5mm or more in HIV positive children).
- Symptoms suggestive of TB.
- HIV positive children should be screened for TB exposure and symptoms at each clinical visit.

HIV testing in childhood TB suspects:
A HIV test is important in the diagnosis of childhood TB. As with adults, the standard of care is to provide HIV counselling and testing to all child TB suspects and their parents/caregivers. Families should be given the necessary information about HIV to help make an informed choice about an HIV test. The HIV test should be strongly recommended and consent for testing sought (from parents or the legal guardian of children if younger than 12 years of age).
- In children younger than 18 months – An HIV ELISA or HIV rapid test is used for screening. A positive test could be due to maternal antibodies and an HIV DNA PCR test is used to confirm the diagnosis.
- In children over 18 months of age – HIV ELISA or HIV rapid tests are used both for screening and confirmation of the diagnosis.

The diagnosis of TB disease in HIV-infected children is exactly the same as for HIV-uninfected children except that there is greater uncertainty because:
- The symptoms of TB can be confused with the symptoms of HIV disease.
- The chest x-ray is more difficult to interpret.

Diagnosis of TB in children:

Any child presenting with a history of exposure to an infectious TB case or with confirmed infection (positive Mantoux) is regarded as a TB case if:

- There are symptoms of TB
  and
- An abnormal chest x-ray suggestive of TB

Any child presenting with symptoms of TB is regarded as a case of TB if there is:

- History of exposure to an infectious TB case or confirmed infection (positive Mantoux)
  and
- An abnormal chest x-ray suggestive of TB

The diagnosis can be confirmed by collecting a gastric aspirate or sputum for smear and culture.

In areas where a **chest x-ray is not available** a case of TB can be diagnosed in children:

- Presenting with symptoms of TB
  and
- A history of exposure to an infectious TB case or a positive Mantoux skin test.

All children who have been diagnosed with TB disease must be recorded in the TB treatment register and provided with a full course of the appropriate TB regimen. Trials of TB treatment are not recommended. A child either has TB or not. The TB treatment regimen should be continued until completion, unless an alternative diagnosis has been confirmed.

If a child has symptoms of TB and there is no history of exposure to an infectious TB case, the Mantoux is negative and the chest x-ray is normal, the child should be followed up as a TB suspect and an alternative diagnosis sought.

11.4.1 Chest x-rays

Chest x-rays need to be of good quality and the results depend on the expertise of the person reading them. A lateral chest x-ray is helpful in the evaluation of possible hilar lymph nodes. The most common radiological signs of TB in children are:

- An enlarged hilar region of the lung or a widened mediastinum due to enlarged hilar or mediastinal glands. Compression of the airways due to the enlarged lymph glands may be observed. The enlarged lymph glands can occlude the airway resulting in collapse of a lobe.
- A parenchymal lesion can enlarge causing widespread opacification in a segment or lobe of the lung.
- Acute dissemination causes widespread fine millet-sized (1-2 mm) lesions (miliary TB).
- Pleural effusions may occur in children older than six years.

The changes on chest x-ray are often non-specific and TB should not be diagnosed from the chest x-ray alone. The usefulness of the chest x-ray in HIV-infected children is reduced due to the overlap with other HIV related lung diseases e.g. lymphoid interstitial pneumonitis (LIP).

11.4.2 Smear and culture

Pulmonary TB in young children is usually smear-negative because the disease is paucibacillary (few organisms) and the collection of adequate samples is difficult. If conditions in the health facility allow, it is useful to collect gastric aspirates or fine needles aspirates from peripheral lymph nodes for staining and culture.

However, older children (8 years or older) should be able to produce sputum and sputum samples should be sent for smear and / or culture as per adult diagnostic algorithms.

TB cultures are of particular value in children with complicated TB or when drug resistance is of concern. Specimens for culture can be collected via gastric aspirates or induced sputum.

11.4.3 Diagnosis of extra-pulmonary TB

The commonest forms of extra-pulmonary TB are
- Lymph node involvement
- Pleural effusion
- TB meningitis
- Disseminated TB (miliary TB).

Lymph node TB can be diagnosed and treated in the primary heath care facility, but the other types of extra-pulmonary TB require referral to a hospital for diagnosis and initiation of treatment.

Table 11.2: Level of Care for Diagnosis and Evaluation of Extrapulmonary TB

Site of TB Disease	Practical approach to diagnosis	Level of diagnosis and initiation of treatment
Peripheral lymph nodes (especially cervical)	Fine needle aspiration (FNA) Lymph node biopsy	Primary health facility Hospital
Miliary TB (Disseminated TB)	Chest x-ray Lumbar puncture	Hospital
TB meningitis	Lumbar puncture (and CT scan where available) Chest x-ray	Hospital
Pleural effusion (older children and adolescents)	Chest x-ray, pleural tap for chemistry and culture	Hospital
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound and ascitic tap for chemistry and culture	Hospital
Osteoarticular TB	X-ray, joint tap, or synovial biopsy	Hospital
Pericardial TB	Ultrasound and pericardial tap	Hospital

11.4.4 Diagnosis of lymph node TB

Tuberculous external lymph nodes usually occur in the neck (cervical neck glands) and can be diagnosed as TB glands if the following are present:
- Glands present for more than 14 days
- There is no lesion on the head that could cause the lymph glands
- There is no response to antibiotics.

The child should be regarded as a case of extra-pulmonary TB, recorded as such and treated. The certainty of the diagnosis can be improved by a positive Mantoux skin test, chest x-ray and fine needle aspirate.

11.4.5 Diagnosis of TB meningitis

TB meningitis is a very serious form of TB in children. Complications include obstruction of cerebrospinal fluid (CSF) flow, hydrocephalus, inappropriate anti-diuretic hormone secretion, hemi- or quadriplegia, convulsions, deafness, blindness and mental retardation.

Typical history and symptoms include:
- Contact with an infectious TB case.
- Headache, especially if accompanied by early morning vomiting.
- Irritability, drowsiness, convulsions.
- Weight loss.

Physical signs include:
- Neck pain and resistance to neck flexion due to meningeal irritation.
- Cranial nerve palsies.
- Altered level of consciousness.

Investigations:
- Lumbar puncture - CSF has raised protein, low glucose, low chloride, predominantly lymphocytes; the gram stain is negative and acid fast bacilli are seldom found.
- The Mantoux skin test can however be negative and chest x-ray normal in children with TBM.

Always consider TB meningitis in children diagnosed with meningitis not responding to treatment. TB meningitis is a very serious form of TB and should not be treated at a primary health facility. These children should be urgently referred to a hospital for management.

11.5 Management of a child with TB

Children with TB usually have paucibacillary disease and are not a risk to other children or adults. However, some children, mainly school-aged children and adolescents, have smear-positive TB with cavities on chest x-ray. These children are as infectious as smear-positive adults and other children in contact with them must be investigated as if they were in contact with an adult infectious case.

When a young child is diagnosed with any form of TB, the parents and household contacts (if not already on TB treatment) should be carefully evaluated to make sure one of them is not the source case. The parents should receive advice on an adequate diet for the child and malnourished children should be provided with appropriate nutritional supplements.

All children on treatment for TB must be recorded in the TB register and should be reported to the TB programme as part of the routine quarterly cohort reports. The same case definitions apply to both adults and children. It is particularly important to document the age of the child in the register for reporting purposes.

As with adults, the standard of care is to provide HIV counselling and testing to all children with TB and their parents/caregivers. Families should be given the necessary information about HIV to help make an informed choice about an HIV test. The HIV test should be strongly recommended and consent for testing sought (from parents or the legal guardian of children if younger than 12 years of age).

Appropriate HIV-care is essential to help reduce morbidity and mortality of co-infected children. Whilst an HIV positive child is on TB treatment, it is the responsibility of the TB staff to ensure that the child accesses appropriate HIV care. Where possible, these services should be provided to the child at the same time as clinical visits for TB.

Important things to do in a child diagnosed with TB:
- Exclude HIV infection
- Refer HIV-infected children to the local HIV clinic
- Consider referral for nutritional support
- Complete the TB Register
- Make a note in the Road to Health Card
- Ask about other children or adults in the household and screen them for TB

11.5.1 Directly observed treatment short course

Children are treated using the same principles as adults and the DOTS Expansion and Enhancement Strategy is applicable to all clients with tuberculosis, including children. There should be direct observation of the treatment and fixed drug combinations should be used. The drug dosages depend on the body weight of the child and should be **adjusted as weight changes** during the course of treatment. Children should be weighed after 1 and 2 months of therapy and drug doses duly adjusted. Parents and caregivers should be counselled about TB and the importance of adherence to the treatment regime.

High success rates are achievable in children with uncomplicated TB and less severe forms of EPTB such as TB lymphadenopathy and pleural effusion. Like adults, children also receive 2 phases of treatment: an intensive phase of 2 months and a continuation phase of 4 months. Fewer drugs are required to treat paucibacillary TB because the risk of resistance is much lower due to the low numbers of bacilli. These children receive a regimen with 3 three drugs during the intensive phase (HRZ) and 2 drugs in the continuation phase (HR).

Children who are sputum smear-positive or have a cavity visible on chest x-ray have a high bacillary load and should be treated in the same way as newly diagnosed smear-positive adult clients on regimen 1. They are treated with 4 drugs (HRZE) in the intensive phase and 2 drugs (HR) in the continuation phase.

All children with severe forms of tuberculosis (meningitis, spine, peritonitis, miliary, skeletal) and those suspected of having MDR-TB (in contact with MDR case or not responding to first line therapy) should be referred for management. In these children the drug therapy may be given for a longer time but still through directly observed therapy (DOT). Children with severe disease are also treated with 4 drug regimens. It is important that on discharge from the hospital, the treatment is continued at the primary health facility at the drug dosages recommended by the referral centre.

Table 11.3: Recommended Doses For First-Line TB Drugs In Children

Drug	Dose (mg/kg)	Range (mg/kg)
Isoniazid (H)	10	10-15
Rifampicin (R)	15	10-20
Pyrazinamide (P)	35	30-40
Ethambutol (E)	20	15-25
Streptomycin (S)	15	12-18

11.5.2 Regimen 3: 2(RHZ) / 4 (RH)

2(RHZ)/4(RH) given 7 days a week is the recommended regimen for treatment of uncomplicated TB and EPTB such as lymph node TB and TB pleural effusion in children. Children should receive regimen 3 for 6 months and there should be direct observation of the treatment.

Table 11.4: Regimen 3 dosages for the treatment of uncomplicated TB in children younger than 8 years of age[4]

Body weight	Intensive Phase (2 months) Treatment given 7 days a week	Continuation phase (4 months) Treatment given 7 days a week
	RHZ* 60,30,150	RH 60,30
2 - 2.9 kg	½ tab	½ tab
3 - 5.9 kg	1 tab	1 tab
6 - 8.9 kg	1½ tabs	1½ tab
9 - 11.9 kg	2 tabs	2 tabs
12 - 14.9 kg	2½ tabs	2½ tab
15 - 19.9 kg	3 tabs	3 tabs
20 - 24.9 kg	4 tabs	4 tabs
25 - 29.9 kg	5 tabs	5 tabs
30 – 35.9 kg	6 tabs	6 tabs

R = rifampicin, H= isoniazid, P = pyrazinamide.

[4] At present, the fixed drug combinations (FDCs) available have a lower dose of INH than is currently recommended for children. The option of adding additional INH is not recommended to avoid the risk of INH monotherapy being administered and of complicating the treatment regimen. Dosages will be revised as soon as appropriate FDCs are available.

11.5.3 Regimens 1 and 2

Children with smear positive or cavitatory TB (usually about 5% of cases) should be treated with Regimen 1, using 4 drugs (RHZE) in the intensive phase and 2 drugs (RH) in the continuation phase, as with adults.

Children under 8-years of age, who are smear negative and who require retreatment, must be treated with Regimen 1. Those who are smear-positive treated with Regimen 2. If there is a poor response to treatment, children must be referred to a higher level of care for assessment.

Children above 8 years of age and adolescents should be treated like adult clients with Regimen I for newly diagnosed and Regimen 2 for retreatment cases.

Dosages for all regimens are calculated based on the child's weight.

11.5.4 Use of steroids in children with TB

Indications for oral steroids in children with TB include:
- TB meningitis
- TB pericarditis
- Mediastinal lymph glands obstructing the airways.
- Severely ill children with disseminated TB (miliary)

The dosage is prednisone 1-2 mg/kg daily orally for 4-6 weeks added to the TB drugs. The dose can be tapered to stop over 2 weeks.

11.5.5 Response to therapy

Children should be monitored at least on a monthly basis for the first 3 months. Children responding to therapy will have resolution of symptoms and will gain weight. This should include, at a minimum, a symptom assessment, an assessment of adherence, enquiry about any adverse events and weight measurement.

Medication dosages should be adjusted to account for any weight gain. Review the treatment card to assess adherence.

The chest x-ray is a poor indicator of response as the hilar and mediastinal lymph glands can enlarge as a result of the improvement in the immunity of the child. Therefore follow-up chest x-rays are not routinely required in children with uncomplicated TB, particularly as many children will have a slow radiological response to treatment. In an asymptomatic child, a routine chest x-ray is not indicated during or at the end of therapy.

Adolescents and younger children with smear-positive PTB should be followed through the same routine as adult clients. The response to treatment is evaluated by sputum examinations at 2 and at 5 months for cases on regimen 1 and at 3 and 7 months for cases on regimen 2 (See Chapter 8).

11.5.6 Immune reconstitution inflammatory syndrome (IRIS)

Temporary exacerbations of symptoms, signs or x-ray manifestations sometimes occur after beginning TB therapy. This can simulate worsening disease, with fever, increased size of lymph nodes or tuberculomas. It is usually the result of immune reconstitution brought about by improved nutritional status, TB treatment itself, or antiretroviral therapy (ART) in HIV-infected children.

TB treatment and ART should be continued, though in some cases the addition of corticosteroids might be useful. If in doubt, refer the child for evaluation.

11.5.7 A child who deteriorates on TB treatment

Children may sometimes deteriorate (experience a worsening of symptoms) despite adequate therapy; the most important questions to answer are:

- Is the drug dosage correct?
- Is the child taking the drugs as prescribed (good adherence)?
- Is the child HIV-infected?
- Was the child severely malnourished?
- Is there a reason to suspect drug-resistant TB (index case has drug resistant TB, is a re-treatment case or is also not responding to therapy)?
- Has the child developed IRIS?
- Is there another reason for the child's illness, other than or in addition to TB?

Any child with persistent symptoms or who deteriorates on TB treatment should be referred for assessment.

11.5.7 Adverse events

Adverse events caused by TB drugs are much less common in children than in adults. The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampicin, or pyrazinamide. Serum liver enzyme levels should not be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (<5 times normal values) is not an indication to stop treatment.

However, the occurrence of liver tenderness, hepatomegaly, or jaundice should lead to urgent referral for further investigation. Liver function tests should be performed and all drugs stopped. Clients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce hepatotoxic drugs until liver functions have normalized. An expert should be involved in the further management of such cases. If treatment for TB needs to be continued for severe forms of TB, non-hepatotoxic TB drugs should be introduced (e.g. ethambutol, an aminoglycoside and a fluoroquinolone).

Isoniazid may cause symptomatic pyridoxine deficiency, particularly in severely malnourished children and HIV-infected children on antiretroviral therapy. Supplemental pyridoxine at a dosage of 12.5 mg/day (½ tablet) is recommended in:

- Malnourished children
- HIV-infected children
- Pregnant adolescents.

11.6 MDR-TB in children

Children are as susceptible to drug resistant as to drug susceptible TB. Drug resistant TB is a laboratory diagnosis. Drug resistant TB should be suspected if any of the features below are present.

- **Features in the index case suggestive of MDR-TB**
  - Index case remaining smear-positive after 2 months of treatment
  - History of previous treatment of TB, treatment default or relapse after treatment, or treatment failure
- **Features in a child suspected of having drug resistant TB**
  - Contact with a known case of MDR-TB
  - Child not responding to the TB treatment regimen
  - Child with recurrence of TB after completing TB treatment.

The diagnosis and treatment of drug resistant TB in children is complex and children suspected of having MDR or XD- TB should be referred to a tertiary level bhospital for evaluation.

11.7 TB and HIV co-infection in children

HIV positive children are at increased risk of TB. Their parents are more likely to be HIV-infected, develop tuberculosis and increase the child's risk of exposure. The progression from infection to TB disease also occurs more frequently and rapidly in HIV-infected children.

These children often have other lung disease related to their HIV infection, including Pneumocystis jiroveci (PCP), lymphoid interstitial pneumonitis (LIP) and viral and bacterial pneumonias. The final common pathway of multiple lung infections is bronchiectasis and chronic lung disease for many HIV-infected children. Most of these diagnoses must be made clinically, often resulting in confusion about which opportunistic infections are causing the child's illness. There may be multiple and concurrent opportunistic infections, so the presence of one diagnosis does not exclude other causes of illness.

11.7.1 TB diagnosis in HIV positive children

In HIV positive children the diagnosis of tuberculosis is more complex because:

- The symptoms and signs of tuberculosis and those of other HIV related lung diseases could be indistinguishable. Symptoms such as chronic cough, weight loss and persistent fever are common to both HIV related lung disease and TB.
- The Mantoux skin test is frequently negative even though the child may be infected with TB or has TB disease.
- Although the radiological features are usually similar to that found in HIV-negative children, the picture could also be atypical. Radiological changes of HIV related lung diseases are confused with those caused by tuberculosis e.g. LIP may look very similar to miliary TB.
- The differential diagnosis of pulmonary TB in HIV-infected children is much broader and includes: bacterial pneumonia, viral pneumonia, fungal lung disease, pneumocystis jiroveci pneumonia (previously known as PCP), pulmonary lymphoma and Kaposi's sarcoma.

It is for these reasons that an HIV test is included as the standard of care in all child TB suspects. If there is uncertainty of the TB diagnosis, the child should be treated with antibiotics for 5-7 days and the chest x-ray repeated after two weeks depending on the clinical picture of the child.

There is both the risk that TB will be over-diagnosed in children and they will be treated unnecessarily or that TB may be missed, and therefore an opportunity to treat an HIV-infected child for a curable disease will also be missed. LIP is the most difficult condition to distinguish from TB due to radiological similarities, although LIP normally has typical clinical signs that include clubbing, parotid enlargement and generalised lymph gland enlargement. Bacteriologically confirmed TB can occur in children with an underlying diagnosis of LIP, bronchiectasis or any other lung infection.

In spite of the difficulties TB (if present) can be diagnosed with a fair degree of accuracy in the great majority of HIV infected children.

11.7.2 TB treatment

TB in HIV-infected children should be treated with the same six-month regimen as in HIV-uninfected children. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance and alternative diagnoses should be investigated in children who are not improving on TB treatment. As HIV infected children have a slower response to treatment, prolonged treatment for 9 months may be considered by a specialist.

A trial of TB treatment is not recommended in HIV-infected children. A decision to treat any child for TB should be carefully considered, and once this is done, the child should receive a full course of treatment, unless an alternative diagnosis is confirmed.

11.7.3 General HIV care for co-infected children

Once a child with TB has been diagnosed HIV positive, it is the responsibility of TB staff to ensure that the child and family receive appropriate HIV-related care, including:

- Counselling and social services support (eg. access to child support grants).
- Clinical and immunological (CD4%) staging of disease.
- Treatment of other concurrent opportunistic infections.
- Prophylaxis against other opportunistic infections (cotrimoxazole).
- Regular monitoring of growth and development.
- Nutritional supplements (including micronutirents).
- Appropriate completion of the immunisation schedule.
- Evaluation for antiretroviral therapy.

- Referral for palliative care if required.

Table 11.5: World Health Organisation Staging Of Children With Confirmed HIV Infection
Stage One
1 Asymptomatic
2 Persistent generalised lymphadenopathy (PGL)
Stage Two
3 Hepatosplenomegaly
4 Papular pruritic eruptions
5 Seborrhoeic dermatitis
6 Extensive human papilloma virus infection
7 Extensive molluscum contagiosum
8 Fungal nail infections
9 Recurrent oral ulcerations
10 Lineal gingival erythema (LGE)
11 Angular cheilitis
12 Parotid enlargement
13 Herpes zoster
14 Recurrent or chronic RTIs (otitis media, otorrhoea, sinusitis)
Stage Three
15 Moderate unexplained malnutrition not adequately responding to standard therapy
16 Unexplained persistent diarrhoea (14 days or more)
17 Unexplained persistent fever (intermittent or constant, for longer than one month)
18 Oral candidiasis (outside neonatal period)
19 Oral hairy leukoplakia
20 Acute necrotizing ulcerative gingivitis/periodontitis
21 Pulmonary (intrathoracic) TB and cervical TB adenitis
22 Severe recurrent presumed bacterial pneumonia
23 Unexplained anaemia (<8g/dl), and or neutropenia (<1000/mm3) and or thrombocytopenia (<50 000/ mm3) for more than one month
24 Chronic HIV-associated lung disease including brochiectasis
25 Symptomatic lymphoid interstitial pneumonitis (LIP)
Stage Four
26 Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy
27 Pneumocystis pneumonia
28 Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
29 Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration)
30 Extrathoracic TB, except cervical TB adenitis
31 Kaposi's sarcoma
32 Oesophageal candidiasis
33 CNS toxoplasmosis (outside the neonatal period)
34 HIV encephalopathy
35 CMV infection (CMV retinitis or infection of organs other than liver, spleen or lymph nodes; onset after 1 month of age)
36 Extrapulmonary cryptococcosis including meningitis
37 Crytosporidiosis
38 Isosporiasis
39 Disseminated non-tuberculous mycobacterial infection
40 Candidiasis of trachea, bronchi or lungs
41 Visceral herpes simplex infection
42 Acquired HIV-associated rectal fistula
43 Cerebral or B-cell non-Hodgkins lymphoma
44 Progressive multifocal leucoencephalopathy (PML)
45 HIV-associated cardiomyopathy or nephropathy

11.7.4 Cotrimoxazole prophylaxis

Daily cotrimoxazole prophylaxis prolongs survival in HIV-infected children and reduces the incidence of respiratory infections and hospitalization. All HIV-infected children should be started on cotrimoxazole, which should be continued until antiretroviral therapy is commenced and immune reconstitution occurs in a child over 1-year of age.

The recommended dosage for children is trimethoprim 6-8 mg/kg, sulphamethoxazole 20 mg/kg. Cotrimoxazole syrup contains trimethoprim/ sulphamethoxazole 40/200mg and the recommended dosage is therefore 0.625 ml/kg.

Table 11.6: Cotrimoxazole Prophylaxis Dosing Schedule For Children

Weight	Cotrimoxazole (ml)
<5 kg	2.5 ml
5-9.9. kg	5 ml
10-14.9 kg	7.5 ml
15-21.9 kg	10 ml or 1 single (480mg) strength tablet
>22 kg	15 ml or 1.5-2 single (480mg) strength tablets

11.7.5 Antiretroviral therapy

All children with TB and HIV co-infection require antiretroviral therapy (ART). Clinical criteria for eligibility for ART include any one of the following:

- Recurrent hospitalisations (>2 episodes per year) or prolonged hospitalisation (> 4 weeks)
- WHO Clinical Stage 3 or 4 disease (See Table 11.4)
- CD4 <20% for children under 18 months and <15% if over 18 months

Children with intrathoracic TB and cervical TB adenitis are classified as WHO Stage 3

Children with extrathoracic TB without cervical TB adenitis are classified as WHO Stage 4.

All HIV-infected children with TB therefore meet the criteria for ART.

Appropriate arrangements for access to antiretroviral drugs should be made for children who meet the clinical indications for treatment and where a caregiver is available to supervise ART treatment.

In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment is the priority. The optimal timing for initiation of ART during TB treatment is not known. The decision on when to start ART after starting TB treatment involves a balance between the child's severity of disease, pill burden, potential drug interactions, overlapping toxicities and possible immune reconstitution syndrome versus the risk of further progression of immune suppression and the associated increase in mortality and morbidity. Many clinicians will start ART 4-8 weeks after starting TB treatment in a severely immune compromised child.

If a child presents with TB before starting ART:

- Stage 3 disease and CD4 is >20% (under 18 months) and >15% (over 18 months)
  - Can complete the TB treatment before starting ART
- Stage 4 disease and CD4 is <20% (under 18 months) and <15% (over 18 months)
  - Start ART after 4 – 8 weeks of TB treatment
- Suggested first line regimen is stavudine (D4T), lamivudine (3TC) and either Kaletra® (if failed PMTCT, <3 years-old or <10kg in weight) or efavirenz.
- If the child is started on Kaletra® – current recommendations are to use use “boosted” Kaletra® (providing additional ritonavir so that the dose of lopinavir and ritonavir is equivalent) for the duration of TB therapy and for 1-2 weeks after TB therapy is stopped.
- Monitor ALT monthly

For further information refer to the latest National Antiretroviral Treatment Guidelines, National Department of Health

Rifampicin causes liver enzyme induction, resulting in significantly reduced serum drug levels of nevirapine and lopinavir, the active protease inhibitor contained in Kaletra®. Therefore, the doses of these two drugs

need to be adjusted during concurrent TB and HIV treatment. The liver enzyme induction caused by rifampicin persists for 1-2 weeks after rifampicin is stopped.

Immune reconstitution inflammatory syndrome (IRIS) has been observed in clients on TB treatment who start ART. This syndrome is characterized by a worsening of disease after initial clinical improvement (hence also sometimes known as a paradoxical reaction). The reaction may occur during the first three months of ART, is generally self-limiting and lasts 10-40 days.

If a child develops TB on ART, the regimen may need to be changed as follows:

- If on Kaletra® (lopinavir and ritonavir)
  - Use "boosted" Kaletra® (see above)
- If on nevirapine and less than 3 years old or 10kg in weight
  - Switch to "boosted" Kaletra®
- If on nevirapine and over 3 years old and 10kg in weight
  - Switch to efavirenz (no dose adjustment necessary)
- Monitor ALT monthly
- If any severe adverse effects are noted – discuss with a local TB AND HIV expert

The development of TB in a child on ART could be indicative of immune reconstitution, due to a new TB infection or failure of the ART regimen. TB treatment should be started without delay in these children.

Clinically significant drug interactions occur between the rifamycins, especially rifampicin, and some of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). The adverse events of the TB drugs and the antiretroviral drugs are similar and can cause confusion as to which drugs need to be stopped.

Given the complexity of co-administration of TB treatment and antiretroviral therapy, consultation with an expert in this area is recommended before initiation of concurrent TB treatment and ART.

Recommended antiretroviral treatment regimens evolve rapidly. This document reflects protocols from the current "Guidelines for the management of HIV-infected children, National Department of Health, 2005" and "National Antiretroviral Treatment Guidelines, National Department of Health, 2004". Consult revised guidelines for new recommendations as these become available.

12 TB AND HIV

12.1 Introduction

HIV infection leads to progressive immunodeficiency and increased susceptibility to infections, including TB. As HIV infection progresses, CD4 lymphocytes decline in number and function. The immune system is less able to prevent the growth and local spread of Mycobacterium tuberculosis, leading to the progression of recent or latent TB infection to active TB disease.

In the absence of HIV infection, only about 10% of people infected with M. tuberculosis get sick with TB during their lifetime. In people with HIV, about 50% will develop active TB disease at some stage. Currently, about 53% of TB clients are co-infected with HIV in South Africa. The high levels of active TB in persons living with HIV and AIDS poses an increased risk of TB transmission to the general community.

HIV not only increases the number of TB cases but also alters the clinical course of TB disease. Although tuberculosis can occur at any point in the course of progression of HIV infection, the clinical pattern of disease changes. As HIV related immunosuppression increases, there are increasing numbers of smear-negative pulmonary TB, extra-pulmonary TB and cases of disseminated TB. TB is also more difficult to diagnose as immunosuppression progresses. Co-infected clients have an increased mortality due both to late diagnosis and other opportunistic infections.

Three approaches can help to minimise the impact of TB on those with HIV:

1. TB preventive therapy to reduce an individual client's risk of developing TB
2. Early, prompt diagnosis of TB through intensified case-finding
3. Appropriate case management of TB including the provision of comprehensive HIV care to the co-infected

This will prolong the lives of people living with HIV and AIDS, help minimize the negative effects of TB on the course of HIV and interrupt the transmission of M. tuberculosis. In terms of priorities, the most effective way of breaking the transmission chain and preventing infection and disease in the community is to find and cure infectious cases of TB.

12.2 TB preventive therapy

TB preventive therapy with isoniazid (INH 5mg/kg daily up to a maximum 300mg per day) for 6 months has been shown to decrease the risk of TB disease in those with latent TB and is part of the package of care for people living with HIV. It does not aim to control TB on a public health scale and it is not an alternative to the DOTS strategy for controlling TB. It is an effective intervention for HIV infected individuals prior to starting antiretroviral therapy (ART).

It is critical to exclude active TB before starting preventive therapy. This avoids the provision of INH monotherapy to clients with active TB who require a full course of TB treatment. Failure to do so poses a threat, as clients will not be cured of TB, risk death and can develop resistance to INH.

To exclude TB, specifically ask about signs and symptoms of tuberculosis:

- Cough for more than 2 weeks
- Fever for more than 2 weeks
- Drenching night sweats
- Weight loss of greater than 5 % of body weight in the past 4 weeks: weight should be measured at each clinic visit to document weight loss. A weight loss of more than 5 % of body weight is an indicator to screen for TB.

All clients with one or more of the symptoms and signs must be investigated further for TB and are not eligible for TB preventive therapy, until TB is excluded. Two sputum specimens must be collected for microscopy and a third for culture.

Trials have shown that a routine chest x-ray does not improve case detection. Chest x-ray is an additional barrier for people to access TB preventive therapy and is therefore not recommended in the routine screening for preventive therapy.

12.2.1 Eligibility for TB preventive therapy

TB preventive therapy is beneficial to HIV positive people with latent TB as indicated by a positive tuberculin skin test. TB preventive therapy sterilises latent TB infection. It should not be considered in clients with active tuberculosis within the past 2 years, as they would not have latent bacilli if adequately treated. Two years is used as a pragmatic cut-off point; clients who were treated for tuberculosis more than 2 years earlier may have been re-infected with TB and should be screened for preventive therapy.

All HIV positive people with no signs and symptoms of TB and a positive tuberculin skin test (transverse induration ≥5mm diameter) or a PTB contact are eligible for TB preventive therapy.

Particular consideration should be given to the following populations: miners, prisoners, TB contacts of infectious cases and health care personnel.

The following people are not eligible for TB preventive therapy:

- Clients with active liver disease or alcohol abuse are not eligible because of potential hepatotoxicity of INH
- Clients requiring or on ART are not eligible. The added benefits of INH prophylaxis are unclear and the additional pill burden undesirable. Clients already on INH preventive therapy who start ART can complete their INH preventive therapy as there is no interaction between INH and the current ART regimen used.

12.2.2 When and how to start TB preventive therapy

All HIV positive clients should be educated about the signs and symptoms of TB and encouraged to present early to health facilities if these occur. They should also be informed of the benefits of TB preventive therapy. It is not recommended that TB preventive therapy be offered immediately after giving the HIV test result to the client. Evaluation for TB preventive therapy should be part of the baseline clinical assessment for those with HIV and should only takes place once the CD4 count and WHO clinical stage are known.

At the first visit:

- The client is screened for TB symptoms. It is essential to exclude active tuberculosis. Specifically enquire about all of the signs and symptoms of TB. If symptomatic, the client should be investigated for TB.
- If the client has no symptoms of TB, has not had TB in the last 2 years, does not have liver disease or alcoholism and is not eligible for ART, do a tuberculin (Mantoux) skin test (See Annexure 1 for full details). Ask the client to return to the clinic in 48 – 72 hours to read the Mantoux skin test

At the second visit:

- Read the Mantoux test. The reaction at the site of the injection is measured noting the widest **transverse** point across the edges of the raised, thickened area.
- To help measure accurately, mark the edges of the induration at the widest point with a pen and measure the exact distance between the two points in millimetres.
- In an HIV positive client, a positive Mantoux test is equal to or greater than 5mm in diameter
- Provide a 1-month supply of isoniazid (INH) 5mg/kg daily (up to a maximum 300mg per day) to all asymptomatic adults with a positive Mantoux or PTB contact.
- Provide vitamin B6 (Pyridoxine) 50 mg daily to prevent peripheral neuropathy
- Counsel the client about the importance of adherence, possible side effects of INH (particularly hepatitis) and the symptoms of active TB. Emphasise the importance of seeking care if they develop side effects to INH or symptoms of TB. Clarify that TB preventive therapy decreases the risk of getting TB but the TB may still occur.

At monthly visits:

- Screen symptomatically for TB at every visit and do appropriate tests if symptomatic
  - If the client develops active TB, stop the preventive therapy and start the full TB treatment regimen. Do sputum culture and drug susceptibility testing.
- Ask about side effects to INH (peripheral neuropathy; jaundice and vomiting due to hepatitis)
  - If peripheral neuropathy develops prescribe 100 mg pyridoxine (vitamin B6) daily until symptoms disappear
  - If the client develops signs and symptoms suggestive of hepatitis, stop INH preventive therapy immediately and refer for further investigations and assessment.
- Monitor adherence to preventive therapy
  - Do pill counts
  - If adherence to preventive therapy is poor or the client interrupts therapy, enquire about the possible reasons and counsel on the importance of adherence
  - If the client interrupts for the second time, consider stopping the preventive therapy
  - Ensure that the 6-month's therapy is taken within a 9-month period.

12.3 Diagnosis of TB in HIV positive clients

Tuberculosis can occur at any point in the course of HIV infection. Pulmonary tuberculosis is the most common manifestation of tuberculosis in adults infected with HIV. The clinical pattern of tuberculosis correlates with the client's immune status:

- In the early stages of HIV infection when immunity is only partially compromised, the features are more typical of post-primary or secondary TB.
- As immune deficiency worsens, HIV-infected clients present with atypical pulmonary disease resembling primary TB or with extra-pulmonary TB or disseminated disease.

Table 12.1: Clinical picture, sputum smear and chest x-ray appearance in HIV infection

	Early HIV Infection	Late HIV Infection
Clinical picture	Often resembles post-primary TB	Often resembles primary TB
Sputum smear results	Often positive	Often negative
Chest X-ray appearance	Often cavities	Hilar lymphadenopathy, infiltrates, no cavities. Can be normal.

Unlike many other infections that develop when the CD4 counts falls below 250/mm^3, TB develops when the CD4 count falls below 400/ mm^3. This means that TB is one of the earlier infections to occur in an HIV positive client; it may therefore happen that TB is diagnosed before HIV in co-infected clients.

12.3.1 Diagnosis of pulmonary tuberculosis

Clinical features:
Generally there is little difference between the clinical presentation of TB in HIV positive and HIV-negative clients. However, among HIV positive clients cough is reported less frequently, probably because there is less cavitation, inflammation and endobronchial irritation as a result of decreased cell-mediated immunity. Similarly, haemoptysis, which results from caseous necrosis of the bronchial arteries, is less common.

Sputum Microscopy and Culture:
Sputum microscopy is the cornerstone to diagnosis of TB even in high HIV-prevalence areas. All clients suspected of having TB should have two sputum specimens collected for microscopy and culture. HIV positive, smear-positive clients tend to excrete significantly fewer organisms per ml of sputum than HIV-negative clients, which can lead to AFB being missed if the appropriate numbers of sputum samples and high power fields are not examined microscopically.

Sputum culture is the gold standard for TB diagnosis. Amongst those with previous TB, a sputum culture and DST is done routinely. In an HIV positive client with no previous TB two initial sputum specimen should be collected for a smear and a third for culture if the first two are smear negative or discordant to confirm the diagnosis. The diagnosis of smear-negative, culture-positive TB requires a negative sputum smear result

and a positive sputum culture. The use of culture as part of the diagnostic algorithm substantially improves the diagnosis of TB in HV-positive clients.

Amongst those with HIV, smear-negative pulmonary TB has a worse prognosis than smear-positive pulmonary TB, probably reflecting a greater degree of immunosuppression. Delays in the diagnosis of TB have been associated with worse outcomes, so initiation of treatment as soon as possible is recommended.

The advent of HIV has made the diagnosis of TB more difficult, and the false diagnosis of TB is probably not infrequent among clients affected by other HIV-related pulmonary illnesses. These false-positive diagnoses account for a small proportion of all forms of TB notified, and do not negate the huge increases observed in TB notifications in HIV-endemic areas.

12.3.2 Extra-pulmonary tuberculosis

Extra-pulmonary disease has been reported in up to 70% of HIV-related TB cases when the CD4 count is less than 100 cells/mm^3. The main types of extra-pulmonary TB seen in HIV-infected clients are lymphadenopathy, pleural effusion, pericardial effusion and miliary TB.

Presentation of extra-pulmonary TB is generally no different between HIV positive and HIV-negative clients, however:

- HIV-related TB lymphadenopathy can occasionally be acute and resemble an acute pyogenic bacterial infection. Diagnosis can be made using simple techniques such as needle aspiration and examination of direct smears.
- In TB meningitis, the CSF may be completely normal in HIV-infected persons.
- Pericardial TB is not rare and may be diagnosed presumptively based on the characteristic balloon-shaped appearance of cardiac shadow on chest X-ray.
- Disseminated TB may be difficult to diagnose.

The definitive diagnosis of extra-pulmonary TB is often difficult because of the scarcity of diagnostic facilities.

12.3.3 TB recurrence

There are 2 possibilities for TB recurring after a previous cure:

- True relapse: reactivation of Mycobacterium tuberculosis persisters not killed by TB drugs.
- Re-infection: due to re-exposure to another source of infection.

The proportions of recurrences due to each are not known. The relapse rate of TB is low in HIV-infected TB clients who complete a rifampicin containing short-course treatment regimen. Relapse is more common with self-administered compared to directly observed treatment.

12.3.4 Multi-drug resistant TB

Outbreaks of multi-drug resistant TB have been reported amongst HIV positive clients in various countries. Whilst the risk of MDR-TB is the same as that of drug susceptible TB, HIV fuels the spread of MDR-TB by increasing susceptibility to infection and accelerating the progression from infection to disease.

12.4 Treatment of TB in HIV positive clients

In general, TB treatment is the same for HIV positive and HIV-negative clients.

12.4.1 Response to treatment

Clients who complete treatment show the same clinical, x-ray and microbiological response to short-course treatment irrespective of whether they are HIV positive or negative. The only exception might be with weight gain, which is usually slower in HIV positive than in HIV-negative clients.

12.4.2 Side effects to TB drugs

Adverse drug reactions are more common in HIV positive than in HIV-negative TB clients. The risk of drug reactions increases with increased levels of immunosuppression. Most adverse reactions occur in the first 2 months of treatment.

- Skin rash is the commonest reaction; fever often precedes and accompanies the rash. Mucous membrane involvement is common. The drugs usually responsible are streptomycin and rifampicin. Severe skin reactions, which may be fatal, include exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis.
- The commonest reactions necessitating a change in treatment include gastrointestinal disturbances and hepatitis.
- There is an increased risk of rifampicin associated shock and thrombocytopenia.

12.4.3 Case fatality

HIV positive clients have higher mortality rates during and after TB treatment compared to HIV-negative clients. This is partly due to TB itself, but largely due to other HIV-related problems like septicemia, diarrhoea, pneumonia, anaemia, Kaposi's sarcoma and cryptococcal meningitis.

Direct observation of treatment (DOT) is even more important for HIV positive TB clients to ensure treatment completion and prevent the emergence of MDR–TB. Self-administration of treatment is associated with higher case fatality rates.

Common HIV-related infections (pneumonia, diarrhoea, fungal infections) cause considerable morbidity during treatment of HIV-infected TB clients and contribute to the increased case fatality rate. Providing clients with appropriate HIV care during TB treatment helps to prevent, identify and treat these infections early.

12.5 Diagnosis of HIV in TB clients

The definitive diagnosis of HIV infection rests on a positive HIV test. The standard of care required in TB services is to provide HIV counselling and testing to all TB clients. Clients should be given the necessary information about HIV to help make an informed choice about an HIV test. All clients should be strongly advised to have an HIV test and consent sought for testing. In children under 12 years of age, parents or the legal guardian of the child should be counselled and asked to provide consent for the test. Ideally, the offer of an HIV test should take place soon after the initiation of TB treatment, as the morbidity and mortality of co-infected clients is highest in the first 2 months of treatment.

The benefits of counselling and testing for TB clients include:

- The opportunity for clients to know their HIV status and prognosis.
- Early diagnosis and management of other HIV-related illnesses.
- Opportunities for prevention of other infections (e.g. using cotrimoxazole).
- Access to HIV care (psychosocial, nutritional, medical)
- Decreased HIV transmission and re-infection through condom use.

12.6 HIV care for co-infected adult TB clients

Appropriate HIV-care of co-infected clients is essential to help reduce their morbidity and mortality. Whilst an HIV positive client is on TB treatment, it is the responsibility of the TB staff to ensure that the client is provided with or accesses appropriate HIV care. Where possible, these services should be provided to the client at the same clinical visits for TB.

All HIV positive clients require a baseline HIV assessment soon after confirmation of diagnosis to help determine the extent of progression of their HIV and their HV treatment plan.

Components of HIV care to be provided to TB and HIV co-infected clients include:

- WHO Clinical Staging (see Table 12.2)
  - HIV positive clients with PTB are classified as at least WHO Stage 3. If the client has any other Stage 4 defining illness at present or in the past, they are classified as WHO Stage 4.
  - Clients with EPTB are classified as WHO Stage 4.
  - All WHO Stage 4 clients require antiretroviral therapy.
  - WHO staging should be repeated when the client presents with any major new illness or on a regular basis.
- Immunological staging with CD4 counts:
  - The CD4 count assesses the number of T-helper immune cells in the blood and is an indication of the level of immunosuppression.
  - If the CD4 count is less than 200 cells/mm^3, refer the client for ART.
  - If the CD4 count is less than 50 cells/mm^3 the client urgently requires ART.
  - Repeat the CD4 count annually if it is greater than 350 cells/mm^3 and 6-monthly if between 200-350 cells/mm^3.
  - It is beneficial for the client to have an early CD4 count, despite the fact that the CD4 count will recover during TB treatment. The rationale is that in South Africa ART is commenced at lower CD4 counts (below 200 rather than the 350 used in some countries) and even with moderate CD4 recovery, the client would still benefit from ART. In addition, many clients are found to have very low CD4 counts and the early morbidity and mortality in these clients is high.
  - If the client is WHO Stage 3 and has a CD4 count of more than 200 cells/mm^3, ART is not yet required. Treat the client's TB; the need for ART should be reassessed on completion of TB treatment.
- An RPR test to screen for syphilis.
- PAP smears for all HIV positive women.
- Symptomatic screening for STI's at every visit and syndromic management of STI's.
- Reproductive health-care with an emphasis both on effective contraception whilst on TB treatment and the use of condoms to prevent transmission of HIV and to avoid re-infection.
- Cotrimoxazole prophylaxis against opportunistic infections.
- Diagnosis and management of other opportunistic infections.
- Nutritional assessment and the provision of nutritional supplements.
- A social assessment including:
  - Family circumstances and the status of caregivers.
  - Identification of orphans or vulnerable children.
  - Applications for disability grants, child support grants or care dependency grants.
- On-going counselling support
  - To assess how the client is dealing with their HIV status.
  - To discuss disclosure and support available to the client.
  - To emphasise messages about reducing re-infection and transmission through safer sexual practices.
  - To reinforce good adherence to treatment.

All HIV positive TB clients should be provided both with TB and HIV care at clinical visits. This will help reduce morbidity and mortality of co-infected clients and help improve treatment outcomes. It is important to ensure that the clients discharged from the TB programme access on-going HIV care.

12.7 Cotrimoxazole prophylaxis

Prophylaxis against inter-current infections decreases morbidity and mortality in HIV positive TB clients. Cotrimoxazole prophylaxis is highly effective in preventing pneumocystis carinii pneumonia and toxoplasmosis. It also has activity against pneumococcus, Salmonella and Nocardia. Cotrimoxazole prophylaxis has been shown to decrease hospitalisations and mortality in HIV infected TB clients and has been recommended as part of a minimum package of care for HIV positive adults and children.

The national HIV and AIDS Policy Guideline recommends trimethoprim/ sulphamethoxazole (cotrimoxazole) 160/ 800mg (960mg) daily for all HIV positive adults (whether they have TB or not) who:

- Have symptomatic HIV disease (WHO Clinical stage 2,3 or 4), or
- Have a CD4 count less than 200 cells/mm^3, or

- Have already had pneumocystis carinii pneumonia (also known as pneumocystis jiroveci).

HIV positive clients with TB are all in WHO clinical stage 3 (PTB) or 4 (EPTB). It is therefore recommended that all HIV positive TB clients be provided with cotrimoxazole prophylaxis:

- Wait until the client has completed one month of TB treatment. This helps differentiate between side effects from TB drugs and from cotrimoxazole.
- Counsel clients on the effectiveness and side effects of cotrimoxazole:
  - That cotrimoxazole can help prevent pneumonia and other infections
  - That it is only effective while the client takes it, so it should be taken for the rest of their lives (unless on ARVs with CD4 count recovery to above 200)
  - That it can cause a rash and other side effects.
  - Provide cotrimoxazole 960mg (2 single strength or 1 double strength tablet) daily to adults.

Table12.2: World Health Organisation Clinical Staging For Adults

Stage One

1 Acute retroviral infection (seroconversion illness)
2 Asymptomatic
3 Persistent generalised lymphadenopathy

Stage Two

4 Unintentional weight loss < 10% of body weight
5 Minor mucocutaneous (e.g. seborrhoea, prurigo, fungal-nail infections, oral ulcers, angular cheilitis)
6 Herpes zoster within the last five years
7 Recurrent upper respiratory tract infection (e.g. bacterial sinusitis)

Stage Three

8 Unintentional weight loss > 10% of body weight
9 Chronic diarrhoea > one month
10 Prolonged fever > one month
11 Oral candidiasis
12 Oral hairy leukoplakia
13 Pulmonary TB within the last year
14 Severe bacterial infections (pneumonia, pyomyositis)
15 Vulvovaginal candidiasis > one month / poor response to therapy

Stage Four

16 HIV wasting (weight loss > 10% and diarrhoea or fever for > 1month)
17 Pneumocystis carinii pneumonia
18 CNS toxoplasmosis
19 Cryptosporidiosis diarrhoea > one month
20 Isosporiasis diarrhoea
21 Cytomegalovirus infection other than liver, spleen or lymph node
22 Herpes simplex infection (visceral or > one month mucocutaneous)
23 Progressive multifocal leucoencephalopathy
24 Disseminated mycosis
25 Candidiasis of the oesophagus, trachea or lungs
26 Atypical mycobacteriosis disseminated
27 Non-typhoidal Salmonella septicaemia
28 Extra-pulmonary tuberculosis
29 Lymphoma
30 Kaposi's sarcoma
31 HIV encephalopathy
32 Recurrent pneumonia

12.8 Antiretroviral therapy and TB

Co-infected clients who are WHO Stage 4 **or** have a CD4 count below 200/mm^3 require ART. Those who are WHO Stage 3 and have a CD4 count above 200/mm^3 do not require ART at present and should be reassessed for ART after completing TB treatment.

Antiretroviral therapy (ART) is not a cure for HIV and AIDS. It is effective only in slowing down the replication of the virus. The drugs act by blocking the enzymes involved in the replication and function of the human immunodeficiency virus. They have to be used in combination, usually of 3 drugs, to prevent the development of drug resistance.

There are 3 categories of antiretroviral drugs:
- Nucleoside reverse transcriptase inhibitors (NRTI) e.g. zidovudine, didanosine, zalcitabine, stavudine, lamivudine and abacavir.
- Non-nucleoside reverse transcriptase inhibitors (NNRTI) e.g. nevirapine and efavirenz.
- Protease inhibitors (PI) e.g. ritonavir, lopinavir, saquinavir and idinavir.

The management of TB therapy and ART is determined by whether the client develops TB whilst on ART or presents with TB before commencing ART. Three issues complicate the co-management of TB and ART:
- The interaction of rifampicin with NNRTIs and Pis.
- Increased drug toxicity.
- Increased pill burden and the impact on adherence.

12.8.1 Drug interactions

Nucleoside reverse transcriptase like zidovudine, didanosine, zalcitabine, stavudine, lamivudine and abacavir can be safely co-administered with anti-tuberculosis drugs.

Isoniazid, ethambutol, pyrazinamide and streptomycin can be concurrently used with protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

Rifampicin stimulates the activity of the cytochrome P450 liver enzyme that metabolizes PIs and NNRTIs. This can lead to a reduction in the blood levels of PIs and NNRTIs. PIs and NNRTIs can also enhance or inhibit this same enzyme system and lead to altered blood levels of rifampicin. The potential drug interactions may result in ineffectiveness of antiretroviral drugs, ineffective treatment of TB, increased risk of drug toxicity as well as potential development of resistance.

If a protease inhibitor or non-nucleoside reverse transcriptase inhibitor is to be started after giving rifampicin, then at least two weeks should elapse after the last dose of rifampicin. This time gap is necessary for a reduction of the enzyme inducing activity of rifampicin prior to commencing antiretroviral drugs.

Table 12.4: Shared Side Effects of TB and Antiretroviral Therapy

Side effects	Antiretroviral treatment	Tuberculosis treatment
Nausea and vomiting	Didanosine, zidovudine, ritonavir, saquinavir	Pyrazinamide
Hepatitis	Nevirapine, efavirenz	Rifampicin, isoniazid, pyrazinamide
Peripheral neuropathy	Stavudine, didanosine	Isoniazid
Rash	Nevirapine, efavirenz	Rifampicin, isoniazid, pyrazinamide

12.8.2 Client develops TB while on antiretroviral therapy

Antiretroviral therapy should be continued throughout TB treatment, with changes to the regimen and monitoring as follows:
- **Regimen 1:** A change to efavirenz is recommended for clients on nevirapine wherever possible. If this is not possible (e.g. intolerant of efavirenz or significant risk of falling pregnant), nevirapine may be continued in selected cases, with monthly ALT monitoring. Discuss these cases with an antiretroviral

expert.

- **Regimen 2:** Lopinavir / ritonavir 400/100mg every 12 hours should change to lopinavir / ritonavir 400/400 mg every 12 hours (increasing the dosage of ritonavir by adding three extra capsules of ritonavir). This should be continued until 2 weeks after completion of TB treatment, when the extra ritonavir can be stopped.

12.8.3 Client presents with TB before commencing antiretroviral therapy

- The optimal time to commence ART in a co-infected client is unknown. Mortality in the first 2 months of TB treatment is high, especially if HIV disease is advanced, and early ART can be life saving.
- If the client is WHO Stage 4 or has a CD4 count of 50-200 cells/mm^3, start TB treatment and add ART after completing 2 months of TB treatment.
- However, if the client has a CD4 count of less than 50 cells/mm^3 or other serious HIV-related illness, complete at least two weeks of TB treatment and initiate ART. Make sure that the client is tolerating TB treatment before initiating ART. Clients in this group should be started on first-line therapy consisting of stavudine, lamivudine and efavirenz. Nevirapine should generally be avoided because drug levels might decrease with TB medication and there is a danger of shared hepatotoxicity.

Table 12.5: Antiretroviral Treatment for Adults with Concomitant TB

TB develops while on ART	TB diagnosed before starting ART
Continue ARV therapy throughout TB treatment. **First-line regimen** containing nevirapine should generally be swapped to efavirenz. Regimen is as follows: 1. Stavudine 40mg 12 hourly (or 30mg if weight <60kg) 2. Lamivudine 150mg every 12 hours 3. Efavirenz 600mg at night **Second-line regimen** should be changed to the following: 1. Zidovudine (AZT) 300mg 12 hourly 2. Didanosine (ddI) 400mg daily on an empty stomach (250mg daily if weight <60kg) 3. Lopinavir/ritonavir 400/400mg 12 hourly	**CD4 count 50 - 200/mm^3:** Delay ART for two months (until intensive phase of TB therapy complete). Then start first line therapy as follows: 1. Stavudine 40mg 12 hourly (or 30mg if weight <60kg) 2. Lamivudine 150mg 12 hourly 3. Efavirenz 600mg at night **CD4 count of <50/mm^{3}or other serious HIV illness:** Introduce ART regimen above as soon as the client is stabilized on TB therapy (at least 2 weeks between starting TB therapy and starting ART).

12.8.4 Immune reconstitution inflammatory syndrome (IRIS)

Clients with advanced HIV disease, particularly those with a CD4 count of less than 50 cells/mm^3 may become ill with an immune reconstitution illness during the first few weeks of antiretroviral therapy.

Immune reconstitution illnesses occur when the improving immune function unmasks a previously occult opportunistic infection (an infection that was present in the client's body, but was not clinically evident). Tuberculosis is one of the common immune reconstitution illnesses.

An immune reconstitution illness is not indicative of drug failure or a drug side effect. It is not a reason to stop antiretroviral therapy. If tuberculosis is unmasked after commencing ART the client needs to be changed to a compatible TB-compatible ART regimen. If a life-threatening immune reconstitution develops, the client needs to be referred to a specialist.

Opportunistic infections may present in atypical ways during immune reconstitution. An experienced HIV clinician should be consulted for advice regarding their investigation and management.

12.8.5 Counselling of co-infected clients

Clients on TB medication and ART should be counselled about specific problems they are likely to encounter:

- They will be taking a large number of tablets and may struggle with adherence.
- When antiretroviral treatment is commenced, the client's TB symptoms may transiently worsen as part

of IRIS.
- High rates of drug intolerance and drug interactions may occur between TB and ARV drugs

Adequate preparation and support will help improve adherence to both regimens.

13 MDR and XDR-Tuberculosis

At no time in recent history has tuberculosis been as widespread a concern as it is today. Despite highly effective drugs, disease and deaths due to Mycobacterium tuberculosis are increasing worldwide fuelled by HIV. A serious aspect of the problem has been the emergence of multidrug-resistant tuberculosis, which poses a threat to individuals as well as to communities.

Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis disease caused by strains of M. tuberculosis that are resistant, in vitro, to both rifampicin and isoniazid, with or without resistance to other drugs.

Since the mid-eighties cases of MDR-TB have been diagnosed in each of the nine provinces in South Africa. WHO estimates an MDR rate of 1.8% in new TB cases and 6.7% in previously treated cases in South Africa, with approximately 8000 new MDR-TB cases each year.

MDR-TB is difficult and expensive to treat. The social and economic burden of this problem is already evident in South Africa where the cost of treating a case of MDR-TB is up to 25 times the cost of treating an uncomplicated, drug-susceptible case.

There is ample reason to believe that the full brunt of MDR is still to be faced in the country. Several epidemiological and genetic studies have confirmed ongoing transmission of drug-resistant tuberculosis. Nosocomial outbreaks of MDR-TB associated with HIV infection have been documented where HIV positive clients being treated in hospitals for drug susceptible tuberculosis have been re-infected with MDR strains. Experience in other countries too has shown that clients with active, untreated MDR-TB can infect large numbers of HIV positive individuals, leading to significant outbreaks of MDR-TB with high case-fatality rates.

It is therefore of utmost importance that MDR-TB be prevented by rigorous adherence to the principles of the National Tuberculosis Control Programme (DOTS Expansion and Enhancement Strategy) and by building partnerships with clients, their families and communities to cure cases of tuberculosis at the first attempt. **Prevention is the key to effective MDR-TB control.**

Whilst the implementation of sound tuberculosis control based on the DOTS Expansion and Enhancement Strategy is the top priority, it is recognised that MDR tuberculosis poses a considerable risk to the effectiveness of this strategy. The policy guidelines for the “Management of Drug-Resistant Tuberculosis in South Africa” (June 2007) bring the management of MDR-TB within the National Tuberculosis Control Programme and make the following mandatory:

- Standardised MDR-TB treatment in provincial MDR-TB centres
- Provincial MDR-TB management teams responsible for initiating and changing treatment.
- All MDR-TB clients to be treated in hospital until at least two consecutive monthly sputum cultures are negative.

13.1 Factors contributing to MDR-TB

As with other forms of drug resistance, MDR tuberculosis is a man-made problem, being largely the consequence of human error in any, or all of the following:

- Management of drug supply.
- Client management, including prescription errors.
- Client adherence.

Preventing MDR requires systems and processes that address all the factors contributing to MDR-TB.

13.1.1 Poor management of drug supply

The most common errors observed in the management of drug supply are:

- Frequent or prolonged shortages of first line anti-tuberculosis drugs due to poor stock management and / or procurement problems.
- Use of tuberculosis drugs (or drug combinations) of unproven bioavailability.

- The use of single first line drugs rather than fixed-dose combination tablets.

13.1.2 Poor client management

Health system failures that lead to poor management of clients on first line regimens, inadequate or inappropriate treatment and poor adherence all contribute to MDR-TB, including:

- Poor relationships between clients and health care personnel due to the uncaring staff attitudes, showing little empathy for clients, being paternalistic and failing to adopt a problem solving approach to help resolve issues all contribute to poor adherence.
- Inadequate counselling of clients resulting in low knowledge levels, poor understanding of what is expected of them and of the importance of completing treatment and monitoring the response to treatment also contribute to poor adherence to first line regimens.
- Ineffective systems, including lack of support for directly observed therapy and unsupervised clients; poor record keeping, follow-up of clients and referral.
- Staffing issues including frequent staff changes, poor staff morale, lack of regular support and supervision and low accountability of staff for programme outcomes.
- Prescription errors including:
  - The use of 2 or 3 drugs when 4 or 5 first line drugs should be used
  - Adding one extra drug to a failing regimen.

Insufficient contact tracing and follow-up of MDR cases also contributes to the spread of MDR-TB.

13.1.3 Client-related factors

Client adherence is most often a problem when:

- The client is homeless, has an alcohol or drug problem, and is unemployed and/or looking for a job.
- A family member has been unsuccessfully treated previously.
- Access to health care is difficult.

13.2 The PHC role in MDR-TB management

Although the specialist MDR units in each of the provinces have the key responsibility for MDR-TB, primary health facilities have an essential role to play by:

- Preventing MDR-TB by implementing effective TB control and reducing the likelihood of resistance developing.
- Ensuring early diagnosis of potential MDR in clients who fail to respond to regimen 1 and 2.
- Assisting with MDR contact tracing.
- Providing on-going care post discharge from the MDR unit and liasing with the MDR unit.
- Providing counselling and support to MDR clients, their families and contacts.

13.3 Preventing MDR-TB

Preventing the development of drug resistance is an important objective of the TB programme. This requires:

- Cooperation of all TB treatment providers, including the private health sector, in implementation of TB programme policies.
- Standardised first line regimens for new and retreatment clients
- Health system compliance
  - Providing the right drugs, in the right dosages for the correct period of time
  - Ensuring good adherence to treatment
  - Adequate counselling of clients and their families; empathic and supportive staff
  - Accessibility of services; addressing barriers to adherence (eg through appropriate referral to social services)
  - Supervision (through directly observed treatment) and monitoring of adherence
  - Systematic monitoring and evaluation of treatment to help ensure good treatment outcomes
- Use of fixed drug combination tablets
- An uninterrupted drug supply
  - Correct forecasting of drug requirements based on 10% above previous years consumption
  - Ensuring a 4-month stock at facility level
- Free treatment and reducing the financial cost to the client accessing treatment.
- Early diagnosis of MDR; prompt initiation of effective treatment and contact tracing and screening

Establishing good systems in implementing TB programme policies can play a major role in decreasing MDR-TB.

13.4 Early diagnosis of MDR-TB

MDR-TB is a laboratory diagnosis, made only by TB culture and drug susceptibility testing. In a client with proven pulmonary TB, who is not improving clinically, one positive culture with resistance to INH and RIF is diagnosed as MDR-TB. It is important to always evaluate the clinical condition of the client and not rely solely on a laboratory result that can be erroneous (due to an administrative error or contamination of the sample for example). A laboratory result that is not consistent with the clinical picture should be repeated if necessary.

Early, prompt diagnosis of MDR-TB through sputum culture and susceptibility testing should be sought in the following circumstances:

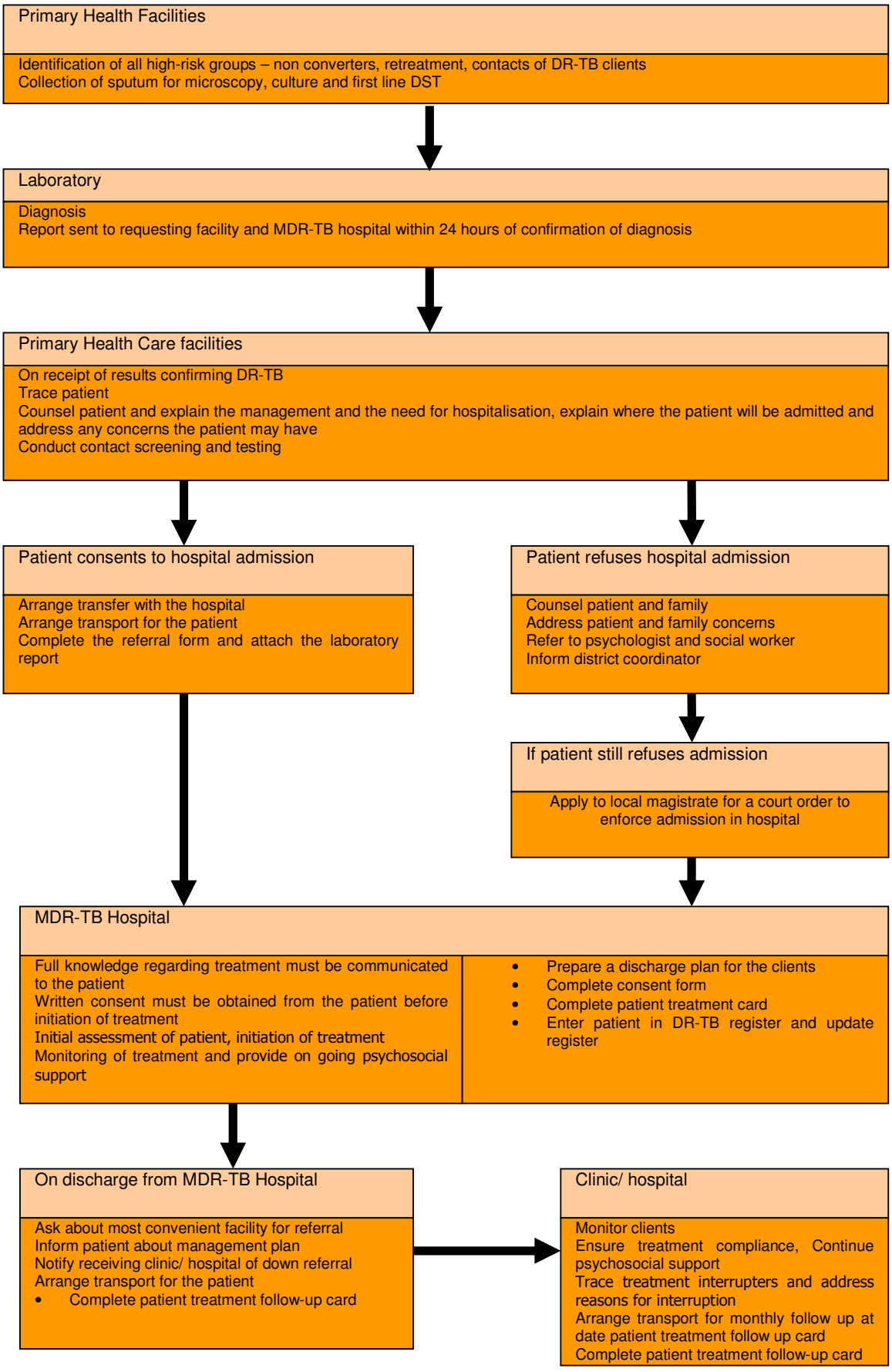
- MDR-TB contacts who are symptomatic for TB.
- TB suspects who give a history of close contact with an MDR-TB case.
- Symptomatic clients from high-risk groups including health care personnel, laboratory personnel and prisoners.
- Any client on TB treatment in whom there is clinical deterioration despite good adherence.
- **New smear-positive TB clients**, if despite good adherence:
  - Sputum smears are positive at 2 months and there is no bacteriological improvement (e.g. 2+ smears becoming 1+) or no clinical improvement.
  - When the continuation phase has been extended for a 3rd month and the sputum smear is still positive at the end of the third month.
  - If sputum smears were negative at 2-months but positive at 5-months.
- **Retreatment smear-positive TB clients**, if despite good adherence:
  - Sputum smear remains positive after three months of intensive therapy.
  - Sputum smear was negative at 3 months but becomes positive at 7 months.
- In new or retreatment smear-negative, culture positive TB case that becomes smear-positive after 2 and 3 months of treatment respectively.

Requests for first line DST in these clients should include isoniazid, rifampicin. The diagnosis of MDR-TB is made only on laboratory confirmation of DST results. Clients who are improving clinically and radiologically should have repeat investigations done, as the laboratory result could be incorrect.

MDR-TB should be differentiated from Mycobacterium other than TB (MOTT), also known as non-tuberculous mycobacteria (NTM). These are usually contaminant or commensal organisms and are commonly resistant to both INH and RIF. They do not usually cause clinical illness. Clinical illness due to NTM needs to be referred to a respiratory physician for advice.

In all cases where the National Health Laboratory Service or other laboratory identifies new cases of MDR-TB, the person responsible at the Provincial Health Department, the facility caring for the client and the local MDR unit should be notified within 24 hours. This will help ensure that MDR-TB clients access appropriate care as soon as possible.

Figure 1: Patient flow chart



13.5 Management Of MDR-TB

MDR-TB is the responsibility of the TB programme at all levels: national, provincial, regional, district, sub-district and facility. All MDR-TB clients should be referred to an MDR-TB hospital where experienced clinicians can assess and initiate treatment.

Management of MDR-TB at all levels should include:
- Drug susceptibility testing of specimens from MDR-TB clients
- Standardised MDR-TB treatment in provincial MDR-TB hospital or isolation wards of general hospitals.
- All treatment to be initiated and managed by provincial MDR-TB management teams.
- All MDR-TB clients to be hospitalised until at least two consecutive monthly sputum cultures are negative.
- Provision of appropriate counselling and support
- Provision of key nursing staff to provide continuity of care during the treatment period
- Direct observation of treatment throughout the course of treatment
- Good clinical records and keeping updated registers
- Monitoring compliance
- Developing measures for rapid recall if clients interrupt their treatment
- Increasing education and motivation of clients
- Rapid tracing and evaluation of contacts.

Under ideal circumstances, all MDR-TB clients should be referred to an MDR hospital for the intensive phase of treatment. However, the non-availability of beds at the MDR unit should not prevent the initiation of MDR treatment. It is recommended that the MDR hospital evaluate all MDR cases that cannot be admitted, with a view to commencing treatment in an isolation ward at the client's nearest general or TB hospital. Although standardised treatment regimens are used in MDR-TB, the decision to commence treatment should still be taken by a specialist at the MDR unit.

The Role of Primary Health Care (PHC) facilities in the management of MDR-TB:

- On discharge from MDR hospital, clients will continue treatment at the PHC facility and be evaluated monthly by the MDR unit.
- The responsibility for clients remains with the MDR unit and mechanisms for feedback about clients and monitoring adherence should be established between the MDR unit and PHC facility prior to discharge.
- The PHC facility should receive MDR drugs from the MDR hospital on a client name basis and provide these to the client through clinic DOT or home based care.
- Adequate records of individual client progress as well as hospital registers are required to monitor overall response to treatment and track treatment outcomes.
- All of the issues relating to support and clinical care of clients with drug susceptible TB disease apply to MDR-TB including HIV testing and general HIV care. All MDR-TB clients should therefore be offered HIV counselling and testing as the standard of care. HIV positive MDR-TB clients should be offered the full package of HIV care including screening for antiretroviral therapy.

13.6 MDR-TB Contact Management

Prompt contact tracing should take place for all MDR-TB clients:
- If symptomatic: clients should be appropriately investigated, including the use of sputum culture and DST to identify whether they have MDR-TB or not. It is recommended that symptomatic children ideally be referred to the hospital for evaluation, as MDR-TB diagnosis is more difficult in children than in adults.
- All asymptomatic close contacts of MDR-TB clients should receive clinical follow-up for a period of at least two years at six monthly intervals. HIV positive contacts should be followed-up 3 monthly and if active MDR-TB develops, referred immediately for treatment.
- Asymptomatic clients should also be counselled about the signs and symptoms of TB and asked to present at a health facility immediately if these develop. Early diagnosis, before lung damage occurs, and correct treatment is the best way to improve outcomes of those infected with MDR-TB.

Prophylaxis is recommended for asymptomatic contacts of MDR clients as follows:
- Asymptomatic child contacts of smear or culture positive MDR-TB should be managed according to the standard recommendations for drug susceptible TB.

  - Child contacts under 5-years of age should be given INH preventive therapy, irrespective of tuberculin response.
  - HIV-infected children of any age should be given INH preventive therapy, irrespective of tuberculin response.
  - This is considered acceptable practice because in areas with high endemic levels of TB, child contacts are also likely to have been exposed to multiple strains of TB, including drug susceptible strains.
- On the basis of the current evidence, WHO does not recommend second-line drugs for chemoprophylaxis in MDR-TB contacts.

13.7 Treating Mono and Poly-Resistance

Mono-resistance refers to resistance to a single first line drug whilst poly-resistance refers to resistance to two or more first line drugs, excluding the definition of MDR and XDR-TB.

Clients with mono and poly-resistance must be referred to the MDR-TB hospital for assessment and initiation of treatment but should not be admitted in the hospital. The PHC facility must then monitor the patient throughout the treatment period and treatment outcomes reported to the MDR-TB hospital.

The diagnosis and treatment is made complex by the fact that the DST result received does not reflect the resistance pattern in the current population of bacillus, but that at the time when the sputum was taken, which could be 1-2 months earlier. In the interim period, further drug resistance may have developed.

13.8 XDR-TB

Extensively drug resistant tuberculosis (XDR-TB) refers to a situation in which there is resistance in vitro to:
- Isoniazid and rifampicin **and**
- Any of the fluoroquinolones **and**
- One or more of the second-line injectable drugs (capreomycin, kanamycin, amikacin).

XDR-TB is extremely difficult and expensive to treat. It has very high mortality, with rates of over 90% recorded amongst HIV co-infected XDR clients in Tugela Ferry, KwaZulu-Natal.

Prevention is key to the control of XDR- TB. Just as good case management of new and retreatment cases will prevent MDR-TB, good case management of MDR-TB will prevent XDR-TB. There is probably no difference in the spread of XDR-TB to any other form of TB.

The diagnosis of XDR-TB is a laboratory diagnosis made through second-line DST. The laboratory on confirmation of XDR-TB should conduct second-line DST routinely. Second line DST must be requested under the following circumstances:
Routinely, for all suspected MDR-TB cases.
When investigating symptomatic contacts of known XDR-TB cases.
Bear in mind that DST for second-line drugs is more complex and less reliable than DST for first line drugs.

All XDR-TB clients must be referred to the MDR-TB hospital for admission, assessment, initiation and monitoring of treatment. However, XDR-TB requires an individualised approach to treatment regimes, based on the previous history of drug use and the results of drug susceptibility testing. The duration of stay in the hospital may vary from patient to patient depending on the clinical response to treatment, but at least six months. There is no consensus on the optimum treatment duration and this is determined on a case-by-case basis.

XDR-TB is curable in up to 30% of cases, depending on the extent of drug resistance, the severity of disease and the immune status of the client.

14 Non-Tuberculosis Mycobacteria

It is important to be able to differentiate between Mycobacterium tuberculous (MTB) and Non-Tuberculous mycobacteria (NTM) and to understand the pathogenic potential of NTM.

14.1 Epidemiology and pathogenesis

Synonyms for non-tuberculous mycobacteria (NTM) include: Mycobacteria other than tuberculosis (MOTTS), atypical mycobacteria (ATM).

Although first observed soon after Koch's discovery of the tubercle bacillus, NTM were not widely recognized as human pathogens until the 1950s. NTM are environmental bacteria widely found in soil, plants, animals, fish and water. There are over a 100 different NTM, and new ones continue to be identified.

Their prevalence in humans now appears to be increasing as a result of HIV and AIDS, with *M. avium complex* being the most commonly reported NTM infection in clients with AIDS. Other mycobacteria commonly involved in clinical disease are *M. intracellulare, M. kansasii, M. marinum, M. fortuitum, M. chelonae,* and *M. scrofulaceum.*

Transmission occurs through the aerosolisation of microorganisms into the respiratory tract and direct inoculation into soft tissue. NTM are not spread from person to person.

14.2 Clinical manifestations

NTM are generally less virulent than MTB, but may cause a variety of diseases including pulmonary disease, lymphadenitis, skin and soft tissue abscesses, wound infections, osteomyelitis and disseminated disease particularly in clients with advanced HIV disease.

The illness presents acutely or subacutely in a way that is clinically and radiologically very like that caused by infection with M tuberculosis, although some clients may be asymptomatic. The chest X-ray appearance may be indistinguishable from that of disease caused by M tuberculosis, cavitations occur in 70-90% of cases.

Chronic pulmonary involvement with other non-specific symptoms (due to M. avium and less frequently M. kansasii) is the most frequent clinical manifestation. The associated risk factors are smoking and underlying lung pathology, such as chronic obstructive lung disease, pneumoconiosis, silicosis, active or residual TB, cystic fibrosis or bronchitis. Radiological findings are difficult to interpret due to the underlying pathology and findings are non-specific; however, cavities if present may be thin-walled and effusions are rare.

Peripheral lymphadenitis is most frequently found in children between 1- 5 years of age and occurs typically in the head and neck. The disease is localised and requires surgical excision. Most children present with cervical lymphadentis. Often just one node is involved which may be "hot" or "cold". There is little systemic upset, the glands usually being painless and non-tender. The chest x-ray appears normal and the diagnosis is made by complete resection of the involved gland(s) and culture of the specimen.
Histologically the appearances are the same as those caused by M tuberculosis. Accurate diagnosis and proper treatment will be expedited by close co-operation between chest physicians, paediatricians, and other specialists. In adults the most likely cause of lymphadenitis is M tuberculosis.

The species most frequently causing infections of the skin, soft tissue, and bones are M. fortuitum, M. abscessus, M. marinum, and M. ulcerans. These normally occur after penetrating trauma, surgery or the insertion of catheters and prostheses. M marinum infection may occur following trauma to the skin in contaminated swimming pools or aquaria ("swimming pool" or "fish tank granuloma"). M ulcerans may cause chronic, indolent necrotic skin ulcers known as "Buruli ulcers". Infections of bone, joints, and the genitourinary tract are rare.
Disseminated disease presents in two different ways:

- Clients who are immunosuppressed, not due HIV, may present with fever of unknown origin (commonly due to *M. avium*) or with subcutaneous nodules and abscesses that drain spontaneously (due to *M. kansasii*).
- Severely immunosuppressed AIDS clients (CD4 count < 50 cells/mm^3) present with a high temperature, night sweats, weight loss, abdominal pain, and diarrhoea. This is most commonly due to *M. avium* but

can also be due to *M. kansasii*. The diagnosis can frequently be made through a blood culture.

14.3 Bacteriology

Pulmonary disease in Africa is overwhelmingly due to infection with mycobacterium tuberculosis and acid-fast bacilli seen on sputum should be regarded as TB bacilli until proven otherwise.

The term "Mycobacterial species" sometimes used on preliminary reports by laboratories prior to completion of identification tests can be misleading. It includes Mycobacterium tuberculosis (MTB) as well as the non-tuberculous mycobacteria (NTM).

NTM are acid-fast bacilli that cannot be differentiated from TB bacilli on direct microscopic examination of a sputum or lymph node aspirate. NTM are cultured in the same way as TB bacilli, and differentiated from TB bacilli using biochemical tests and growth characteristics, or rapid molecular tests such as probes and PCR. Some of the biochemical tests take several weeks to complete.

It is importance to differentiate NTM from TB bacilli is that they require a different approach to management.

Significance of positive NTM culture results in sputum:

- In the situation where a client is started on TB treatment and the sputum culture result subsequently returns positive for NTM. Continue with TB treatment; have a second specimen sent for TB culture and drug susceptibility. The client should be referred to a tertiary hospital as indicated below.
- If a single positive NTM culture is from an ill client with AIDS (low CD4 count, fever, night sweats, respiratory symptoms, weight loss, diarrhoea and abdominal pain), that client should be referred to a tertiary hospital as indicated below
- If NTM is reported in sputum culture results of a clinically well client, in most cases this should be considered as contamination. The sputum TB culture should be repeated. No treatment is indicated while awaiting the results.
    - If the second culture is negative, no further action is necessary.
    - If the second specimen is again positive, the patient should be referred as indicated below.
- All cases with positive NTM blood culture require referral for treatment

14.4 Management of NTM

In many cases, the NTM isolated is a contaminant in the specimen, and the client does not need treatment. In some clients, the NTM is merely colonizing an old TB cavity or area of damaged lung, and is not causing any disease. The decision about whether the NTM in the specimen is pathogenic, a contaminant or a colonizer is difficult and needs to be made by an expert. *M. avium complex* isolated from blood in an HIV positive client is always significant and requires urgent treatment.

Where to refer clients with NTM for management

A client that has been diagnosed with symptomatic NTM should be referred to a tertiary hospital specialist clinic, hospital HIV clinics (for adults and children with HIV infection) or hospital respiratory clinics (for HIV negative clients). Clients should not be referred to the MDR-TB hospital, which only treat DR-TB

- Most NTM are resistant to standard TB drugs.
- NTM can therefore be misdiagnosed as MDR-TB.
- NTM should never be treated as MDR-TB.

Standardised NTM drug treatment

NTM do not respond to the usual anti-TB drug regimen. The clinical and radiological details, type of specimen, the number of isolates, and the specific NTM identified are all taken into consideration in treatment decisions. A standardised drug regimen should be used for all clients, with individualised drugs

only used in cases with intolerable side effects or resistance to one or more of the drugs in the standardised regimen.
There is lack of consensus on the treatment of NTM mainly because of the lack of evidence as no large clinical trials designed to assess various regimens have been conducted. For culture confirmed cases, a minimum of three drugs should be used for a period of at least one year. These drugs are clarithromycin, ethambutol, ciprofloxacin (or rifabutin which is not available in the country). A fourth drug – amikacin may be added for severely ill hospitalized clients.
HIV positive clients with NTM disease should be started on ART. Clarithromycin interacts with efavirenz, therefore azithromycin should preferably be used instead for clients receiving efavirenz.

14.4.3 Recommended doses for NTM

Drug	Dose	Dosing Interval	Maximum Daily Dose	Duration of Therapy
Clarithromycin Or Azithromycin Plus Ethambutol	7.5 – 15 mg/kg/day 10 – 12 mg/kg/day 15 – 25 mg/kg/day	Q12 Q24 Q24	500 mg 500 mg 1000 mg	Clients need 12 weeks of treatment to eliminate the organism. Most improve during the first 4 – 6 weeks of therapy
In severe disease, add either				
Ciprofloxacin Or Amikacin	20 – 30 mg/kg/day 15 – 30 mg/kg/day	Q24 Q24	1500mg 1500mg	
After completion of therapy, clients require lifetime secondary prophylaxis with a Macrolide antibiotic.				

Reference: Mofesan LM, et al. Treating Opportunistic Infections Among HIV-Exposed and Infected Children. December 2004; CDC 53(RR14): 1-63.

Recommended prophylaxis against MAC in HIV positive clients:		
1st choice	Azithromycin 1200 mg orally weekly	Indefinitely
2nd choice	Clarithromycin 500 mg orally b.d.	Indefinitely

There is no general agreement about when prophylaxis should be used. Prophylaxis is recommended in clients with a CD4 count less than 200 cells/mm^3, for clients with a CD4 count below 50 cells/mm^3, weekly azithromycin appears to be the most cost effective option.

15 Admission and Discharge Criteria for TB Clients

15.1 Introduction

Hospital care for TB clients is indicated in some circumstances, and specific admission and discharge criteria help to optimise care for all TB clients. TB clients are only admitted to hospital care when either their clinical condition warrants it and / or access to community-based care is not available. It is equally important that TB clients be discharged to outpatient care at clinics as soon as they can be managed effectively in the community with DOT support.

TB clients are not routinely admitted to a hospital. TB hospitals only admit clients with active TB who meet specific criteria and are referred from hospitals or clinics. In areas where there are no TB hospitals, the same criteria apply to the TB wards in general hospitals.

The aims of establishing admission and discharge criteria and processes for TB hospitals are:
- To ensure that clients referred to clinics, TB hospitals by tertiary and district hospitals are appropriate referrals
- To ensure the successful completion of the intensive phase of TB treatment in sputum positive TB clients, where access to a clinic or community based support is not possible.
- To provide appropriate and effective care for TB clients that require hospitalisation, until they are well enough to be treated at a clinic or in the community.
- To reduce treatment interruption by ensuring the continuity of care when clients are discharged form the TB hospital.

15.2 Admission criteria to TB hospitals

Referral from PHC clinics and general hospitals to TB hospitals is indicated if at least one of the following admission criteria are met:
- A medical reason for admission - when clients diagnosed with TB are too ill or too weak to go home, including severely emaciated TB clients without other complications.
- Re-treatment TB cases requiring streptomycin injections that cannot be managed at a clinic.
- Social or socio-medical reasons for admission, when clinic or community supported care cannot be achieved, particularly in the case of high-risk groups like alcohol or drug dependence, mentally disturbed clients or previously non-compliant clients.

In all cases, a completed TB referral form should accompany referrals. This form must include relevant basic personal, clinical and diagnostic information e.g. confirmed sputum smear or culture results or other reasons for making the diagnosis of TB (clinical findings, x-ray report or other).

Admission of clients from general hospitals to TB hospitals should only take place when the TB diagnosis has been confirmed and the client's other medical conditions have been stabilised:
- Clients with negative smears require a culture to confirm PTB. Other conditions such as bacterial or viral pneumonias, congestive cardiac failure, asthma, chronic obstructive lung disease, bronchiestasis and bronchial carcinoma need to be excluded in the differential diagnosis.
- TB clients with medical conditions such as diabetes mellitus, epilepsy and severe hypertension should be stabilized before referral.
- Severely ill clients with extra-pulmonary TB (TB meningitis, TB spine, TB pericarditis) need to be stabilised in general hospitals before transfer to TB hospitals.

Treating MDR-TB clients requires experience and special expertise. MDR-TB clients must be referred for evaluation, treatment and follow-up to a specialised MDR unit.

15.3 Essential elements of in-patient care in TB hospitals

15.3.1 Clinical management

- TB diagnosis, treatment and monitoring:

  - Ensure proper diagnosis for pulmonary TB (i.e. sputum smears and culture for AFB and chest x-rays) and extra-pulmonary cases diagnosed by histology or chemical pathology.
  - Ensure proper classification of the case i.e. new or re-treatment case and site of disease.
  - Ensure correct TB regimen is prescribed.
  - Ensure proper registration of the client.
- A health education plan should be implemented within 2 weeks of admission to counsel the client about TB and to develop an adherence plan to ensure treatment completion.
- All clients should be offered HIV counselling and testing by appropriately trained counsellors during the course of their hospitalisation. It is the responsibility of the TB hospital to offer all dually infected clients the full package of HIV care defined in section 12.6-12.8. Once they are clinically ready for discharge, TB clients with HIV infection can be referred to home-based care services or "step-down" facilities if palliative care is required.
- A social evaluation should be undertaken to assess eligibility for support grants.
- Within one week of hospitalisation, a plan for DOT management on discharge should be developed:
  - Confirm the client's correct address
  - Contact the clinic and organisation providing community DOT to identify a potential DOT supporter.
  - Meet with family members to discuss the treatment plan and to ensure DOT when the client is discharged.

15.4 Criteria for referral from TB hospitals to district / regional hospitals

Clients should be referred to a secondary or tertiary hospital if their clinical condition warrants more specialised care than the TB hospital can provide. This includes:
- All severe complications of TB disease e.g. massive haemoptysis, TB meningitis
- Severe dyspnoea and empyema.
- Severe drug reactions e.g. acute liver failure, Steven Johnson syndrome.
- HIV related diseases that need specialised medical care e.g. cryptococcal meningitis.

15.5 Discharge criteria from TB hospitals to PHC clinics

TB clients should be discharged from TB hospitals to PHC clinics as soon as the following two criteria are met:
- The client is medically stable (no dyspnoea, no haemoptysis, not severely emaciated and afebrile) and able to care for him/herself (or adequate family or community-based care is arranged).
- The client is able to access treatment at a clinic and be monitored either at the clinic or by a DOT supporter.

15.6 Discharge process

- Within 2 weeks of admission a discharge plan must be completed which ensures:
  - Continuation of care (contact with the most accessible clinic, recruitment of a DOT supporter).
  - The client is knows about their TB management (how and when to take medication; duration of treatment; importance of compliance with the treatment; attendance at the nearest clinic for clinical evaluation and provision of sputa to monitor response to treatment; infection control measures to be taken at home).
  - A formal link is established between the client, the PHC clinic and DOT supporter.
- Nutritional support should be arranged for clients with inadequate access to food at home. A social worker needs to be involved to arrange support for clients in need.
- Referral to a local clinic or another hospital should always be done by:
  - Completing the pink referral form in detail with all the relevant information. One copy is for the client to take to the clinic; one copy should be sent to the referral clinic; one is kept at the hospital.
- The green client card should be updated before the client leaves the TB hospital and the clinic or DOT supporter should keep it updated until the TB treatment is completed.
- If possible, the client should be delivered to the clinic, or be accompanied by a DOT supporter or social worker on discharge, or the clinic should collect the client. Where this is not possible, follow up directly with the clinic to confirm that the client has arrived.

16 Infection Control

People with undiagnosed, untreated and potentially contagious TB are frequently seen in health care settings. In an era of increased access to HIV services such as Voluntary Counselling and Testing, Prevention of Mother To Child Transmission and Antiretroviral Therapy, increasing numbers of HIV positive clients are also seen in these facilities. HIV positive clients are particularly vulnerable to TB with a 10% annual risk of developing TB compared to a 10% lifetime risk in those with normal immunity. It is estimated too, that 10% of those newly diagnosed with HIV have undiagnosed TB; half of these are infectious. The increasing numbers of undiagnosed TB, TB suspects, TB clients and immunocompromised clients all present in the same environment create the potential for high levels of nosocomial transmission of TB.

An increased risk of TB has been documented amongst all categories of health care personnel (including facility staff, community health workers and volunteers) compared to the general population. The prevalence of HIV amongst health care personnel correlates with that in the general population. Health care personnel are at risk due both to frequent exposure to clients with infectious TB and because they may also be immunocompromised due to HIV.

It is the responsibility of management and staff to minimise the risk of TB transmission in health settings. Infection control measures should be established to reduce the risk of TB transmission to both the general population and to health care personnel. Since the majority of clients are seen at primary health care level, it is important to ensure that measures to prevent the spread of infection focus not only on hospitals, but are implemented also at primary health care level.

There are three types of infection control measures:
- Administrative control, including appropriate work practices
- Environmental control
- Personal respiratory protection

16.1 Administrative control and appropriate work practices

When an infectious person with TB coughs, sneezes or laughs, tiny droplets containing Mycobacterium TB are released into the air. These droplets are invisible to the naked eye and remain airborne for many hours, until removed by natural or mechanical ventilation. A person who inhales these droplets can become infected with mycobacterium TB and later go on to develop active TB.

Administrative measures aim to reduce droplet nuclei containing Mycobacterium tuberculosis in health facilities and thus to reduce the exposure of staff and clients. A comprehensive, written infection control plan underpins administrative control (For details refer to “National TB Infection Control Guidelines, Department of Health, South Africa, June 2007”). The most important steps to reducing droplet nuclei and thus TB transmission in health care settings include:
- Early recognition of TB suspects or confirmed TB cases through screening all clients entering facility with a cough for 2 weeks or more:
  - Ensuring that TB-suspects spend as little time as possible in the facility by fast-tracking their process through reception to the appropriate services (service that client presented for as well as TB screening)
- Educating clients with a cough on respiratory hygiene:
  - Covering the nose and mouth with a tissue when coughing
  - Spitting / coughing into a tissue and discarding it into a designated bin
  - Use of disposable surgical masks by clients/staff who are coughing to reduce the spread of droplets when coughing.
- Separation of TB suspects from the general waiting area to a designated, well-ventilated sub-waiting area.
- Prompt investigation for TB in symptomatic clients
  - Routine symptomatic screening of clients e.g. at VCT, HIV Care and ARV services to identify symptoms early
  - Collection of sputum samples according to protocols in those with symptoms
  - Prompt follow-up of sputum results and commencing or referring client for treatment if diagnosed with TB.

- Appropriate collection of sputum samples:
  - Collection takes place away from other people.
  - Collection occurs in an area with good air circulation but where privacy is ensured.
  - Collection does not take place in a closed space such as a toilet.
  - There is hand washing after handling of sputum samples.
- Educating health care personnel, clients and communities to seek health care early when signs or symptoms of TB are present and to protect themselves and others e.g. through appropriate cough hygiene and good ventilation in the household.
- Improved TB AND HIV integration in the health facility, with symptomatic TB screening of HIV positive clients at routine clinical visits and appropriate tests for those who are symptomatic, to aid early diagnosis.

An infection control officer should be identified who will be responsible for documenting the plan; monitoring it and arranging training for health care personnel. The plan needs to clearly identify high-risk areas (general waiting areas, outpatient departments, TB wards, TB hospitals, bronchoscopy suites, sputum induction and collection rooms, TB rooms) and address ways of reducing transmission in these areas. Particular emphasis should be placed on reducing the exposure of HIV positive clients to those with MDR-TB.

All health care personnel need to be trained to ensure that they understand the importance of infection control and how best to protect themselves and their clients. All health care personnel should also be trained on the screening of TB suspects; this will help to reduce screening and diagnostic delays and improve TB case finding.

Administrative controls have the greatest impact on TB control and should be the priority. Environmental controls and personal respiratory protection will not work in the absence of solid administrative control measures. Since it is not possible to eliminate all exposure, other control measures can be added to reduce the concentration of droplet nuclei in the air and to prevent their inhalation.

16.2 Environmental control measures

Environmental controls are the second line of defence in preventing the spread of TB. They are only effective if administrative controls are in place. These include:
- Ventilation (natural and mechanical)
- Ultraviolet germicidal irradiation

Ventilation is the movement of air through a building so that it is replaced by air from outside. Natural ventilation relies on open doors and windows. There should be adequate numbers of windows and doors opening to the outside to allow good ventilation. Windows on opposites sides of the room allow good cross ventilation. Controlled natural ventilation implies that measures are in place to ensure that windows and doors stay open. Unrestricted openings (that cannot be closed) on opposite sides of the room offer the most effective natural ventilation. Assisted ventilation using propeller fans on the ceiling, desk, floor or window mounted is an inexpensive way to improve natural ventilation. Good natural ventilation plays an important role in preventing TB particularly in waiting areas, examination rooms and sputum collection areas.

Mechanical ventilation can be used in areas where there may be high concentrations of infectious droplets. These are systems that facilitate air entry into the room and extraction from the room to the outside. The most cost effective are exhaust fans that are placed in windows. It is important to ensure that airflow is adequate and that air flows across the room.

Exhaust ventilation systems allow for exchange of air in the room as well as extraction of air to the outside. In negative pressure ventilation, the room is kept at negative pressure by directly exhausting air to the outside, thus ensuring that fresh air is drawn into the room.

Ultraviolet germicidal irradiation (UVGI) may be used as an adjunctive measure. Ultraviolet rays kill the bacilli. For this to be effective the contaminated air has to come into contact with the rays; therefore circulation of air is important. It is ineffective in humid and dusty environments. UVGI lamps are expensive, have to be installed properly for maximum effect and require a regular programme of maintenance. If not adequately maintained, lamps are ineffective and can cause acute or chronic skin and eye problems

16.3 Personal respiratory protection

Personal protection refers to the use of respirators that contain a special filter material that protects the wearer from inhaling the bacilli. They are used as the last resort where all the other measures have not completely eliminated the risk. They are most appropriately used for short-term protection against high-risk exposures e.g. during sputum inducing procedures and bronchoscopy. Long-term use of respirators is not feasible due to the discomfort, difficulty in speaking clearly through the mask and the cost involved.

The recommended respirator is the type that covers the mouth and nose and is fitted with a special particulate filter to filter out very small particles. U.S. certified N95 or greater or E.U. specified FFP2 or greater are recommended for use in health care settings. They are ineffective if facial hair is present that prevents a seal between the mask and the face.

Surgical masks do not protect the person wearing it from inhaling infectious particles as they are not sealed and have a limited filtration capacity. They are meant to prevent the spread of infectious particles from the person wearing the mask to others. These are recommended for infectious clients/staff on a short-term basis. The concern is that they could perpetuate stigma. Although less effective, using a tissue to capture large wet particles near the mouth and nose when coughing may be preferable.

16.4 Protection of health care personnel

All categories of health care personnel have an increased risk of TB when compared to the general population. In addition to reducing their exposure, specific measures that target health care personnel are required:

- Informing health care personnel of the signs and symptoms of TB and encouraging early recognition of symptoms and presentation for sputum tests
  - Ensure that all health care personnel with signs and symptoms are evaluated as “high risk TB suspects” and have 2 sputum specimens sent for evaluation: a spot specimen for smear and an early morning specimen for smear and culture and drug susceptibility testing.
- Providing VCT and encouraging health care personnel to know their HIV status
  - Advocating / providing precautionary measures for HIV positive staff, such as TB preventive therapy and antiretroviral therapy.
  - Appropriate placement of HIV positive staff in low TB risk areas of the facility.

17 Monitoring and Evaluation

A key element of the DOTS Strategy is the establishment and maintenance of a system to monitor case detection and treatment outcomes. A monitoring and evaluation (M&E) system is essential to programme management since it provides the basis for assessing progress made towards achieving programme goals. In addition, it allows the size of the tuberculosis problem and its evolution over time to be evaluated.

Staff and managers need to have a thorough understanding of the content and process of TB programme monitoring and evaluation to enable them plan adequately and to use information to drive service improvements. M&E is an important management tool at every level in programme management. It plays an important role in the day-to-day management of health programmes and provides programme managers with the information and insight needed for strategic planning, programme design and implementation, and decision-making about human and financial resources, especially in resource-limited settings.

M&E provides an indication of how well objectives have been achieved, whether activities have been undertaken as intended and whether services are effective in reaching programme goals. It can be used to address weaknesses in programme design and implementation. Using information in decision-making can help to ensure accountability of staff and managers.

A good M&E system is required at every level in the health system, characterized by the following:

- Clear goals, objectives and targets (that are cumulative, with facility targets leading to sub-district targets leading to district targets leading to provincial targets leading to national targets)
- The selection of indicators which are valid, reliable, specific, operationally feasible and comparable over time and in different districts, provinces and countries
- Quality assurance procedures to ensure that quality data is collected
- The timely submissions and processing of data
- The ability to process and analyse data
- Data dissemination in both directions

Both monitoring and evaluation are done on a “cohort” basis. This ensures that all clients recorded in the register within a specified calendar quarter are accounted for within the analysis.

17.1 Monitoring

Monitoring is the routine tracking of key elements of programmes performance through careful record keeping and regular reporting. Monitoring is used to assess whether or not activities are carried out as planned. It focuses on the activities implemented and results achieved. It provides continuous information on the progress being made to achieve goals and alerts staff and managers to problems, providing an opportunity for these to be resolved early.

Effective monitoring relies on accurate records being maintained for all clients and periodic, regular reporting of activities. The tools that have been developed by the TB Programme help standardise the way in which information is collected.

The most important indicator of programme success monitored is the cure rate for new smear positive cases, which should be at least 85%.

Whilst the main stated goal of the TB programme is to cure 85% of new smear-positive TB cases, the intention is also to cure 85% of retreatment smear–positive cases and to ensure the successful treatment of all other categories of TB. The outcomes of other categories of clients, such as smear-negative, culture-positive TB and EPTB may also be analysed as separate cohorts.

17.2 Evaluation

Monitoring and evaluation are closely linked and systematic monitoring is essential to evaluation. Evaluation is an episodic, in-depth analysis of programme performance. It assesses progress towards operational targets and epidemiological objectives. It relies on data generated through routine information as well as from other sources such as research studies.

There are various types of evaluation. Process evaluation measures the quality of programme implementation and assesses coverage. Outcome and impact evaluations measure programme results and the effect on the target population. Outcome evaluations also measure the extent to which stated objectives are achieved with respect to the programme's goals.

Evaluation is an essential management tool, not only for the analysis of results, but also for the management of the TB programme, particularly for guiding implementation, ordering drugs and laboratory reagents, training of health staff, identifying problems in service delivery and eventually the expansion of the health structures involved in the TB programme.

Regular evaluation is required not simply for surveillance purposes but is necessary for efficient management of the programme. An evaluation of the extent to which targets set by the TB programme are reached helps identify parts of the programme that are not functioning well. Regular collation of essential information is an integral part of the routine operations of the TB programme and should not be compromised or minimized due to other pressures.

Programme indicators to be evaluated include:

- Case detection - this compares the notified and expected annual rates (per 100,000 population) of smear-positive pulmonary TB cases. The notified rates are determined from the quarterly report on case finding. The expected rates can be estimated from TB prevalence studies. WHO have set case detection targets at 70% and this is the target used for national purposes. However, calculation of the case detection rate is problematic because it is difficult to establish the denominator of real incidence, due to high levels of HIV and the absence of reliable data on the Annual Risk of Infection.
- Evaluation of coverage - in general it is expected that at least 2% of adult outclients will have respiratory symptoms and that 5-15% of these will be sputum positive.
- Diagnostic practises can be evaluated by determining the proportion of smear positive cases among all pulmonary cases diagnosed. If the proportion who are smear positive is <50%, either smear examinations are being done poorly, or there is over-diagnosis of smear negative TB or both.

17.3 Surveillance

Surveillance is the routine collection of epidemiological data (i.e. disease outcomes) to track trends in disease incidence or prevalence over time. Data may be collected through seroprevalence surveys or through the routine reporting of cases seen by health facilities. Although surveillance data is an important source for M&E, surveillance should not be confused with, or substituted for, actual programme monitoring.

17.4 Standard tools used in The National TB Control Programme

The following standard tools used by the TB programme are described in detail in the "Guidelines For The Use Of The TB Paper-based Recording And Reporting System, National Department of Health, 2008":

- **Case Identification and Follow Up Register (GW 20/13):** Used at facility level to record symptomatic clients reporting to that facility, to assist the follow-up of results and initiation of treatment.
- **Laboratory request form for Sputum Examination:** A specific TB laboratory request form, available from the National Health Laboratory should be used by all facilities. Correct completion can help assess case-finding.
- **Clinic/Hospital card (GW 20/12):** The blue clinic/hospital card is used in all facilities to collect all the information about the client, treatment and outcomes (demographic, disease classification, treatment regimen, monitoring and outcomes). This is the source document used to complete the register.
- **Client treatment card (GW 20/15):** The green client-held card is used to record details of treatment including daily doses taken for all TB clients on treatment.
- **Tuberculosis Register (GW 20/11):** Used in all facilities to summarise key information from the clinic / hospital card on each registered client (demographic, disease classification, treatment regimen, monitoring and outcomes). Information from the register is collated electronically and forms the basis for

monitoring and evaluation of the TB programme. The register needs to be updated on a daily basis. It provides an overview of all registered clients and should be used as a clinical and programme management tool at facility level.
- **Transfer form (GW20/14):** Used in all facilities to report on the key client information from the register when the client is transferred/moved from one district/facility to another.

17.4.1 The electronic TB register

The electronic TB register (ETR.net) is a programme management tool used at sub/district level. The information submitted to the sub/district is entered into the electronic register and data validation and analysis is done using this tool.

The following reports can be generated by the system for a specified period or as a summary over time:
- Reports on Case Finding
- Reports on Sputum Conversion
- Reports on Treatment Outcome
- Facility Profile Reports

Data is transmitted electronically from the sub/district level to the provincial level where it is aggregated and analysed before it is passed on to the national level. Client based data is exported to the Notification system. Aggregated data is also exported to the district health information system (DHIS) at sub/district level, as well as to the Notifiable Medical Disease (NMD) System in the DHIS.

17.5 Standard reports

The following reports should be analysed on a quarterly basis:
- **Quarterly report on case detection and case finding**: Completed at sub/district level and reports on the completed quarters cohort.
- **Quarterly report on smear conversion**: Completed at sub/district level and reports on the previous quarter's cohort.
- **Quarterly report on treatment outcomes for new and retreatment smear positive cases of pulmonary TB**: Completed at sub/district for the cohort registered 9 months earlier.
- **Quarterly report on HIV indicators:** Completed at sub/district for the cohort registered 3 months earlier.
- **Quarterly report on programme management**: Compiled at sub/district level, and is mainly a narrative report.

17.6 Information flow

Information is collected at facility level in the client-held green card and blue clinic or hospital record card and used to update the register. This should be done on a regular (daily) basis. Good data is dependent on the quality of information in the paper-based TB registers. These need to be reviewed throughout the month for completeness and correctness. As soon as a TB register sheet is completed, it needs to be sent to the sub-district office for data capturing. TB Register sheets (pink, yellow and green) must be sent to the sub-district office and data captured throughout the month to allow sufficient time for data validation and analysis at the end of a cohort period.

Timely reporting is central to effective programme management. Reporting on quarterly cohorts does not mean that data is collated on a quarterly basis only. This results in reports being produced too late for meaningful action to be taken and will result in sub/districts and provinces not meeting the targets for timely reporting. Monthly data collation is required at the lowest level at which data is collated (sub-district or district level).

Recommended timelines for data collation:
- In the 1st week after a month, the TB Coordinator and sub-district data capturer / health information officer need to ensure that all the TB Register sheets due but still outstanding are collected.
- In the 2nd week after a month, the data capturer / health information officer needs to ensure that all outstanding data (new cases and updates) is captured.
- During the 3rd week after a month, the TB Coordinator and data capturer / health information need to run

data checks and ensure that all the data that has been captured is correct and complete.
- At the end of the 3rd week, dispatch files need to be sent to the next level.

Due dates for final cohort reporting:
- Case finding data is due at the end of the quarter
- Smear conversion data is due 3 months after the end of the quarter
- Treatment outcome data is due 9 months after the end of the quarter.

In each instance, sub-district data should be submitted to the district within 3 weeks, district data submitted to the province a week later and provincial data submitted to the national office 1 week later. National data should be collated within a week and disseminated back to provinces.

Table 17.1: Information Processing and Flow

Client records:
- Update on a daily and weekly basis

Facility TB Register (Paper-based):
- Update on a daily to weekly basis
- Submit TB Register sheets to the sub-district office weekly:
  - Pink sheets – as soon as all client identification information, disease information and pre-treatment sputum results have been entered.
  - Yellow sheets – as soon as all the smear conversion sputum results at the end of the intensive phase (2 or 3 months) have been captured
  - Green sheets – as soon as all outcomes have been recorded (the correct outcome as well as the outcome date).

Sub-district register (Electronic):
- Update on a weekly basis
- Run checks to validate data
- Submit reports to district level within 3 weeks of:
  - End of quarter for case finding
  - 3 months after end of quarter for smear conversion
  - 9 months after end of quarter for treatment outcomes
- Generate facility reports (used to provide feedback to facilities)

District register (Electronic):
- Update on a quarterly basis
- Run checks to validate data
- Submit reports to provincial level within 4 weeks of:
  - End of quarter for case finding
  - 3 months after end of quarter for smear conversion
  - 9 months after end of quarter for treatment outcomes
- Generate sub-district reports (used to provide feedback to sub-districts)

Provincial register (Electronic):
- Update on a quarterly basis
- Run checks to validate data
- Submit reports to national level within 5 weeks of:
  - End of quarter for case finding
  - 3 months after end of quarter for smear conversion
  - 9 months after end of quarter for treatment outcomes
- Generate district reports (used to provide feedback to districts)

National register (Electronic):
- Update on a quarterly basis
- Run checks to validate data
- Collate National report within 6 weeks of:
  - End of quarter for case finding
  - 3 months after end of quarter for smear conversion
  - 9 months after end of quarter for treatment outcomes
- Generate provincial reports (used to provide feedback to the provinces)

Table 17.2: Timelines for Reporting			
Start of Treatment	**Report**	**Level**	**Date of Analysis**
01 January – 31 March	CASE FINDING	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of April
		Provincial level	1st Week of May
		National	2nd Week of May
	SMEAR CONVERSION	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of July
		Provincial level	1st Week of August
		National	2nd Week of August
	TREATMENT OUTCOME	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of January
		Provincial level	1st Week of February
		National	2nd Week of February
01 April – 30 June	CASE FINDING	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of July
		Provincial level	1st Week of August
		National	2nd Week of August
	SMEAR CONVERSION	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of October
		Provincial level	1st Week of November
		National	2nd Week of November
	TREATMENT OUTCOME	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of April
		Provincial level	1st Week of May
		National	2nd Week of May
01 July – 30 September	CASE FINDING	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of April
		Provincial level	1st Week of May
		National	2nd Week of May
	SMEAR CONVERSION	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of January
		Provincial level	1st Week of February
		National	2nd Week of February
	TREATMENT OUTCOME	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of July
		Provincial level	1st Week of August
		National	2nd Week of August
1 October – 31 December	CASE FINDING	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of January
		Provincial level	1st Week of February
		National	2nd Week of February
	SMEAR CONVERSION	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of April
		Provincial level	1st Week of May
		National	2nd Week of May
	TREATMENT OUTCOME	Facility level	Monthly
		Sub-district level	Monthly
		District level	4th Week of October
		Provincial level	1st Week of November
		National	2nd Week of November

17.7 Using monitoring and evaluation as a management tool

Substantial effort is made to collect information in the TB programme, but the quality of information and the way in which it is used at all levels in the health system limits the potential benefits of M&E. Common problems in M&E include:

- Poor quality data is collected.
- Data is collected but never analysed.
- Data is analysed but not used to improve current practices or policy.

An M&E system is only as good as the data that is collected. The data should be appropriate, complete, consistent, and provided in a timely manner. Many current efforts at routine data collection result in poor-quality data because of a lack of proper training and supervision. If the individuals recording the data are not using the data and do not fully appreciate programme data management needs beyond the facility level, the quality of data is likely to remain poor. This in turn leads to declining use of the data. One of the key functions of an M&E system is to oversee all data collection, ensure that data is appropriately used and that results are disseminated throughout the system, but especially to the facility level.

Changes in health programmes that are directly based on evidence from the field reinforce efforts at the peripheral level to complete routine reporting. When health care providers understand the importance of the data they are collecting, quality is likely to improve, building more confidence in the data being collected and increasing the likelihood that the data will be used. The key challenge is to use the data collected to drive quality improvement initiatives in the TB programme.

Overall sub-district or district results can hide significant differences in programme performance between individual facilities. Data needs to be disaggregated and analysed at facility level because this is the level at which quality improvements have to be made. It is recommended that on a quarterly basis standard facility reports are generated and tracked over time. A standard facility report should include:

- **Case detection indicators**
  - % TB suspect smears that are positive

- **Case finding indicators:**
  - Total TB
  - New cases and retreatment cases
  - Smear positive - New and retreatment
  - All no smear provided and Children 0-7 no smear provided
  - EPTB

- **Case holding indicators:**
  - New and retreatment smear conversion rates
  - % Cases not converted at end of intensive phase at 2 months and 3 months
  - % Cases no smear at end of intensive phase at 2 months and 3 months
  - % Clinic and Community / Workplace DOT

- **Treatment outcome for new and retreatment smear positive cases:**
  - Cure rates
  - Completion rates
  - Defaulter rates
  - Death rates
  - Transfer out rates
  - Not evaluated rates

- **TB AND HIV Indicators**
  - % TB cases tested for HIV
  - % TB cases tested positive for HIV
  - % HIV positive TB cases with CD4 test done
  - % HIV positive TB cases on ART pre-TB treatment
  - % HIV positive TB cases not on ART pre-TB and requiring ART
  - % HIV positive TB cases commenced on ART whilst on TB treatment.
  - % HIV positive TB cases commenced on cotrimoxazole

An analysis of the facility data should answer the following questions:

- What does the data show?
- How is the facility performing in comparison to previous quarters?
- How well is the facility performing relative to the targets that have been set?
  - In which areas is the facility performing well?
  - Which are areas of concern?
- What can we learn from the things that we are doing well?
- What are the most important problems that should be addressed?
- What factors at different points in the TB service contribute to these problems?
- What activities will be undertaken to remedy the problems at each point in the service?
- What resources will be required to undertake the activities?
- Who will undertake each of the activities?
- What is the target set for each of the indicators where quality improvement is sought?
- How will the facility manager monitor whether these activities are undertaken?

Information from additional sporadic evaluation can be extremely useful in providing insights into the factors contributing to the facility's performance. This information may come from different sources such as the Facility Supervisory Checklist or the TB, HIV, AIDS and STI Integrated Audit Tool. The TB components of the latter are provided in Section 17.9. The tool has many benefits, particularly in terms of promoting TB and HIV integration. From a management perspective, the data is readily converted into indicators that complement routine monitoring and evaluation.

Trying to identify the underlying practices that contribute to poor programme performance is a challenge. All too frequently staff and managers become defensive and provide explanations for programme performance that are not borne out by the data available. Building data analysis skills and instilling the practice of self-reflection is necessary at all levels in the health system in working towards systematic improvements.

17.8 Programme monitoring indicators

17.8.1 Case finding indicators

Indicator	Description	Source	Collection	Level	Target
1. TB case notification rate	**Numerator:** Total TB cases reported in the past year (× 100,000) **Denominator:** Total population in the specified area	ETR.net	Quarterly	All	-
2. PTB case notification rate	**Numerator:** Total PTB cases reported in the past year (× 100,000) **Denominator:** Total population in the specified area	ETR.net	Quarterly	All	-
3. Case detection rate (Smear positive)	**Numerator:** Annual number of new smear-positive TB cases notified **Denominator:** Annual number of new smear-positive TB cases estimated (incidence)	ETR.net Surveillance data	Annual	National	70%
4. Bacteriological coverage	**Numerator:** Number of PTB cases diagnosed by bacteriological tests (smear and or culture) **Denominator:** Total PTB cases reported, excluding children 0–7 years with no smear	ETR.net	Quarterly	All	100%
5. TB suspect smear positivity rate	**Numerator:** Number of sputa found to be smear-positive amongst TB suspects **Denominator:** Total number of sputum smear samples sent for TB suspects	TB Case Identification & Follow-up register	Quarterly	All	10%
6. Proportion smear-positive pulmonary TB cases	**Numerator:** Number of smear positive pulmonary TB cases **Denominator:** Total number of pulmonary TB cases	ETR.net	Quarterly	All	50-70%
7. Smear-positive retreatment ratio	**Numerator:** Number of retreatment smear positive pulmonary cases **Denominator:** Total number of smears positive pulmonary cases (new and retreatment).	ETR.net	Quarterly	All	-
8. Smear-positive sputum turn around time*	**Numerator:** Number of smear positive results received from the laboratory within 48 hours of the specimen being taken (spot specimen) including weekends and public holidays. **Denominator:** Total number of smears submitted	TB Case Identification & Follow-up register	Quarterly	All	80% within 48 hours

* Sub/districts report on the % of facilities that meet the target of 80% sputum TAT for all smear microscopy results within 48 hours.

17.8.2 Case holding indicators

Indicator	Description	Source	Collection	Level	Target
1. Smear-positive treatment commencement ratio	**Numerator:** Number of smear positive pulmonary clients in TB register that started treatment **Denominator:** Total number of smear positive clients diagnosed (from TB Sputum register)	TB register; TB Case Identification & Follow-up register	Quarterly	All	95-100%
2. New smear-positive conversion rates	**Numerator:** Number of new smear positive cases that convert from smear positive to smear negative at 2 months **Denominator:** Total number of new smear-positive cases	ETR.net	Quarterly	All	> 85%
3. New smear-positive conversion results not available	**Numerator:** Number of new smear positive cases for whom the smear conversion result at 2 months is not available* **Denominator:** Total number of new smear-positive cases	ETR.net	Quarterly	All	
4. New smear-positive conversion sputum not taken	**Numerator:** Number of new smear positive cases that did not have sputum taken for evaluation at 2 months **Denominator:** Total number of new smear-positive cases	ETR.net	Quarterly	All	
5. Retreatment smear-positive conversion rates	**Numerator:** Number of retreatment smear positive cases that convert from smear positive to smear negative at 3 months **Denominator:** Total number of retreatment smear-positive cases	ETR.net	Quarterly	All	> 85%
6. Retreatment smear-positive conversion results not available	**Numerator:** Number of retreatment smear positive cases for whom the smear conversion result at 3 months is not available** **Denominator:** Total number of retreatment smear-positive cases	ETR.net	Quarterly	All	
7. Retreatment smear-positive conversion sputum not taken	**Numerator:** Number of retreatment smear positive cases that did not have sputum taken for evaluation at 3 months **Denominator:** Total number of retreatment smear-positive cases	ETR.net	Quarterly	All	
8. Clients under direct observation of therapy (DOT)	**Numerator:** Number of TB clients receiving direct observation of 80% of doses of medication per TB guidelines at a specific time. **Denominator:** Total number of TB clients receiving therapy at that time	ETR.net	Quarterly	All	
9. Clients under clinic direct observation of therapy (DOT)	**Numerator:** Number of TB clients receiving direct observation of 80% of doses of medication per TB guidelines at the clinic at a specific time. **Denominator:** Total number of TB clients receiving therapy at that time	ETR.net	Quarterly	All	
10. Clients under Community/ Workplace direct observation of therapy (Community/Workplace DOT)	**Numerator:** Number of TB clients receiving direct observation of 80% of doses of medication per TB guidelines in the community or at the workplace at a specific time. **Denominator:** Total number of TB clients receiving therapy at that time	ETR.net	Quarterly	All	

* Result not available at the clinic or not available within the specified time frame of 29-70 days for new or ** 29-100 days for retreatment clients, from treatment start date

17.8.3 TB and HIV indicators

Indicator	Description	Source	Collection	Level	Target
1. HIV testing rates	**Numerator:** Number of TB cases (adults and children) with known current HIV status i.e. tested for HIV currently or previously if HIV positive **Denominator:** Total number of TB cases registered	ETR.net	Quarterly	All	90%
2. HIV seroprevalence amongst TB cases	**Numerator:** Number of registered TB cases known to be HIV positive **Denominator:** Total number of registered TB cases tested for HIV	ETR.net	Quarterly	All	-
3. CD4 testing rate amongst HIV positive TB cases	**Numerator:** Total number of registered HIV positive TB cases with CD4 test / CD4% done **Denominator:** Total number of registered TB clients known to be HIV positive				100%
3. Proportion of HIV positive TB cases on ART pre-TB treatment	**Numerator:** Total number of registered TB clients on ART prior to commencing TB treatment **Denominator:** Total number of registered TB clients known to be HIV positive	ETR.net	Quarterly	All	
4. Proportion of HIV positive TB cases not on ART pre-TB now requiring ART	**Numerator:** Total number of registered HIV+ TB clients not on ART pre-TB treatment who require ART (Child: WHO Stage 3 or 4 or CD4<20% in child <18 months or <15% in child >18months or recurrent hospitalisation. Adult with CD4<200 or WHO Stage 4.) **Denominator:** Total number of registered TB clients who are known to be HIV positive	ETR.net	Quarterly report	All	
5. Proportion HIV+ TB cases commenced on ART whilst on TB treatment	**Numerator:** Total number of registered HIV+ TB clients not on ART who commence ART whilst on TB treatment **Denominator:** Total number of registered HIV+ TB clients not on ART pre-TB treatment who require ART ((Child: WHO Stage 3 or 4 or CD4<20% in child <18 months or <15% in child >18months or recurrent hospitalisation. Adult with CD4<200 or WHO Stage 4.)	ETR.net	Quarterly report	All	100%
6. Cotrimoxazole coverage rates amongst HIV positive TB cases	**Numerator:** Total number of registered HIV+ TB clients commencing cotrimoxazole **Denominator:** Total number of registered HIV+ TB clients requiring cotrimoxazole (all HIV+ TB clients except adult or child over 6 years on ARV with CD4>200 or child over 18 months with CD4%>15% for at least 6 months)	ETR.net	Quarterly	All	100%

17.8.4 TB treatment outcome indicators - new smear-positive cases

Indicator	Description	Source	Collection	Level	Target
1. New smear-positive cure rates	**Numerator:** Number of new smear-positive cases that are smear negative in the last month of treatment and on at least one other occasion at least 30 days prior **Denominator:** Total number of new smear-positive cases registered	ETR.net	Quarterly	All	85%
2. New smear-positive completion rates	**Numerator:** Number of new smear-positive cases that complete the full course of treatment who did not meet the criteria for cure or failure **Denominator:** Total number of new smear-positive cases registered	ETR.net	Quarterly	All	Less than 5%
3. New smear-positive defaulter rate	**Numerator:** Number of new smear-positive cases that interrupted treatment for more than 2 consecutive months **Denominator:** Total number of new smear-positive cases registered	ETR.net	Quarterly	All	Less than 5%
4. New smear-positive death rate	**Numerator:** Number of new smear-positive cases that died during treatment, irrespective of cause **Denominator**: Total number of new smear-positive cases registered	ETR.net	Quarterly	All	Less than 5%
5. New smear-positive treatment failure	**Numerator:** Number of new smear-positive cases that are smear-positive 5 months or later after initiating treatment or that are diagnosed as MDR-TB **Denominator:** Total number of new smear-positive cases registered	ETR.net	Quarterly	All	Less than 5%
6. New smear-positive transfer-out rate	**Numerator**: Number of new smear-positive pulmonary TB cases registered that were transferred to another sub/district and for whom there is no treatment outcome information **Denominator:** Total number of new smear-positive pulmonary TB cases registered during the same period	ETR.net	Quarterly	All	-
7. New smear-positive not evaluated	**Numerator:** Number of new smear-positive cases that have no outcome at the end at the end of the continuation phase of treatment and that did not complete the full course of treatment **Denominator:** Total number of new smear-positive cases registered	ETR.net	Quarterly	All	0%

17.8.5 TB Treatment outcome indicators - retreatment smear-positive cases

Indicator	Description	Source	Collection	Level	Target
1. Retreatment smear-positive cure rates	**Numerator:** Number of retreatment smear-positive cases that are smear negative in the last month of treatment and on at least one other occasion at least 30 days prior **Denominator:** Total number of retreatment smear-positive cases registered	ETR.net	Quarterly	All	85%
2. Retreatment smear-positive completion rates	**Numerator:** Number of retreatment smear-positive cases that complete the full course of treatment who did not meet the criteria for cure or failure **Denominator:** Total number of retreatment smear-positive cases registered	ETR.net	Quarterly	All	Less than 5%
3. Retreatment smear-positive interrupter rate	**Numerator:** Number of retreatment smear-positive cases that interrupted treatment for more than 2 consecutive months **Denominator:** Total number of retreatment smear-positive cases registered	ETR.net	Quarterly	All	Less than 5%
4. Retreatment smear-positive death rate	**Numerator:** Number of retreatment smear-positive cases that died during treatment, irrespective of cause **Denominator**: Total number of retreatment smear-positive cases registered	ETR.net	Quarterly	All	Less than 5%
5. Retreatment smear-positive treatment failure	**Numerator:** Number of retreatment smear-positive cases that are smear-positive 5 months or later after initiating treatment or that are diagnosed as MDR-TB **Denominator:** Total number of retreatment smear-positive cases registered	ETR.net	Quarterly	All	Less than 7%
6. Retreatment smear-positive transfer-out rate	**Numerator**: Number of retreatment smear-positive pulmonary TB cases registered that were transferred to another sub/district and for whom there is no treatment outcome information **Denominator:** Total number of retreatment smear-positive pulmonary TB cases registered during the same period	ETR.net	Quarterly	All	-
7. Retreatment smear-positive not evaluated	**Numerator:** Number of retreatment smear-positive cases that have no outcome at the end at the end of the continuation phase of treatment and that did not complete the full course of treatment **Denominator:** Total number of retreatment smear-positive cases registered	ETR.net	Quarterly	All	

17.8.6 Programme management indicators

Indicator	Description	Source	Collection	Level	Target
1. DOTS Coverage	**Numerator:** Population living in the districts implementing the DOTS strategy **Denominator:** Total population	Progress report	Annual	Province National	100%
2. Facility DOTS Coverage	**Numerator:** Number of primary health care facilities clinics offering DOTS services (diagnostics and daily observed therapy) **Denominator**: Total number of primary health care facilities	Progress report	Annual	Province National	100%
3. Timely Reporting rates (Province/District)	**Numerator:** Number of provinces / districts submitting correctly validated quarterly reports by the due dates to national / provincial level **Denominator**: Total number of provinces / districts	Progress report	Quarterly report	Province National	100%
4. Supervisory visit rates	**Numerator:** Number of supervisory visits undertaken at district level **Denominator**: Number of supervisory visits planned at district level	Progress report	Quarterly report	Province National	100%
5. Drug stocks out rates*	**Numerator:** Number of TB facilities with a drug stock-out of any regimen 1 or regimen 2 drug in a 6-month period **Denominator**: Total number of TB facilities	Progress report	Quarterly	District, Province	0%
6. Sputum smear quality control	**Numerator:** Proportion of false positive or false negative slides in QA sample **Denominator**: Number of slides evaluated	QA report	Supervision	Province National	FP: 0-2% FN: 0-5%
7. Accessibility of laboratory culture services	**Numerator:** Number of NHLS laboratories with sputum culture services **Denominator**: Number of NHLS laboratories providing smear microscopy.	Progress reports	Half-yearly evaluation meetings	Province National	Area specific
8. MDR resistance rates in new TB cases	**Numerator:** Number of cases of MDR-TB with no history of previous TB or previous TB treatment for 1 month or less **Denominator**: Total number of new TB cases	NHLS Report	Quarterly	Province National	0-1%
9. MDR resistance rates in previously treated TB cases	**Numerator:** Number of cases of MDR-TB with one or more episodes of previous TB treatment **Denominator**: Total number of retreatment TB cases	NHLS Report	Quarterly	Province National	2-4%

17.9 TB, HIV and STI integrated audit tool (TB programme components)

Components of Facility Manager Questionnaire That Supplement Routine Data

	Part B: Staffing					
B3	Total number of clinical staff (professional nurses and medical officers) working at this facility. [1 FT PN=1; 1 Part-time PN=1; 1 FT MO=1; 1 sessional MO=1]					
B5	Number of clinical staff (professional nurses and medical officers) that have attended a TB clinical training programme.					
B14	Is there a specific nurse allocated to manage the TB programme in the facility?				Yes	No
B15	Number of community health workers involved in the TB programme					
B16	Number of community health workers involved in the TB programme who have undergone DOTS training					
	Part C: Health Services and Systems					
C4	Is daily screening for TB and daily DOT for TB available?				Yes	No
C12	Is there a mechanism in place to recall clients to the clinic? PROMPT and look for evidence					
		I) Who does the recall? (Answer "Yes" if responsibility allocated; "No" if not)	II) How often is recall done? (Answer "Yes" if done at a minimum on a weekly basis; "No" if not)	III) How do staff members know who to recall? (Answer "Yes" if process exists for keeping track/getting feedback about those recalled; "No" if	IV) Mechanism in place? Answer "Yes" if the answer to I, II and III was "Yes"	
	a) Positive TB suspects					
	b) TB defaulters					
	c) TB contacts					
	e) CD4 below 200					
	Part D: Drug / Stock Review					
	Have you had stockouts of any of the following items in the last 6 months? (If "Yes" provide details)					
D1	Rapid tests (screening or confirmatory)	No	Yes		Details:	
D2	Cotrimoxazole (Bactrim)	No	Yes		Details:	
D4	TB Drugs (Regimen 1 or 2)	No	Yes	N/A	Details:	
	Ask and observe whether there is a mechanism in place to monitor stock levels of these items (Bin cards, electronic system etc)					
D7	Rapid tests (screening or confirmatory)	No	Yes		Mechanism:	
D8	Cotrimoxazole (Bactrim)	No	Yes		Mechanism:	
D10	TB Drugs	No	Yes	N/A	Mechanism:	

TB Folder Review

Sampling procedure: From the TB register, starting on a date 4 months ago and working backwards to 6 months ago, select sequential TB clients until 10 folders are found. The sequence used (every 2nd or 3rd folder etc) will be determined by the number of clients registered monthly. The goal is to get a spread of clients registered over the period. Note any folders that are not possible to locate in this process. Answer the questions below as Yes (Y), No (N) or Not Applicable (N/A).

Number of folders retrieved from the folder system _____ Number of folders requested for review but not found in the folder system _____

		FOLDER RESULTS										SUMMARY RESULTS		
		Folder 1	Folder 2	Folder 3	Folder 4	Folder 5	Folder 6	Folder 7	Folder 8	Folder 9	Folder 10	Total Yes	Total No	Total N/A
1	Are all contact details for the client entered on the Blue Folder? (Name, Surname, home and work address and telephone numbers of client and next of kin details)													
2	Did smear positive clients commence treatment within 5 days? (5 days from first sputum taken to commencement of treatment, including weekends and holidays)													
3	Is patient category correct? (Confirm against client history)													
4	Are the relevant sputum results filed or results noted?													
5	Is the date for recall of 2/3 month and 5/7 month sputa and end of treatment noted?													
6	Is the patient placed on the correct regimen? (Regime, dosage, duration of intensive and continuation phase to date)													
7	Is there a record that the client had an HIV test? (current or previous)													
8	Was client HIV positive?													
9	Was the routine HIV stationery used to record clinical care of HIV positive clients?													
10	If HIV+, has a CD4 count and WHO staging been done?													
11	If HIV+, is cotrimoxazole (Bactrim) prophylaxis prescribed?													
12	Were the contraceptive needs assessed for men and women & due date for repeats recorded for women?													
13	Are child contacts under 5 years of age recorded?													
14	Are child contacts under 5 years of age investigated & commenced on prophylaxis?													
15	Is the ICD code, patient category, smear conversion and discharge code (if discharged) correctly transferred into the register?													

References

The following source documents have been used in compiling these guidelines:

1 The Stop TB Strategy: Building on and enhancing DOTS to meet the TB-related Millennium Development Goals, World Health Organization, 2006.

2 Treatment of Tuberculosis: Guidelines for National Programmes, 3rd Edition, World Health Organisation, 2003.

3 International Standards for Tuberculosis Care (ISTC). Tuberculosis Coalition for Technical Assistance. The Hague: Tuberculosis Coalition for Technical Assistance, 2006.

4 Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents - Recommendations for HIV-prevalent and resource-constrained settings. World Health Organisation, 2007.

5 A Tuberculosis Guide for Specialist Physicians, International Union Against Tuberculosis and Lung Disease, 2003.

6 Guidelines for National Tuberculosis Programmes on the Management of Tuberculosis in Children, World Health Organisation, 2006.

7 Tuberculosis Treatment Support and Adherence Guidelines, National Department of Health South Africa, 2006.

8 Interventions for Tuberculosis Control and Elimination, International Union Against Tuberculosis and Lung Disease, 2002.

9 Management of Drug-Resistant Tuberculosis in South Africa, Policy Guidelines, June 2007.

10 Guidelines for the management of HIV-infected children, Department of Health, South Africa, 2005.

11 National Antiretroviral Treatment Guidelines, Department of Health, South Africa, 2004.

12 National TB Infection Control Guidelines, Department of Health, South Africa, June 2007.

13 Guidelines for the Prevention of Tuberculosis in Health Care Facilities in Resources Limited Settings, World Health Organisation, 1999.

14 Compendium of Indicators for Monitoring and Evaluating National Tuberculosis Programs, Stop TB Partnership, August 2004.

15 The TB AND HIV /STI Integrated Audit Tool, School of Public Health, University of the Western Cape, Provincial Health Department of the Western Cape, City of Cape Town Health Directorate and Medical Research Council, February 2008.

Annexure 1: Tuberculin Skin Testing

The tuberculin skin test (TST) has limited value in clinical work, especially where TB is common. The test shows hypersensitivity to proteins of the TB bacillus, as a result either of infection with M. tuberculosis or induced by Bacille Calmette-Guérin (BCG) vaccination. It indicates infection and not TB disease. In children, infection is one of the criteria used in the diagnosis of TB. In adults, it is used to diagnose latent infection in immunosuppressed clients who would benefit from INH prophylactic therapy.

The test involves injecting tuberculin purified protein derivative (PPD) into the skin. Previous exposure results in a local delayed type hypersensitivity reaction within 24-72 hours. The reaction is identified as palpable induration (hardness) at the site of injection. The response only indicates hypersensitivity. It shows that the person has at some time been infected with M. tuberculosis or been vaccinated. By itself, it does not indicate the presence or extent of tuberculosis disease.

The reaction after previous BCG is usually weaker than the reaction to natural infection and remains positive for several years thereafter. It should also be noted that a negative result does not rule out the diagnosis of TB disease. Various conditions, including HV may suppress the reaction.

Performing a Mantoux Tuberculin Skin Test

- The Mantoux TST is the most reliable test available. The test requires:
  - 2 units of tuberculin purified protein derivative PPD-RT23 2TU or
  - 5 units of PPD-S 5TU.
- Use a single-dose tuberculin syringe and a short 27-gauge needle with a short bevel to do the test.
- Draw up 0.1ml of PPD of the correct strength into the syringe.
- Clean an area of skin in the mid anterior section of the forearm. The PPD is injected between layers of skin (intradermally). Keep the needle almost parallel to the skin, with the bevel pointing upwards during insertion. It is important to ensure that the injection goes into and not under the skin. A small papule should form at the injection site; if it does not, the PPD has been injected too deeply and the test should be repeated at a different site.
- The reaction to the test at the site of the injection is measured 48-72 hours later by noting the widest **transverse** point across the edges of the raised, thickened area. This area of induration and not redness is measured.
- To help measure accurately, mark the edges of the induration at the widest point with a pen and measure the exact distance between the two points in millimetres.

Reading the Tuberculin Skin Test		
Immune Status	**HIV positive, malnourished, severe illness**	**Others (including previous BCG)**
Diameter of induration in positive test	≥ 5 mm	≥ 10 mm

Interpreting a positive TST

- A positive test indicates infection with TB, but not necessarily TB disease.
- In a child under 5 years or an HIV-infected child of any age, a positive skin test indicates recent infection and is a risk factor for progression to disease. In the presence of other features such as a history of a TB contact, signs and symptoms of TB and chest x-ray changes, a positive tuberculin skin test is suggestive of TB disease in children (see Section 11.4).
- Children under the age of 5 years, HIV-infected children of any age and HIV-infected adults, who have a positive skin test and no symptoms or signs of TB, should be put on TB prophylaxis for six months. (see sections 11.1.3 and 12.2).

Interpreting a negative TST

- A negative tuberculin skin test does not exclude TB; various conditions may cause a false negative reaction including:
  - HIV infection
  - Malnutrition
  - Severe viral infections (e.g. measles, chicken pox)
  - Cancer
  - Immuno-suppressive drugs (e.g. steroids)
  - Severe disseminated TB.

Annexure 2: Essential Tuberculosis Drugs

1 Isoniazid

Group: antimycobacterial agent
Tablet: 100mg, 300mg
Injection: 25 mg/rn/in 2-ml ampoule

General information

Isoniazid, the hydrazide of isonicotinic acid is highly bactericidal against replicating tubercle bacilli. It is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than one hour in fast acetylators to more than three hours in slow acetylators. It is largely excreted in the urine within 24 hours, mostly as inactive metabolites.

Clinical information

Uses

- A component of all TB chemotherapeutic regimens currently recommended by WHO
- Isoniazid alone is occasionally used to prevent:
  - Transmission to close contacts at high risk of disease.
  - Progression of infection to primary complex in recently infected, asymptomatic individuals.
  - Development of active TB in immunodeficient individuals.

Dosage and administration

- Isoniazid is normally taken orally but it may be administered intramuscularly to critically ill clients.

Treatment (combination therapy)

- Adults 5 (4-6) mg/kg daily, maximum 300 mg
- Children 10 (8-12) mg/kg daily, maximum 300 mg

Preventive therapy:

- Adults: 300 mg daily for six months at least
- Children: 10 mg/kg daily (maximum 300 mg) for six months at least

Contraindications:

- Known hypersensitivity
- Active hepatic disease

Precautions

- Monitoring of serum concentrations of hepatic transaminases, where possible, is useful in clients with pre-existing chronic liver disease.
- Clients at risk of peripheral neuropathy as a result of malnutrition, chronic alcohol dependence or diabetes should additionally receive pyridoxine, 10-50 mg daily. Where the standard of health in the community is low, this should be offered routinely.
- Isoniazid interacts with anti-convulsants used for epilepsy. It may be necessary to reduce the dosage of these drugs during treatment with isoniazid.

Use in pregnancy

- Whenever possible, the six-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used.

Adverse effects

- Isoniazid is generally well tolerated at recommended doses. Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment.
- The risk of peripheral neuropathy is excluded if vulnerable clients receive daily supplements of pyridoxine. Other less common forms of neurological disturbance, including optic neuritis, toxic psychosis arid generalized convulsions, can develop in susceptible individuals, particularly in the later stages of treatment and occasionally necessitate the withdrawal of isoniazid.
- Hepatitis is an uncommon but potentially serious reaction that can usually be averted by prompt withdrawal of treatment. More often, however, a sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is not of clinical significance, and usually resolves spontaneously during continuation of treatment.

Drug interactions

- Isoniazid tends to raise plasma concentrations of phenytoin and carbamazepine by inhibiting their metabolism in the liver.
- The absorption of isoniazid is impaired by aluminium hydroxide.

Overdosage

- Nausea, vomiting, dizziness, blurred vision and slurring of speech occur within 30 minutes to three hours of overdosage.
- Massive poisoning results in coma preceded by respiratory depression and stupor. Severe intractable seizures may occur. Emesis and gastric lavage, activated charcoal, anti-epileptics and IV sodium bicarbonate can be of value if instituted within a few hours of ingestion. Subsequently, haemodialysis may be of value. Administration of high doses of pyridoxine is necessary to

prevent seizures.

Storage
- Tablets should be kept in well-closed containers, protected from light. Solution of injection should be stored in ampoules protected from light

2 Rifampicin

Group: antimycobacterial agent
Capsule or tablet: 150 mg, 300 mg

General information
A semi synthetic derivative of rifamycin, a complex macrocyclic antibiotic, inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extra cellular locations. Rifampicin is lipid-soluble. Following oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and body fluids; if the meninges are inflamed, significant amounts enter the cerebrospinal fluid.

A single dose of 600 mg produces a peak serum concentration of about 10 micrograms/ml in two to four hours, which subsequently decays with a half-life of two to three hours. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces. Since resistance readily develops, rifampicin must always be administered in combination with other effective antimycobacterial agents.

Clinical information
Uses
- A component of all six and eight month TB chemotherapeutic regimens currently recommended by WHO.

Dosage and administration
- Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food. This however may not be clinically significant and food can reduce intolerance to drugs.
- Adults and children: 10 mg/kg (8-12 mg/kg) daily, maximum 600mg daily, two or three times weekly.

Contra-indications
- Known hypersensitivity to rifamycins
- Hepatic dysfunction

Precautions
- Serious immunological reactions resulting in renal impairment, haemolysis or thrombocytopenia are on record in clients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation it should be immediately and definitely withdrawn.
- Careful monitoring of liver function is required in the elderly and in clients who are alcohol-dependent or have hepatic disease. Clients should be warned that treatment may produce reddish coloration of urine, tears, saliva and sputum, and that contact lenses may be irreversibly stained.

Use in pregnancy
- Whenever possible, the six-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used.
- Vitamin K should be administered at birth to the infant of a mother taking rifampicin because there is a risk of postnatal haemorrhage.

Adverse effects
- Rifampicin is well tolerated by most clients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe.
- Other adverse effects (fever, influenza-like syndrome and tbrombocytopenia) are more likely to occur with intermittent administration, and skin rashes just as likely.
- Exfoliative dermatitis is more frequent in HIV positive TB clients.
- Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported in clients taking the drug three times weekly. These reactions usually subside if the regimen is changed to one with daily dosage.
- Moderate rises in serum concentrations of bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur which is potentially fatal. It is consequently important not to exceed the maximum recommended daily dose of 10 mg/kg (600 mg).

Drug interactions
- Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. These include corticosteroids, steroid contraceptives, oral hypoglycaemic agents, oral anticoagulants, phenytoin, cimetidine, cyclosporin and digitalis glycosides.
- Since rifampicin reduces the effectiveness of the oral contraceptive pill, women should consequently be advised to choose between one of the following two options for contraception.
  - Following consultation with a physician, she could take an oral contraceptive pill containing a higher dose of oestrogen (50mcg).
  - Alternatively she could use a non-hormonal method of contraception throughout rifampicin treatment and for at least one month subsequently. Current antiretroviral drugs (non-nucleoside reverse transcriptase inhibitors and protease inhibitors) interact with rifampicin. This may result in the ineffectiveness of antiretroviral drugs, ineffective treatment of TB or an

increased risk of drug toxicity. Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B12 disturbed.

Overdosage

- Gastric lavage may be of value if undertaken within a few hours of ingestion. Very large doses may depress central nervous function. There is no specific antidote and treatment is supportive.

Storage

- Capsules and tablets should be kept in tightly closed containers, protected from light.

3 Pyrazinamide

Group: antimycobacterial agent
Tablet: 400 mg

General information
A synthetic analogue of nicotinamide that is only weakly bactericidal against M tuberculosis, but has potent sterilizing activity, particularly in the relatively acidic intracellular environment of macrophages and in areas of acute inflammation. It is highly effective during the first two months of treatment while acute inflammatory changes persist and its use has enabled treatment regimens to be shortened and the risk of relapse to be reduced. It is readily absorbed from the gastrointestinal tract and is rapidly distributed throughout all tissues and fluids. Peak plasma concentrations are attained in two hours and the plasma half-life is about 10 hours. It is metabolized mainly in the liver and is excreted largely in the urine.

Clinical information
Uses

- A component of all six and eight month TB chemotherapeutic regimens currently recommended by WHO.

Dosage and administration

- Adults and children (for the first two or thee months):
  - 25 mg/kg (20-30 mg/kg) daily
  - 35 mg/kg (30-40 mg/kg) three times weekly

Contraindication

- Known hypersensitivity
- Severe hepatic impairment

Precautions

- Clients with diabetes should be carefully monitored since blood glucose concentrations may become labile.
- Gout may be exacerbated.

Use in pregnancy

- The six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used whenever possible.

Adverse effects

- Pyrazinamide may cause gastro intestinal intolerance.
- Hypersensitivity reactions are rare, but some clients complain of slight flushing of the skin.
- Moderate rises in serum transaminase concentrations are common during the early phases of treatment. Severe hepatotoxicity is rare.
- As a result of inhibition of renal tubular secretion, a degree of hyperuricaemia usually occurs, but this is often asymptomatic. Gout requiring treatment with allopurinol occasionally develops. Arthralgia, particularly of the shoulders, may occur and is responsive to simple analgesics (aspirin). Both hyperuricaemia and arthralgia may be reduced by prescribing regimens with intermittent administration of pyrazinamide.

Overdosage

- Little has been recorded of pyrazinamide overdose. Acute liver damage and hyperuricaemia have been reported. Treatment is essentially symptomatic. Emetic and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.

Storage

- Tablets should be stored in tightly closed containers, protected from light.

4 Streptomycin

General information
An aminoglycoside antibiotic derived from Streptomyces griseus that is used in the treatment of TB and sensitive Gram-negative infections. Streptomycin is not absorbed from the gastrointestinal tract but, after intramuscular administration, it diffuses readily into the extracellular component of most body tissues and it attains bactericidal concentrations, particularly in tuberculous cavities. Little normally enters the cerebrospinal fluid, although penetration increases when the meninges are inflamed. The plasma half-life, which is normally two to three hours, is considerably extended in the new-born, in the elderly and in clients with severe renal impairment. It is excreted unchanged in the urine.

Clinical information

Uses

- A component of several TB chemotherapeutic regimens currently recommended by WHO.

Dosage and administration

- Streptomycin must be administered by deep intramuscular injection.
- Adults and children
  - 15 mg/kg (12-18 mg/kg) daily
  - Clients over 60 years may not be able to tolerate more than 500-750 mg daily.

Contraindications

- Known hypersensitivity
- Auditory nerve impairment
- Myasthenia gravis

Precautions

- Hypersensitivity reactions are rare; if they occur (usually during the first weeks of treatment) streptomycin should be withdrawn immediately. Once fever and skin rash have resolved, desensitization may be attempted.
- Streptomycin should be avoided, when possible, in children because the injections are painful and irreversible auditory nerve damage may occur.
- Both the elderly and clients with renal impairment are also vulnerable to dose-related toxic effects resulting from accumulation. Where facilities are available to monitor and function closely it may be possible to give streptomycin in reduced doses to clients with renal impairment. Where possible, serum levels should be monitored periodically and dosage adjusted appropriately to ensure that plasma concentrations, as measured when the next dose is due, do not rise above 4 mg/ml.
- Protective gloves should be worn when streptomycin injections are administered, to avoid sensitisation dermatitis.

Use in pregnancy

- Streptomycin should not be used in pregnancy. It crosses the placenta and can cause auditory nerve impairment and nephrotoxicity in the fetus.

Adverse effects

- Injections are painful and sterile abscesses can form at injection sites.
- Hypersensitivity reactions are common and can be severe. Impairment of vestibular function is uncommon with currently recommended doses.
- Dosage should be reduced if headache, vomiting, vertigo and tinnitus occur.
- Streptomycin is less nephrotoxic than other aminoglycoside antibiotics. Dosage must be reduced by half immediately if urinary output falls, if albuminuria occurs or if tubular casts are detected in the urine.
- Haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia and lupoid reactions are rare adverse effects.

Drug interactions

- Other ototoxic or nephrotoxic drugs should not be administered to clients receiving streptomycin. These include other aminoglycoside antibiotics, amphotericin B, cefalosporins, etacrynic acid, cyclosporin, cisplatin, furosemide and vancomycin.
- Streptomycin may potentiate the effect of neuromuscular blocking agents administered during anaesthesia.

Overdosage

- Haemodialysis can be beneficial. There is no specific antidote and treatment is supportive.

Storage

- Solutions retain their potency for 48 hours after reconstitution at room temperature and for up to 14 days when refrigerated.
- Powder for injection should be stored in tightly closed containers protected from light.

5 Ethambutol

- Group: antimycobacterial agent
- Tablet: 100 mg, 400 mg (hydrochloride)

General information

A synthetic congener of I ,2-ethanediamine that is active against M. tuberculosis, M. bovis and some non-specific mycobacteria. It is used in combination with other TB drugs to prevent or delay the emergence of resistant strains. It is readily absorbed from the gastrointestinal tract. Plasma concentrations peak in 2-4 hours and decay with a half-life of 3-4 hours. Ethambutol is excreted in the urine both unchanged and as inactive hepatic metabolites, about 20% is excreted in the faeces as unchanged drug.

Clinical information

Uses

- An optional component of several TB chemotherapeutic regimens currently recommended by WHO.

Dosage and administration

- Adults: 15 mg/kg (15-20 mg/kg) daily
- Children: maximum 15 mg/kg daily
- Dosage must always be carefully calculated on a weight basis to avoid toxicity, and should be reduced in clients with impaired renal function.

Contraindications
- Known hypersensitivity.
- Pre-existing optic neuritis from any cause.
- Creatinine clearance of less than 50 ml/minute.

Precautions
- Clients should be advised to discontinue treatment immediately and to report to a doctor should their sight or perception of colour deteriorate. Whenever possible, renal function should assessed before treatment.

Use in pregnancy
- The six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used.
- Ethambutol should be used if a fourth drug is needed during the initial phase.

Adverse effects
- Dose-dependent optic neuritis can result in impairment of visual acuity and colour vision. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Ocular toxicity is rare when used for 2-3 months at recommended doses.
- Signs of peripheral neuritis occasionally develop in the legs

Overdosage
- Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.

Storage
- Tablets should be stored in well-closed containers.

Annexure 3: Clinically Significant Drug Interactions

Drug class	Drugs whose concentrations are substantially reduced by Rifampicin	Comments
Anti-infectives	Protease inhibitors (Saquinavir, Indinavir, Nelfinavir, Ritonavir, Lopinavir/ ritonavir) NNRTI (Nevirapine, Efivarenz)	Saquinavir/ ritonavir can be used with Rifampicin, Lopinavir/ ritonavir can also be used with adjustment of ritonavir dosage Doses of Nevirapine and Efivarenz need to be increased
	Macrolide antibiotic (clarithromycin, erythromycin)	Azithromycin has no significant interaction
	Doxycycline Azole antifungal agents (Ketoconazole, Itraconazole, voriconazole)	May require use of a drug other than doxycycline Concentrations of these drugs may be sub therapeutic. Fluconazole may be used but dose might need to be increased
	Mefloquine	Consider alternate form of malaria prophylaxis
	Chloramphenicol	Consider an alternate antibiotic
	Atovaquone	Consider alternate form of pneumocystis carinii treatment or prophylaxis
Hormone therapy	Ethinyl estradiol, norethindrone	Women on oral contraception should be advised to add a barrier method of contraception May require alternate therapy
	Tamoxifen	May require increased dose of levothyroxine.
	Levo-thyroxine	Monitoring of serum TSH recommended
Narcotics Anticoagulants	Methadone Warfarin	May require methadone dose increase May require 2-3 fold dose increase, monitoring prothrombin time recommended
Immuno-suppresive agents	Cyclosporine, tacrolimus	Monitoring of cyclosporin serum concentrations may assist with dosing
	Corticosteroids	Monitor clinically, may require 2-3 fold increase in corticosteroid dose
Anticonvulsants	Phenytoin, Lamotrigine	Therapeutic drug monitoring recommended may require anticonvulsant dose increase
Psychotropic drugs	Nortiptyline	Therapeutic drug monitoring recommended, may require dose increase or change to alternate psychotropic drug.
	Haloperidol, Quetiapine	Monitor clinically may require dose increase or use of alternate psychotropic drug Monitor clinically may require dose increase or use of alternate psychotropic drug
Hypolipidemics	Benzodiazepines (diazepam, tria zolam, zolpidem, buspirone) -	Monitor hypolipidemic effect, may require use of an alternate hypolipidemic drug
Sulfonurea hypoglycaemics	Simvastatin, Fluvastatin	Monitor blood glucose, may require dose increase or change to an alternate hypoglycaemic drug
Bronchodilators	Tolbutamide, chlorpropamide, glimepiride, repaglinide, glyburide	Therapeutic drug monitoring recommended, may require theophylline dose increase
Cardiovascular agents	Theophylline	Clinical monitoring recommended, may require change to alternate cardiovascular agent
	Verapamil, Nifedipine,	Clinical monitoring recommended, may require dose
	Diltiazem	increase or change to alternate cardiovascular agent
	Propranolol, metoporol	Clinical monitoring recommended, may require dose increase or change to alternate cardiovascular agent
	Enalapril, Losartan	Therapeutic drug monitoring recommended, may require dose increase
	Digoxin (in clients with renal insufficiency), Digitoxin	Therapeutic drug monitoring recommended, may require quinidine dose increase
	Quinidine	Clinical monitoring recommended, may require change to alternate cardiovascular agent

Annexure 4: Recommended treatment regimens for children

Regimen	Definition	Initial phase Daily treatment	Continuation phase Daily treatment
Regimen 3	New smear positive PTB, smear negative with extensive parenchymal involvement, severe forms of extra pulmonary TB	HRZE for 2 months	HR for 4 months
Regimen 3 a	Previously treated smear positive PTB returning after default, failure or relapse	HRZE + Streptomycin for 2 months followed by HRZE for 1 month	HRE for 5 months
Regimen 3 b	New smear negative PTB without parenchymal involvement, Less severe forms of extra pulmonary TB	HRZ for 2 months	HR for 4 months
Regimen 3 c	TB Meningitis	HRZS for 2 months	HR for 4 months
		HRZ (S or Ethionamide) for 2 months	HR for 7-10 months
		HRZ + Ethionamide for 6 months only	