

TB/HIV

A CLINICAL MANUAL



second edition



WORLD HEALTH ORGANIZATION

TB/HIV

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Second edition

Stop TB Department
Department of HIV/AIDS
Department of Child and Adolescent Health and Development



World Health Organization
Geneva

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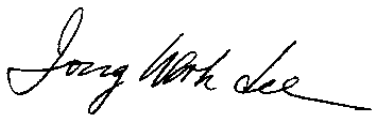
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WHO is committed to achieving major progress in global public health. Goals for tuberculosis include a worldwide cure rate of 85% and a case detection rate of 70% by 2005. Goals for human immunodeficiency virus include treating 3 million people with HIV infection in developing countries with antiretroviral drugs by 2005. The Millennium Development Goals include targets for improved child health and survival and for improved control of priority communicable diseases (including TB and HIV) by 2015. Progress in improving TB/HIV clinical care will contribute to achieving these goals. Clinicians have a vital contribution to make, not only to the clinical care of patients, but also to public health.

The public health foundation of TB control is good clinical care, through identification and effective treatment of TB patients. A cornerstone of public health activities for HIV prevention is to increase the proportion of HIV-infected people who choose to know their HIV status. One of the benefits of testing positive for HIV should be access to good clinical care. This is crucial in promoting community confidence in HIV/AIDS care, and therefore encouraging the uptake of HIV testing. This manual provides practical guidance on the clinical care of patients of all ages with HIV infection, including the treatment of HIV infection with antiretroviral drugs and of HIV-related diseases, including TB.

TB and HIV are overlapping epidemics. For clinicians, the patient is at the centre of public health activities to tackle TB/HIV. For example, clinicians are usually in a good position to offer TB patients voluntary counselling and testing for HIV. When patients with TB find out they are HIV-positive, clinicians are well placed to ensure directly or by referral that they receive lifelong care. Lifelong care should comprise the following: treatment of HIV infection; prevention and treatment of HIV-related diseases; support to decrease risk of HIV transmission; and social and psychological support.

This manual provides valuable guidance for clinicians caring for patients with TB/HIV. Their efforts are crucial to the collective achievement of global public health goals.




Dr JW Lee
Director-General, World Health Organization
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Doctors and other health professionals working in sub-Saharan Africa will be only too aware of the many patients they encounter with TB. They will also be all too well aware of the epidemic of HIV infection and the effect this has had on dramatically increasing the TB burden. They will know that in many patients development of clinical TB is the first sign of underlying HIV infection. This excellent book is designed for the busy clinician. It summarizes the characteristics of both diseases and of their interactions. It concentrates particularly on the clinical problems of diagnosis and management, both in adults and children. It summarizes the other HIV-related diseases which the clinician may encounter in TB/HIV patients. It provides a most useful review to those new to the problems and a handy reference for the experienced clinician when faced with some particular difficulty. It is well set out and easy to use.

The modern treatment of TB in HIV-infected patients is highly successful. This not only benefits the patient but reduces the spread of TB to families and the community. Other treatments can help to improve or control many HIV-related diseases. This book well summarizes the range of treatments available. It also provides useful guides on counselling and on interagency cooperation, both essential components of TB/HIV management.

The enormous problems of HIV and TB in sub-Saharan Africa are now also increasing in Asia and South America, where the book should prove equally useful.

I congratulate WHO on deciding to produce this valuable book and the authors on the imaginative and practical way they have presented the problems and their management.



Sir John Crofton
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University of Edinburgh, Scotland

PREFACE TO SECOND EDITION

Recognition of the impact of HIV on the clinical management of TB prompted WHO to publish the first edition of this manual in 1996. In response to popular demand, the manual was adapted for different regions and translated into many languages. The total number of copies distributed has run to well over 100000. Recognition of the strengths and weaknesses of the first edition and developments in the TB/HIV field have now prompted a second edition.

There is increasing attention to the need to ensure high quality care of children with TB within National TB Programmes. Therefore this second edition provides improved guidance on dealing with TB in children.

HIV fuels the TB epidemic in populations where there is overlap between those infected with HIV and those infected with *Mycobacterium tuberculosis*. Intense transmission of *M. tuberculosis* increases the pool of HIV-infected people exposed to, and subsequently infected with, *M. tuberculosis*. In populations with high HIV prevalence, many people infected with HIV develop TB, and many TB patients are coinfecting with HIV. Unfortunately, at present a very small proportion of all people infected with HIV have access to antiretroviral treatment. However, this proportion is sure to increase and clinicians involved in managing TB patients need to know about antiretroviral treatment. For these reasons this edition includes a new chapter on antiretroviral drugs in the treatment of HIV infection.

The new expanded framework for TB control and the strategic framework to control TB/HIV reflect the development of TB control policies since 1996. Chapter 2 incorporates these new policies.

With the above changes, the manual provides up-to-date guidance on clinical management of patients with TB and HIV.

This manual is mainly for doctors and other health professionals working in district hospitals and health centres in high HIV and TB prevalence countries. It deals mainly with sub-Saharan Africa, since this is the region most badly affected by HIV and HIV-related TB. However, we hope it will also be helpful in other parts of the world facing similar problems.

Facilities vary from hospital to hospital and from health centre to health centre. In this manual we assume your hospital has a small laboratory and X-ray service. Even if you do not have these facilities, the manual

should still be useful. Health professionals who care for TB patients now need to know how to diagnose and treat TB, the principles of diagnosis and treatment of HIV and other HIV-related diseases. This manual will help you in this task.

The manual fits into a white coat pocket so you can use it on the ward, in the clinic and at home. There is not enough room in a pocket manual for all the possible information you may want to know about TB among HIV-infected people. So, at the end of each chapter there are suggestions for further reading. These suggestions include relevant books, background material, reviews and recent articles in journals.

Since English is not the first language of many of the people using this manual, the writing style is deliberately simple. You are welcome to send any comments on the manual to WHO. We will use your comments to help improve future editions. Many of the references in the manual are to WHO publications. To order copies of WHO publications, you should contact Marketing and Dissemination, World Health Organization, 1211 Geneva 27, Switzerland.

GLOSSARY AND ABBREVIATIONS

This glossary explains the abbreviations and acronyms and some of the terms used in this book.

ambulatory	able to walk
acquired resistance	resistance of <i>Mycobacterium tuberculosis</i> to anti-TB drugs in a TB patient who has previously received anti-TB treatment
adherence to treatment	the patient taking the medicines as directed
adjuvant treatment	an addition to other treatment
AFB	Acid-Fast Bacilli
agranulocytosis	absence of polymorph white blood cells
AIDS	Acquired ImmunoDeficiency Syndrome
anorexia	loss of appetite for food
ARC	AIDS-Related Complex
ART	AntiRetroviral Therapy
ARV	AntiRetroViral (drug)
atypical mycobacteria	nontuberculous mycobacteria
bactericidal	kills bacteria
bacteriostatic	stops bacteria from growing
BCG	Bacille Calmette-Guerin
bronchiectasis	irreversibly dilated bronchi with persistently infected sputum
bubo	swollen, pus-containing lymph node
caseation	tissue breakdown by TB bacilli, forming yellow-white, cheese-like material
chemotherapy	treatment with drugs, e.g. anti-TB chemotherapy means treatment with anti-TB drugs
CAT or CT (scan)	Computerized Axial Tomography
CD4 cells	subgroup of T-lymphocytes carrying CD4 antigens
CDC	Centers for Disease Control and Prevention (USA)
CMV	CytoMegaloVirus
CNS	Central Nervous System
coinfection	infection with different pathogens at the same time, e.g. <i>Mycobacterium tuberculosis</i> and HIV
contacts	people (often family members) close to a TB patient and at risk of infection
cotrimoxazole	trimethoprim/sulfamethoxazole (TMP/SMX)
counselling	face-to-face communication in which one person

	(counsellor) helps another (patient/client) to make decisions and act on them
CSF	CerebroSpinal Fluid
CXR	chest X-ray
dactylitis	inflammation of the fingers
default	patient stopping treatment before completion
desensitization	way of overcoming hypersensitivity to a drug in a patient by gradual re-exposure to the drug
disseminated	spread throughout the body to many different organs
dormant	sleeping or inactive
DOT	Directly Observed Treatment (supporter watches patient to ensure the patient takes the tablets)
dyspnoea	shortness of breath
DTO	District TB Officer
EDL	Essential Drugs List
EIA	Enzyme ImmunoAssay
erythema nodosum	painful, tender, red nodules over the front of the legs
empirical treatment	treatment for a certain condition without exact diagnostic confirmation by tests
EPI	Expanded Programme on Immunization
EPTB	extrapulmonary TB; TB outside the lungs
exudate	fluid with a high protein content and inflammatory cells in an area of disease
false-negative test result	a negative test result, when the true result is in fact positive
false-positive test result	a positive test result, when the true result is in fact negative
FBC	Full Blood Count
FDC	Fixed-Dose Combination
fluorochrome stain	stain shines brightly under ultraviolet light
GDF	Global Drug Facility
gibbus	an acute angle in the spine due to vertebral collapse from TB
HAART	Highly Active AntiRetroviral Therapy
haemoptysis	coughing up of blood-stained sputum
HEPA	High Efficiency Particulate Air (filter mask)
hilar	at the root of the lung
hilum	the root of the lung
HIV	Human Immunodeficiency Virus

HIV-negative	absence of (antibodies against) HIV
HIV-positive	presence of (antibodies against) HIV
HIV-related TB	TB occurring in somebody infected with HIV
HIV status	presence or absence of HIV
HIV test	blood test for antibodies against HIV
home care	care for a patient at home rather than in hospital
hypersensitivity reaction	immunological reaction to even a small amount of a drug or other antigen, e.g. tuberculin
IEC	Information, Education and Communication
IMCI	Integrated Management of Childhood Illness
i.m. injection	intramuscular injection
immunosuppressant drugs	drugs that suppress normal immunity
incidence	the number of new cases of a disease in a population in a given time (usually one year)
induration	thickening, e.g. of the skin in a tuberculin test
infant	child less than 12 months of age
initial resistance	resistance of <i>Mycobacterium tuberculosis</i> to anti-TB drugs in a TB patient who has never before received anti-TB drugs
IPT	Isoniazid Preventive Treatment
IUATLD	International Union Against Tuberculosis and Lung Disease
JVP	Jugular Venous Pressure
KS	Kaposi Sarcoma
latent	something that is there but not obvious (it can become obvious later)
lesion	an area of damage or injury to a tissue or organ
LIP	Lymphocytic (lymphoid) Interstitial Pneumonitis
LFTs	Liver Function Tests
MAC	<i>Mycobacterium Avium intraCellulare</i> (one of the atypical mycobacteria)
MCV	Mean Corpuscular Volume
MDR-TB	Multidrug-resistant TB
meningism	presence of clinical features suggestive of meningitis, e.g. headache, neck-stiffness, positive Kernig's sign
monotherapy	treatment with one drug
mutant bacilli	bacilli that suddenly change genetically and become different from the rest of the population

mutation	a sudden genetic change, e.g. a bacillus becoming drug-resistant
NGO	NonGovernmental Organization
NNRTI	non-nucleoside reverse transcriptase inhibitor
NsRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NSAID	Non-Steroidal Anti-Inflammatory Drug
NTP	National TB Programme
opportunistic infection	an infection that "takes the opportunity" to cause disease when a person's immune defence is weak
PAL	Practical Approach to Lung Health
passive case-finding	detection of TB cases by active testing (sputum smear) of TB suspects
pathogenesis	how a disease arises
PCP	<i>Pneumocystis Carinii</i> Pneumonia (now known as <i>Pneumocystis jiroveci</i>)
pericardial effusion	accumulation of fluid in the pericardial cavity
phlyctenular conjunctivitis	painful hypersensitivity reaction of the conjunctiva to primary TB infection, with inflammation and small red spots where the cornea meets the sclera
PGL	Persistent Generalized Lymphadenopathy
PHC	Primary Health Care
PI	Protease inhibitor
pleural effusion	accumulation of fluid in the pleural space
PLWH	People Living With HIV
PML	Progressive multifocal lenkoencephalopathy
pneumothorax	accumulation of air in the pleural space
PPD	Purified Protein Derivative (tuberculin)
preventive treatment	treatment aimed at preventing disease, e.g. isoniazid for the prevention of TB in certain circumstances
PTB	Pulmonary TuBerculosis
PTB suspect	patient presenting with features that make the health worker think the patient may have PTB, most importantly cough of more than 3 weeks' duration
regimen	a drug, or several drugs, given in certain doses for a stated duration
relapse	disease starting again after a patient was declared cured

RNA	Ribonucleic acid
RTI	Reverse transcriptase inhibitor
SCC	Short-Course Chemotherapy
scrofula	tuberculous lymph nodes in the neck
sensitivity test	test of TB bacilli for sensitivity or resistance to anti-TB drugs
seroconversion	the first appearance of HIV antibodies in the blood, usually about 3 months after HIV infection
seroprevalence	the proportion of people testing seropositive (e.g. for HIV) in a population at any one time
slim disease	HIV-related chronic diarrhoea and weight loss
spinal block	obstruction to normal flow of CSF around the spinal cord
sputum smear negative	absence of AFBs on sputum microscopy
sputum smear positive	presence of AFBs on sputum microscopy
STI	Sexually Transmitted Infection
Stevens-Johnson syndrome	a characteristic rash with "target lesions" and inflammation of the mucous membranes
syndrome	a group of symptoms and signs
TB	TuBerculosis
TB suspect	patient with symptoms suggestive of TB
TB/HIV	TB and HIV coinfection
TB/HIV patient	HIV-infected TB patient
TEN	Toxic Epidermal Necrolysis
thrombocytopenia	low platelet count
T-lymphocytes	type of lymphocyte providing cellular immunity
TMP-SMX	TriMethoPrim-SulfaMethoXazole
tubercles	small rounded areas of TB disease
tuberculin	protein extracted from TB bacilli (PPD)
tuberculoma	rounded area of TB disease, usually 1cm or more wide
UNICEF	United Nations Children's Fund
VCT	Voluntary Counselling and Testing (for HIV)
WHO	World Health Organization
window period	the gap of about 3 months between the time when a person becomes infected with HIV and the time when antibodies first appear in the blood
ZN stain	Ziehl-Neelsen stain

INTRODUCTION

Untreated HIV infection leads to progressive immunodeficiency and increased susceptibility to infections, including TB. HIV is driving the TB epidemic in many countries, especially in sub-Saharan Africa and, increasingly, in Asia and South America. TB in populations with high HIV prevalence is a leading cause of morbidity and mortality. TB programmes and HIV/AIDS programmes therefore share mutual concerns. Prevention of HIV should be a priority for TB control; TB care and prevention should be priority concerns of HIV/AIDS programmes. TB and HIV programmes provide support to general health service providers. Previously TB programmes and HIV/AIDS programmes have largely pursued separate courses. However, a new approach to TB control in populations with high HIV prevalence requires collaboration between these programmes.

HIV infection increases the demands on TB programmes, which are struggling to cope with the increased TB case load. The impact of HIV exposes any weaknesses in TB control programmes. The rise in TB suspects is putting a strain on diagnostic services. Extrapulmonary and smear-negative pulmonary TB cases, which are more difficult to diagnose, account for an increased proportion of total cases. There are more adverse drug reactions. There is a higher morbidity and mortality, partly due to other, curable, HIV-related infections. The risk of TB recurrence is higher. The diagnosis of TB in young children has always been difficult and is even more so with HIV.

The objectives of a TB control programme are to decrease morbidity, mortality and transmission of TB, while avoiding the emergence of drug resistance. Up to now, the efforts to tackle TB among HIV-infected people have mainly focused on implementing the DOTS strategy for TB control. At the heart of this strategy is the identification and cure of infectious TB cases (among patients presenting to general health services). This targets the final step in the sequence of events by which HIV fuels TB, namely the transmission of *Mycobacterium tuberculosis* infection by infectious TB cases. The expanded scope of the new approach to TB control in populations with high HIV prevalence comprises interventions against TB and interventions against HIV (and therefore indirectly against TB). Implementing this approach depends on TB and HIV programmes continuing their core activities and, in addition, collaborating in joint activities. These activities address areas of mutual interest, e.g. staff training, public education, drug supply, case detection and management, and surveillance.

This chapter provides background information on tuberculosis (TB), human immunodeficiency virus and acquired immunodeficiency syndrome, and the interaction between them.

I.1 TUBERCULOSIS

I.1.1 Basic facts about TB

Mycobacterium tuberculosis

TB is a bacterial disease caused by *Mycobacterium tuberculosis* (and occasionally by *Mycobacterium bovis* and *Mycobacterium africanum*). These organisms are also known as tubercle bacilli (because they cause lesions called tubercles) or as acid-fast bacilli (AFB). When sputum containing tubercle bacilli is stained with certain dyes and examined under the microscope, the bacilli look red. This is because they are acid-fast (they have kept the dye even after being washed with acid and alcohol). Tubercle bacilli can remain dormant in tissues and persist for many years.

Tuberculous infection and tuberculosis

Tuberculous infection occurs when a person carries the tubercle bacilli inside the body, but the bacteria are in small numbers and are dormant. These dormant bacteria are kept under control by the body's defences and do not cause disease. Many people have tuberculous infection and are well. Tuberculosis is a state in which one or more organs of the body become diseased as shown by clinical symptoms and signs. This is because the tubercle bacilli in the body have started to multiply and become numerous enough to overcome the body's defences.

Sources of infection

The most important source of infection is the patient with TB of the lung, or pulmonary TB (PTB), and who is coughing. This person is usually sputum smear-positive (see Chapter 3). Coughing produces tiny infectious droplet nuclei (infectious particles of respiratory secretions usually less than 5 µm in diameter and containing tubercle bacilli). A single cough can produce 3000 droplet nuclei. Droplet nuclei can also be spread into the air by talking, sneezing, spitting and singing, and can remain suspended in the air for long periods. Direct sunlight kills tubercle bacilli in 5 minutes, but they can survive in the dark for long periods. Transmission therefore generally occurs indoors. Droplet nuclei are so small that they avoid the defences of the bronchi and penetrate

into the terminal alveoli of the lungs, where multiplication and infection begin. Two factors determine an individual's risk of exposure: the concentration of droplet nuclei in contaminated air and the length of time he or she breathes that air.

TB of cattle (bovine TB) occurs in some countries. Milk-borne *M. bovis* may infect the tonsils presenting as scrofula (cervical lymphadenitis), or the intestinal tract, causing abdominal TB.

Routes by which TB is not transmitted

TB is not transmitted through food and water or by sexual intercourse, blood transfusion, or mosquitoes.

Risk of infection

An individual's risk of infection depends on the extent of exposure to droplet nuclei and his or her susceptibility to infection. The risk of infection of a susceptible individual is high with close, prolonged, indoor exposure to a person with sputum smear-positive PTB. The risk of transmission of infection from a person with sputum smear-negative PTB is low, and even lower from someone with extrapulmonary TB (EPTB).

Risk of progression of infection to disease

Infection with *M. tuberculosis* can occur at any age. Once infected with *M. tuberculosis*, a person can stay infected for many years, probably for life. The vast majority (90%) of people without HIV infection who are infected with *M. tuberculosis* do not develop TB. In these, asymptomatic but infected individuals, the only evidence of infection may be a positive tuberculin skin test.

Infected persons can develop TB at any time. The disease can affect most tissues and organs, but especially the lungs. The chance of developing disease is greatest shortly after infection and steadily lessens as time goes by. Infected infants and young children are at greater risk of developing disease than older people because they have an immature immune system. TB is also more likely to spread from the lungs to other parts of the body in this age group. Children who develop disease usually do so within two years following exposure and infection. Most do not develop disease in childhood but may do so later in life. Various physical or emotional stresses may trigger progression of infection to disease. The most important trigger is weakening of immune resistance, especially by HIV infection.

Natural history of untreated TB

Without treatment, by the end of 5 years 50% of PTB patients will be

dead, 25% will be healthy (self-cured by a strong immune defence) and 25% will remain ill with chronic infectious TB.

Epidemiology

M. tuberculosis infects a third of the world's population. In 2000 there were an estimated 8.3 million new cases of TB worldwide. 95% of TB cases and 98% of TB deaths are in developing countries. 75% of TB cases in developing countries are in the economically productive age group (15–50 years). In 2000, Sub-Saharan Africa had the highest TB incidence rate (290/100000 per year) and the highest annual rate of increase of cases (6%). There were 1.8 million deaths from TB in 2000, with 226000 attributable to HIV (12%). TB deaths comprise 25% of all avoidable adult deaths in developing countries.

A direct consequence of increasing numbers of adults with TB is an increase in childhood TB. Neonatal BCG immunization has had limited effect in preventing childhood TB in developing countries. Infants and young children (less than 5 years) are at particular risk for infection and disease. Accurate definition of the burden of childhood TB is difficult because of difficulties with diagnosis, particularly in regions where childhood HIV infection is common. Chapter 4 deals with these issues in more detail.

1.1.2 Pathogenesis of TB

Primary infection

Primary infection occurs in people who have not had any previous exposure to tubercle bacilli. Droplet nuclei, which are inhaled into the lungs, are so small that they avoid the mucociliary defences of the bronchi and lodge in the terminal alveoli of the lungs. Infection begins with multiplication of tubercle bacilli in the lungs. The resulting lesion is the Ghon focus. Lymphatics drain the bacilli to the hilar lymph nodes. The Ghon focus and related hilar lymphadenopathy form the primary complex. Bacilli may spread in the blood from the primary complex throughout the body. The immune response (delayed hypersensitivity and cellular immunity) develops about 4–6 weeks after the primary infection. The size of the infecting dose of bacilli and the strength of the immune response determine what happens next. In most cases, the immune response stops the multiplication of bacilli. However, a few dormant bacilli may persist. A positive tuberculin skin test would be the only evidence of infection. In a few cases the immune response is not strong enough to prevent multiplication of bacilli, and disease occurs within a few months.

Outcomes of primary infection

primary complex	→	no clinical disease positive tuberculin skin test (usual outcome: 90% of cases)
	→	hypersensitivity reactions e.g. erythema nodosum phylyctenular conjunctivitis dactylitis
	→	pulmonary and pleural complications e.g. tuberculous pneumonia hyperinflation and collapse/consolidation pleural effusion
	→	disseminated disease lymphadenopathy (usually cervical) meningitis pericarditis miliary disease

PRACTICAL POINT

Following primary infection, rapid progression to intra-thoracic disease is more common in children less than 5 years of age. Chest X-Ray (CXR) may show intrathoracic lymphadenopathy and lung infiltrates.

Post-primary TB

Post-primary TB occurs after a latent period of months or years following primary infection. It may occur either by reactivation of the dormant tubercle bacilli acquired from a primary infection or by reinfection. Reactivation means that 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. Reinfection means a repeat infection in a person who has previously had a primary infection.

The immune response of the patient results in a pathological lesion that is characteristically localized, often with extensive tissue destruction and cavitation. Post-primary TB usually affects the lungs but can involve any part of the body. The characteristic features of post-primary PTB are the following: extensive lung destruction with cavitation; positive sputum

smear; upper lobe involvement; usually no intrathoracic lymphadenopathy. Patients with these lesions are the main transmitters of infection in the community.

Post-primary TB

Pulmonary TB	
e.g. cavities upper lobe infiltrates fibrosis progressive pneumonia endobronchial	
Extrapulmonary TB	
Common	Less common
Pleural effusion	Empyema
Lymphadenopathy (usually cervical)	Male genital tract (epididymitis, orchitis)
Central nervous system (meningitis, cerebral tuberculoma)	Female genital tract (tubo-ovarian, endometrium)
Pericarditis (effusion/constrictive)	Kidney
Gastrointestinal (ileocaecal, peritoneal)	Adrenal gland
Spine, other bone and joint	Skin (lupus vulgaris, tuberculids, miliary)

PRACTICAL POINT

Post-primary infection with pulmonary disease usually occurs in adults and leads to microscopy-positive sputum smears.

1.2 HUMAN IMMUNODEFICIENCY VIRUS

1.2.1 Introduction: HIV and AIDS

Since the first description of AIDS in 1981, researchers have identified two types of HIV, the cause of AIDS. HIV-1 is the predominant type worldwide. HIV-2 occurs most commonly in West Africa, and occasional

infections have occurred in East Africa, Europe, Asia and Latin America. Both types cause AIDS and the routes of transmission are the same. However, HIV-2 transmission is slightly less easy and the progression of HIV-2 infection to AIDS may be slower.

1.2.2 HIV/AIDS epidemiology

By the end of 2002, there were an estimated 42 million adults and children living with HIV or AIDS. Of these, 28.5 million (68%) were living in sub-Saharan Africa, and 6 million (14%) in South and South-East Asia. In 2002, an estimated 5 million adults and children became infected with HIV, and an estimated 3.1 million adults and children died from HIV/AIDS. 2.4 million (77%) of these deaths occurred in sub-Saharan Africa. Sub-Saharan Africa is the region with the highest overall HIV seroprevalence rate in the general adult (15–49 years) population (9% as of end 2002).

Of 25 countries with an adult HIV seroprevalence rate above 5% in 2001, 24 are in sub-Saharan Africa. The only other country with an adult HIV seroprevalence greater than 5% is Haiti. In 9 countries (all in Southern Africa), the adult HIV seroprevalence rate is 15% or above. Sub-Saharan Africa thus bears the largest burden of the HIV/AIDS epidemic. However, certain countries in other regions are also badly affected by HIV, with an adult HIV seroprevalence of 1–5%, e.g. Cambodia, Myanmar and Thailand (South-East Asia) and Belize, Guatemala, Guyana, Haiti, Honduras, Panama, and Suriname (the Americas). HIV seroprevalence appears to be stabilizing in sub-Saharan Africa but is still increasing in some other large populations, e.g. in the Russian Federation.

1.2.3 HIV transmission

Worldwide the most common route of HIV transmission is through sexual intercourse. Other sexually transmitted infections (especially those that cause genital ulcers) increase the risk of HIV transmission. The main routes of HIV transmission vary between regions. The main routes of transmission of HIV in sub-Saharan Africa are through sexual intercourse, blood and from mother to infant. In most low-income countries roughly equal numbers of men and women are HIV-infected. Bloodborne HIV transmission occurs through contaminated blood transfusion, injections with contaminated needles and syringes, and the use of non-sterile skin-piercing instruments. The commonest route of HIV transmission in the fast-growing HIV epidemics in the Russian Federation and Ukraine is through injecting drug use.

About one-third of children born to HIV-infected mothers are also HIV-infected, with infection occurring mainly around the time of birth. There is a smaller risk of HIV transmission through breastfeeding. However, in many low-income countries breastfeeding is still safer than bottle feeding.

There is no evidence that HIV transmission occurs through everyday contact, hugging or kissing, food or drink, or the bites of mosquitoes or other insects.

1.2.4 Prevention of HIV transmission in health units

Transmission to patients

Patients may potentially be at risk of HIV infection from HIV-positive staff and HIV-positive patients. Known HIV-positive staff should not perform surgery or invasive diagnostic or therapeutic procedures on patients. Cross-infection between patients can occur from contaminated medical, surgical or dental equipment. It is vital to follow recommended sterilization procedures. When and where possible, reducing injections helps to decrease the risk of cross-infection.

Transmission to staff

Most HIV-positive health workers acquire HIV infection outside the workplace, by sexual transmission from an HIV-positive partner or spouse. The risk of HIV transmission from patients to staff is small if staff observe standard infection control procedures. The risk is less than that of hepatitis B transmission. Less than 0.5% of health workers exposed by a needle-stick injury to the blood of an HIV-positive patient have acquired HIV infection. Contaminated “sharps” pose a risk of HIV transmission to health staff. Therefore handle all “sharps” carefully and follow local guidelines for their disposal. If you have a needle-stick injury, squeeze the wound to encourage blood flow and wash well with soap and water. In areas of high HIV prevalence, assume that all blood and body fluids are potentially infectious. The table on page 30 indicates measures to prevent transmission of HIV to health workers. Where available, start postexposure prophylaxis with antiretroviral drugs as soon as possible (within 24 hours) after a needle-stick injury.

Exposure to risk	Precautions for prevention of transmission of HIV
venepuncture	wear gloves use a closed vacuum system if available discard needle and syringe into "sharps" box discard gloves and swabs into leakproof plastic bag for incineration label blood bottle and request form "inoculation risk"
invasive procedure, surgery, delivery of a baby	wear gloves and apron protect your eyes (glasses or protective goggles) discard sharps into "sharps" box
spilled blood or other body fluids	clear up as soon as possible using available disinfectant (e.g. glutaraldehyde, phenol, sodium hypochlorite)
resuscitation	avoid mouth-to-mouth resuscitation (use bag and mask)
laundry disposal	wear gloves and apron dispose into leakproof plastic bags wash laundry at high temperatures or with appropriate chemical disinfectant

1.2.5 Immunopathogenesis of HIV infection

How HIV infects cells

HIV infects cells that have the CD4 antigen molecules on their surface. These cells are principally the helper subset of T-lymphocytes, which are central to cell-mediated immunity. They are called CD4+ T-lymphocytes. In recent years it has also been discovered that HIV needs other molecules, called chemokines, on the cell surface to gain entry into the cell. Patients who do not have some of these specific chemokines (for example, CCR5) are more resistant to HIV infection. Others, who have molecular changes in these chemokine receptors, progress more slowly to AIDS.

How HIV destroys the immune system

The critical abnormality resulting from HIV infection is a progressive decline in the number of CD4+ T-lymphocytes. These cells are the most

important cells in the cell-mediated immune response. In addition the surviving CD4+ T-lymphocytes do not perform their functions as well as they did before infection. Progressive HIV infection therefore causes progressive decline in immunity.

I.2.6 Natural history of HIV infection

Acute HIV infection

Acute HIV infection is also called “primary HIV infection” or “acute seroconversion syndrome”. Between 40% and 90% of new HIV infections are associated with symptomatic illness. The time from exposure to onset of symptoms is usually 2–4 weeks. Some people present with a glandular-fever -like illness (fever, rash, arthralgia and lymphadenopathy). Occasionally acute neurological syndromes may occur, which are often self-limiting. These include aseptic meningitis, peripheral neuropathy, encephalitis and myelitis. A severe illness may predict a worse long-term outcome. Most symptomatic patients seek medical help. However, the diagnosis is infrequently made, for several possible reasons. First, the clinician may not consider HIV infection. Secondly, the nonspecific clinical features may be mistaken for another cause, e.g. malaria. Thirdly, standard serological tests at this stage are usually negative. Serological tests first become positive about 4–12 weeks after infection, with over 95% of patients “seroconverting” within 6 months of HIV transmission. The diagnosis of acute HIV infection is best established by demonstration of HIV RNA in plasma.

Asymptomatic HIV infection

In adults, there is a long, variable, latent period from HIV infection to the onset of HIV-related disease and AIDS. A person infected with HIV may be asymptomatic for 10 years or more. The vast majority of HIV-infected children are infected in the perinatal period. The period of asymptomatic infection is shorter in children than in adults. A few infants become ill in the first few weeks of life. Most children start to become ill before 2 years of age. A few children remain well for several years.

Persistent generalized lymphadenopathy (PGL)

PGL is defined as enlarged lymph nodes involving at least two sites other than inguinal nodes. At this time, the lymph tissue serves as the major reservoir for HIV. PGL occurs in about one-third of otherwise healthy HIV-infected people. The enlarged lymph nodes are persistent, generalized, symmetrical, and non-tender. PGL has no particular prognostic significance.

Progression from HIV infection to HIV-related disease and AIDS

Almost all (if not all) HIV-infected people, if untreated, will ultimately develop HIV-related disease and AIDS. Some HIV-infected individuals progress more quickly than others to HIV-related disease and AIDS. The rate of progression depends on virus and host characteristics. Virus characteristics include type and subtype: HIV-1 and certain HIV-1 subtypes may cause faster progression. Host characteristics that may cause faster progression include: age less than 5 years; age more than 40 years; concurrent infections; and genetic factors.

Advancing immunosuppression

As HIV infection progresses and immunity declines, patients become more susceptible to infections. These include TB, pneumonia, recurrent fungal infections of the skin and oropharynx, and herpes zoster. These infections can occur at any stage of progression of HIV infection and immunosuppression. Some patients may develop constitutional symptoms (unexplained fever and weight loss), previously known as "AIDS-related complex" (ARC). Some patients develop chronic diarrhoea with weight loss, often known as "slim disease".

Certain specific HIV-related diseases occur predominantly with severe immunosuppression. These include certain opportunistic infections (e.g. cryptococcal meningitis) and certain tumours (e.g. Kaposi sarcoma). At this late stage, unless patients receive specific therapy for HIV infection, they usually die in less than 2 years. This late stage is sometimes known as "full-blown AIDS".

PRACTICAL POINT

TB can occur at any point in the course of progression of HIV infection.

1.2.7 Clinical staging

WHO clinical staging system for HIV infection and HIV-related disease.

WHO has developed a clinical staging system (originally for prognosis), based on clinical criteria. The definition of symptoms, signs and diseases is according to clinical judgement. Clinical condition or performance score, whichever is the higher, determines whether a patient is at clinical stage 1, 2, 3 or 4 (see table on page 33). Clinical stage is important as a criterion for starting antiretroviral (ARV) therapy.

WHO clinical staging system for HIV infection and related disease in adults (13 years or older)

- Stage 1:**
- Asymptomatic
 - Persistent generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

- Stage 2:**
- Weight loss < 10% of body weight
 - Minor mucocutaneous manifestations (e.g. oral ulcerations, fungal nail infections)
 - Herpes zoster within the last 5 years
 - Recurrent upper respiratory tract infections (e.g. bacterial sinusitis)

and/or Performance scale 2: symptomatic, normal activity

- Stage 3:**
- Weight loss > 10% of body weight
 - Unexplained chronic diarrhoea for more than 1 month
 - Unexplained prolonged fever for more than 1 month
 - Oral candidiasis (thrush)
 - Oral hairy leukoplakia
 - Pulmonary TB
 - Severe bacterial infections (pneumonia, pyomyositis)

and/or Performance scale 3: bedridden < 50% of the day during the last month

- Stage 4:**
- HIV wasting syndrome, as defined by CDC^a
 - *Pneumocystis carinii* pneumonia
 - Toxoplasmosis of the brain
 - Cryptosporidiosis with diarrhoea, for more than 1 month
 - Cryptococcosis, extrapulmonary
 - Cytomegalovirus (CMV) disease of an organ other than liver, spleen, lymph nodes
 - Herpesvirus infection, mucocutaneous for more than 1 month, or visceral any duration
 - Progressive multifocal leukoencephalopathy (PML)
 - Any disseminated endemic fungal infection (e.g. histoplasmosis)

- Candidiasis of the oesophagus, trachea, bronchi or lungs
- Atypical mycobacteriosis, disseminated
- Non-typhoid salmonella septicaemia
- Extrapulmonary TB
- Lymphoma
- Kaposi sarcoma
- HIV encephalopathy, defined by CDC^b

and/or Performance scale 4: bedridden > 50% of the day during the last month

(Note: both definitive and presumptive diagnoses are acceptable)

^a HIV wasting syndrome = weight loss > 10% of body weight, plus either unexplained diarrhoea for more than one month or chronic weakness and unexplained fever for more than one month.

^b HIV encephalopathy = clinical findings of disabling mental or motor dysfunction, interfering with activities of daily living, progressing over weeks and months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.

Children

WHO clinical staging system for HIV infection and related disease in children

- Stage 1:**
- Asymptomatic
 - Persistent generalised lymphadenopathy
- Stage 2:**
- Unexplained chronic diarrhoea
 - Severe persistent or recurrent candidiasis outside the neonatal period
 - Weight loss or failure to thrive
 - Persistent fever
 - Recurrent severe bacterial infections
- Stage 3:**
- AIDS-defining opportunistic infections
 - Severe failure to thrive
 - Progressive encephalopathy
 - Malignancy
 - Recurrent septicaemia or meningitis

1.2.8 Epidemiological surveillance of AIDS

AIDS is a term with an official definition used for epidemiological surveillance. This means that systematic reporting of AIDS cases is useful in helping to monitor the HIV pandemic and to plan public health responses. The term AIDS is not useful in the clinical care of individual patients. In managing patients with HIV-related disease, the aim is to identify and treat whichever HIV-related diseases are present. WHO has recommended case definitions for AIDS surveillance in adults and children where HIV testing facilities are not available.

PRACTICAL POINT

The term AIDS is used for epidemiological surveillance, not for clinical care.

WHO case definitions for AIDS surveillance in adults and children where HIV testing facilities are not available

Adults

The case definition for AIDS is fulfilled if at least 2 major signs and at least 1 minor sign are present.

Major signs

- weight loss > 10% of body weight
- chronic diarrhoea for more than 1 month
- prolonged fever for more than 1 month

Minor signs

- persistent cough for more than 1 month^a
- generalized pruritic dermatitis
- history of herpes zoster
- oropharyngeal candidiasis
- chronic progressive or disseminated herpes simplex infection
- generalized lymphadenopathy

The presence of either generalized Kaposi sarcoma or cryptococcal meningitis is sufficient for the case definition of AIDS.

The advantages of this case definition are that it is simple to use and inexpensive. The disadvantages are its relatively low sensitivity and specificity. For example, HIV-negative TB cases could be counted as AIDS cases because of their similarity in clinical presentation.

^a For patients with TB, persistent cough for more than 1 month should not be considered as a minor sign.

Children

The case definition for AIDS is fulfilled if at least 2 major signs and 2 minor signs are present (if there is no other known cause of immunosuppression).

Major signs

- weight loss or abnormally slow growth
- chronic diarrhoea for more than 1 month
- prolonged fever for more than 1 month

Minor signs

- generalized lymph node enlargement
- oropharyngeal candidiasis
- recurrent common infections, e.g. ear infection, pharyngitis
- persistent cough
- generalized rash

Confirmed HIV infection in the mother counts as a minor criterion.

The definition for children is not very specific, particularly in poor regions where childhood malnutrition and TB are common. Further, many children present with acute HIV-related illness such as PCP without any clinical evidence of AIDS.

1.3 HIV-RELATED TB

1.3.1 Epidemiology of coinfection of HIV and *M. tuberculosis*

By the end of 2000, about 11.5 million HIV-infected people worldwide were coinfecting with *M. tuberculosis*. 70% of coinfecting people were in sub-Saharan Africa, 20% in South-East Asia and 4% in Latin America and the Caribbean.

Numbers of coinfecting adults (15–49 years) in WHO regions by end 2000

WHO Region	Number of people coinfecting with TB & HIV (thousands)	% of global total
Africa	7979	70
Americas	468	4
Eastern Mediterranean	163	1
Europe	133	1
South-East Asia	2269	20
Western Pacific	427	4
Total	11440	100

I.3.2 HIV infection and risk of TB

HIV probably increases susceptibility to infection with *M. tuberculosis*. HIV increases the risk of progression of *M. tuberculosis* infection to TB disease. This risk increases with increasing immunosuppression. HIV increases not only the risk but also the rate of progression of recent or latent *M. tuberculosis* infection to disease. The table below shows the effect of HIV infection on lifetime risk of an *M. tuberculosis*-infected individual developing TB.

HIV STATUS	LIFETIME RISK OF DEVELOPING TB
negative	5–10%
positive	50%

PRACTICAL POINT

HIV is the most powerful factor known to increase the risk of TB.

I.3.3 TB in the course of HIV progression

TB can occur at any point in the course of progression of HIV infection. The risk of developing TB rises sharply with worsening immune status.

I.3.4 Consequence of HIV/*M. tuberculosis* coinfection

Compared with an individual who is not infected with HIV, a person infected with HIV has a 10 times increased risk of developing TB. TB notifications have increased in populations where both HIV infection and *M. tuberculosis* infection are common. For example, some parts of sub-Saharan Africa have seen a 3–5 fold increase in the number of TB case notifications over the past decade. HIV seroprevalence in these TB patients is up to 75%. In sub-Saharan Africa, one-third or more of HIV-infected people may develop TB.

I.3.5 Impact of HIV on TB control

The principles of TB control are the same even when there are many HIV/TB patients. However, in populations where HIV/TB is common, health services struggle to cope with the large and rising numbers of TB patients.

The consequences include the following:

- overdiagnosis of sputum smear-negative PTB (due to difficulties in diagnosis);
- underdiagnosis of sputum smear-positive PTB (due to excess laboratory workload);
- inadequate supervision of anti-TB chemotherapy;
- low cure rates;
- high morbidity during treatment;
- high mortality rates during treatment;
- high default rates because of adverse drug reactions;
- high rates of TB recurrence;
- increased transmission of drug-resistant strains among HIV-infected patients in congregate settings.

1.3.6 Patterns of HIV-related TB

As HIV infection progresses, CD4+ T-lymphocytes decline in number and function. These cells play an important role in the body's defence against tubercle bacilli. Thus, the immune system becomes less able to prevent the growth and local spread of *M. tuberculosis*. Disseminated and extrapulmonary disease is more common.

Pulmonary TB

Even in HIV-infected patients, PTB is still the commonest form of TB. The presentation depends on the degree of immunosuppression. The table below shows how the clinical picture, sputum smear result and CXR appearance often differ in early and late HIV infection.

How PTB differs in early and late HIV infection

Features of PTB	Stage of HIV infection	
	Early	Late
Clinical picture	Often resembles post-primary PTB	Often resembles primary PTB
Sputum smear result	Often positive	Often negative
CXR appearance	Often cavities	Often infiltrates with no cavities

Extrapulmonary TB

The commonest forms extrapulmonary TB are: pleural effusion, lymphadenopathy, pericardial disease, miliary disease, meningitis, disseminated TB (with mycobacteraemia).

HIV-related TB in children

As in adults, the natural history of TB in a child infected with HIV depends on the stage of HIV disease. Early in HIV infection, when immunity is good, the signs of TB are similar to those in a child without HIV infection. As HIV infection progresses and immunity declines, dissemination of TB becomes more common. Tuberculous meningitis, miliary TB, and widespread tuberculous lymphadenopathy occur.

1.3.7 Impact of TB on HIV

In an individual infected with HIV, the presence of other infections, including TB, may allow HIV to multiply more quickly. This may result in more rapid progression of HIV disease.

SUGGESTIONS FOR FURTHER READING

TUBERCULOSIS

Crofton J, Horne N, Miller F. *Clinical tuberculosis*. Second edition. London, MacMillan Press Limited, 1999.

Schlossberg D, ed: *Tuberculosis and nontuberculous mycobacterial infections*. Fourth edition. Philadelphia, WB Saunders, 1998.

International Union Against Tuberculosis and Lung Disease. *Tuberculosis guide for low income countries*. Fifth edition. Paris, 2000.

Reider HL. *Epidemiologic basis of tuberculosis control*. Paris, International Union Against Tuberculosis and Lung Disease, 1999.

World Health Organization. *Tuberculosis handbook*. Geneva, 1998 (WHO/TB/98.253).

World Health Organization. *Global tuberculosis control: surveillance, planning, financing. WHO report 2003*. Geneva, 2003 (WHO/CDS/TB/2003.316).

HIV/AIDS

Fauci AS. The AIDS epidemic. Considerations for the 21st century. *New England Journal of Medicine*, 1999, 341: 1046–1050.

Royce RA, Sena A, Cates Jr, W Cohen, MS. Sexual transmission of HIV. *New England Journal of Medicine*, 1997, 336: 1072–1078.

World AIDS series. *Lancet*, 2000, 355: WA1–WA40.

Joint United Nations Programme on HIV/AIDS (UNAIDS). *Report on the global HIV/AIDS epidemic: July 2002*. Geneva, (contains country-specific estimates).

Joint United Nations Programme on HIV/AIDS (UNAIDS). *AIDS epidemic update: December 2002*. Geneva, 2002.

CLINICAL STAGING SYSTEM FOR HIV AND HIV-RELATED DISEASE

World Health Organization. *Scaling up antiretroviral therapy in resource-limited settings. Guidelines for a public health approach*. Geneva, 2002.

AIDS CASE DEFINITIONS FOR SURVEILLANCE

Acquired immunodeficiency syndrome (AIDS). WHO/CDC case definition for AIDS. *Weekly epidemiological record*, 1986, 61: 69–73. (WHO clinical case definitions for AIDS in children where HIV testing is not available).

Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morbidity and mortality weekly report*, 1994; 43 (No. RR-12): 1-10. (Case definition for AIDS in children where HIV testing is available).

WHO case definitions for AIDS surveillance in adults and adolescents. *Weekly epidemiological record* 1994, 69: 273-275.

HIV-RELATED TUBERCULOSIS

Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Archives of internal medicine*, 2003, 163: 1009–1021.

Raviglione MC, Harries AD, Msiska R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. *AIDS*, 1997, 11 (suppl B): S115 - S123.

Ya Diul M, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS*, 2001, 15: 143-152.

World Health Organization. *A strategic framework to decrease the burden of TB/HIV*. Geneva, 2002 (WHO/CDS/TB/2002.296; WHO/HIV_AIDS/2002.2).

World Health Organization. *Guidelines for collaborative TB and HIV programme activities*. Geneva, 2003, (WHO/CDS/TB/2003.319; WHO/HIV/2003.01).

2.1 INTRODUCTION

WHO has declared that TB is a global emergency, because TB is out of control in many parts of the world. The following are the main reasons why TB is out of control:

- a) governments in many parts of the world have neglected the disease;
- b) inadequate TB control programmes have led to an increased burden of disease (inadequately treated TB patients live longer with chronic disease and infect other people) and the emergence of drug-resistant TB;
- c) high rates of population growth have contributed to an increased number of TB cases;
- d) the HIV epidemic has led to an enormous increase in the number of TB cases, in places where HIV and TB are both common.

WHO has expanded the framework for TB control in order to reflect experience gained since the development of the original framework in 1994. The expanded framework is relevant in all settings, including where HIV is common. Successful TB control depends on health care workers treating TB patients within this framework in a national TB programme (NTP). Full implementation of the DOTS strategy remains the priority. This means ensuring the accurate diagnosis and effective treatment of all TB patients.

In addition TB and HIV/AIDS programmes must collaborate to counteract the impact of HIV on TB. This depends on implementation of the DOTS strategy and other interventions. In addition to effective TB case-finding and cure, these interventions include: measures to decrease HIV transmission (e.g. promotion of condoms, treatment of sexually transmitted infections); highly active antiretroviral therapy (HAART); TB preventive treatment; and antibiotic prophylaxis against HIV-related bacterial infections.

2.2 COMPONENTS OF EXPANDED TB CONTROL FRAMEWORK

The expanded framework consists of the following:

- I. Goals of TB control.

2. Targets for TB control.
3. TB control policy package.
4. Key operations for DOTS implementation.
5. Indicators to measure NTP progress in TB control.

2.2.1 Goals of TB control

The goals of TB control are to reduce mortality, morbidity and disease transmission (while preventing drug resistance) until TB no longer poses a threat to public health. The aim is also to reduce human suffering and the social and economic burden on families and communities as a consequence of TB. In order to achieve this, it is necessary to ensure access to diagnosis, treatment and cure for each patient.

2.2.2 Targets for TB control (cure and case detection)

- a) To cure 85% of the sputum smear-positive PTB cases detected.
A national TB programme that achieves at least an 85% cure rate in patients with sputum smear-positive PTB has the following impact on TB:
 - i) TB prevalence, TB mortality and rate of TB transmission decrease rapidly;
 - ii) TB incidence decreases gradually;
 - iii) there is less drug resistance (which makes future treatment of TB easier and more affordable).
 Achieving high cure rates is the highest priority. TB programmes with high cure rates rapidly reduce disease transmission. They are likely to attract the majority of existing cases in the community.

- b) To detect 70% of existing cases of sputum smear-positive PTB.
It is important to expand case-finding only when the national TB programme has achieved a high cure rate. A national TB programme that has a low cure rate makes the TB problem worse:
 - i) there are more cases of sputum smear-positive PTB treatment failure;
 - ii) transmission of drug resistance increases.
 A treatable epidemic becomes an untreatable epidemic.

An effective NTP has a high cure rate and a low level of drug resistance.

Provided that a high cure rate is achieved, increased case detection of sputum smear-positive PTB cases will decrease TB transmission.

2.2.3 TB control policy package (the DOTS strategy)

NTPs face new challenges. They need significant strengthening in order to achieve the targets for TB control.

- General public health services need to increase their capacity to sustain and expand DOTS implementation. At the same time they must maintain the quality of case detection and treatment.
- Promoting a patient-centred approach and community involvement in TB care can improve both access to and utilization of health services.
- Collaboration is essential between the public, private, and voluntary sectors to ensure accessible and quality-assured TB diagnosis and treatment.
- The increasing impact of HIV on the incidence of TB requires new approaches and partnerships.
- A high prevalence of drug-resistant TB requires two complementary approaches: NTPs need to cure existing multidrug-resistant (MDR) TB cases as well as prevent new cases (through the DOTS strategy).

The expanded DOTS framework reinforces the five essential elements of the DOTS strategy:

- a. **Sustained political commitment** to increase human and financial resources and make TB control a nationwide activity integral to the national health system.
- b. **Access to quality-assured TB sputum microscopy** for case detection among persons presenting with, or found through screening to have, symptoms of TB (most importantly prolonged cough). Special attention to case detection is necessary among HIV-infected people and other high-risk groups, e.g. people in institutions.
- c. **Standardized short-course chemotherapy (SCC) for all cases of TB under proper case-management conditions including direct observation of treatment.** Proper case management conditions imply technically sound and socially supportive treatment services.

- d. **Uninterrupted supply of quality-assured drugs** with reliable drug procurement and distribution systems.
- e. **Recording and reporting system enabling outcome assessment** of every patient and assessment of the overall programme performance.

2.2.4 Key operations for DOTS implementation

- Establish a **national TB programme (NTP) with a central unit**.
- Prepare a **programme development plan**.
- Prepare the **NTP manual** and make it available at district level.
- Establish a **recording and reporting system** using standardized material allowing categorization of cases registered and cohort analysis for treatment outcomes.
- Plan and initiate a **training programme** covering all aspects of the policy package.
- Establish a **microscopy services network** in close contact with primary health care (PHC) services and subject to regular quality control.
- Establish **treatment services** within the PHC system where **directly observed** short-course chemotherapy is given priority and patient education is provided. Treatment services should achieve total geographical and patient coverage.
- Secure a **regular supply of drugs and diagnostic material** based on previous case notification data.
- Design a **plan of supervision** of the key operations at the intermediate and district level to be implemented from the start of the programme.
- Undertake **social mobilization** through **information, education and communication** activities, in order to mobilize and sustain support for TB control.
- Involve **all health care providers**, e.g. private and voluntary health care providers, nongovernmental organizations (NGOs), religious organizations and employers.

- Undertake **economic analysis and financial planning** to ensure that the NTP is on a sound financial footing.
- Undertake **operational research** as an integral component of DOTS implementation to improve NTP performance.

2.2.5 Indicators to measure NTP progress in TB control

- National TB control policies, as set out in the NTP manual, consistent with the DOTS strategy.
- The number of administrative areas in the country that are implementing the DOTS strategy.
- The cure rate in new smear-positive cases.
- The case detection rate.

The WHO document, “An expanded DOTS framework for effective tuberculosis control” (WHO/CDS/TB/2002.297), provides a full list of indicators.

2.3 DIRECTLY OBSERVED TREATMENT

What is directly observed treatment?

Patient adherence to treatment is necessary to ensure that the treatment cures the patient. Patient adherence to SCC means the patient takes every dose of the recommended treatment regimen. It may be difficult for a patient to adhere to anti-TB treatment for 6 to 8 months. It is difficult to predict which TB patients will adhere to self-administered treatment. One certain way to ensure patient adherence to treatment is direct observation of treatment. This means that someone supports the patient during the course of treatment and watches the patient swallow the tablets. The NTP coordinates the training of patient supporters and monitors their effectiveness in ensuring treatment adherence.

Directly observed treatment as close to the patient's home as possible

TB patients are unlikely to adhere to treatment if they have far to go for treatment. One of the aims of a TB programme is to organize TB services so that patients have treatment as close to home as possible. A TB programme brings treatment to patients wherever they live. Many TB patients live close to a health facility (e.g. health centre, district hospital).

For these patients, the treatment supporter who directly observes treatment could be one of the health staff in the health facility. Some TB patients live far away from a health facility. For these patients, the supervisor may be a trained local community member or a health outreach worker. Family members who provide health care support can also be trained as TB treatment supporters. Some areas have HIV/AIDS community care schemes. With suitable training and supervision, the HIV/AIDS home care providers can support TB patients, including directly observing treatment.

Integration of TB treatment services with general health services

In the past, some TB programmes have relied on special TB hospitals and clinics, separate from the general health service. The problem with that system is that many TB patients live far from a TB hospital or clinic. One reason why TB is out of control in many countries is that TB patients do not have access to TB diagnosis and treatment services. A successful NTP brings TB diagnosis and treatment services to the TB patients. This is why TB treatment services are integrated with existing general health services.

2.4 TB/HIV

TB and HIV are closely interlinked. TB is a leading cause of HIV-related morbidity and mortality. HIV is the most important factor fuelling the TB epidemic in populations with a high HIV prevalence. The WHO global strategic framework to control TB/HIV represents a coordinated response to the joint epidemics of TB and HIV. Collaboration between TB and HIV/AIDS programmes is crucial in supporting general health service providers. These providers need support in delivering the full range of HIV and TB prevention and care interventions. To counteract the impact of HIV on TB, other interventions are required apart from effective TB case-finding and cure. These interventions include

- measures to decrease HIV transmission (e.g. promotion of condoms, treatment of sexually transmitted infections, voluntary counselling and HIV testing, safe intravenous drug use, reduction in the number of sexual partners, prevention of mother-to-child HIV transmission, HIV screening of blood for transfusion, and application of universal HIV precautions by health care workers);
- antiretroviral therapy (ART) (to improve or maintain immune function in people living with HIV infection);
- care for people living with HIV infection (e.g. treatment of HIV-related diseases, prevention of HIV-related infections, TB prevention, palliative care and nutritional support).

High levels of multidrug-resistant TB (MDR-TB) in some areas threaten TB control efforts. MDR-TB is TB that is resistant to at least isoniazid and rifampicin. DOTS-Plus for MDR-TB is a comprehensive management initiative, built upon the five elements of the DOTS strategy. However, DOTS-Plus also takes into account specific issues, such as the use of second-line anti-TB drugs. The goal of DOTS-Plus is to prevent further development and spread of MDR-TB. DOTS-Plus is not intended for universal application, and is not required in all settings. The aim of implementation of DOTS-Plus in selected areas with significant levels of MDR-TB is to combat an emerging epidemic. The underlying principle is that the first step in controlling MDR-TB is prevention by full implementation of DOTS. An effective DOTS-based TB control programme is a prerequisite for implementation of DOTS-Plus.

SUGGESTIONS FOR FURTHER READING

International Union Against Tuberculosis and Lung Disease. *Tuberculosis guide for low income countries*. Fifth edition. Paris, 2000.

Maher D, van Gorkom JLC, Gondrie P, Raviglione MC. Community contribution to tuberculosis care in countries with high tuberculosis prevalence: past, present and future. *International journal of tuberculosis and lung disease*, 1999, 3: 762–768.

World Health Organization. *Guidelines for the management of drug-resistant Tuberculosis*. Geneva, 1997, (WHO/TB/96.210 - Rev.1).

World Health Organization. *What is DOTS? A guide to understanding the WHO-recommended TB control strategy known as DOTS*. Geneva, 1999, (WHO/CDS/CPC/TB/99.270).

World Health Organization. *Anti-tuberculosis drug resistance in the world. Report No.2. Prevalence and trends*. Geneva, 2000 (WHO/CDS/TB/2000.278).

World Health Organization. *The WHO/IUATLD Global Project on anti-tuberculosis drug resistance surveillance*. Geneva, 2000.

World Health Organization. *Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant TB*. Geneva, 2000 (WHO/CDS/TB/2000.279).

World Health Organisation. *An expanded DOTS framework for effective tuberculosis control*. Geneva, 2002, (WHO/CDS/TB/2002.297).

World Health Organization. *A strategic framework to decrease the burden of TB/HIV*. Geneva, 2002, (WHO/CDS/TB/2002.296).

World Health Organisation. *Treatment of tuberculosis: guidelines for national programmes*. Third edition. Geneva, 2003, (WHO/CDS/TB/2003.313).

World Health Organization. *Community contribution to TB care: practice and policy*. Geneva, 2003, (WHO/CDS/TB/2003.312).

World Health Organization. *Guidelines for collaborative TB and HIV programme activities*. Geneva, 2003, (WHO/CDS/TB/2003.319, WHO/HIV/2003.01).

3.1 DIAGNOSTIC APPROACH

The highest priority for TB control is the identification and cure of infectious cases, i.e. patients with sputum smear-positive PTB. Therefore all patients (regardless of HIV status) with clinical features suggestive of PTB must submit sputum for diagnostic sputum smear microscopy. Most TB suspects (people with symptoms or signs suggestive of TB) are ambulatory. The diagnosis of PTB is therefore usually done on an outpatient basis. Some TB suspects are severely ill and/or bed-bound and therefore need investigation as inpatients.

Clinical screening by assessment of symptoms identifies PTB suspects among patients attending health facilities. The most cost-effective method of detecting TB cases among PTB suspects in high-prevalence countries is by sputum smear microscopy. A suspect who has a positive sputum smear has sputum smear-positive PTB. The district TB officer (DTO) registers the TB patient, and treatment is started. In most cases of smear-positive PTB, a chest X-ray is unnecessary.

Sometimes a patient may be negative on sputum smear microscopy but may not improve on a broad-spectrum antibiotic. If you still suspect TB, reassess the patient and do a CXR. If the CXR is typical of PTB, register the patient with the DTO and start TB treatment. If doubtful about the CXR diagnosis of TB, e.g. if the CXR shows nonspecific pulmonary infiltrates, give the patient another course of antibiotics. If there is no clinical improvement, or if the cough disappears only to return shortly afterwards, repeat sputum smear microscopy. If you still think the patient may have TB despite further negative sputum smears, again reassess the patient and repeat the CXR. Then decide whether the diagnosis is TB or not. In cases where diagnostic doubt persists, sputum culture may be useful if suitable facilities are available.

In populations with a high TB prevalence, the tuberculin skin test is of little value in the diagnosis of TB in adults. A positive tuberculin skin test does not by itself distinguish *M. tuberculosis* infection from TB disease. Previous exposure to environmental mycobacteria may also result in a false-positive test result. Conversely, the tuberculin skin test result may be negative, even when the patient has TB. Conditions often associated with a false-negative tuberculin skin test include HIV infection, severe malnutrition and miliary TB.

3.2 CLINICAL FEATURES

Symptoms

The most important symptoms in the diagnosis of PTB are the following:

- cough for more than 2 or 3 weeks;
- sputum production;
- weight loss.

Over 90% of patients with sputum smear-positive PTB develop a cough soon after disease onset. However, cough is not specific to PTB. Cough is common in smokers and in patients with acute upper or lower respiratory tract infection. Most acute respiratory infections resolve within 3 weeks. Therefore a patient with a cough for more than 2 or 3 weeks is a PTB suspect and must submit sputum samples for diagnostic microscopy.

Patients with PTB may also have other symptoms. These may be respiratory or constitutional (general or systemic).

Respiratory: chest pain, haemoptysis, breathlessness.

Constitutional: fever, night sweats, tiredness, loss of appetite, secondary amenorrhoea.

Weight loss and fever are more common in HIV-positive PTB patients than in those who are HIV-negative. Conversely, cough and haemoptysis are less common in HIV-positive PTB patients than in those who are HIV-negative. This is probably because there is less cavitation, inflammation and endobronchial irritation in HIV-positive patients.

Physical signs

The physical signs in patients with PTB are nonspecific. They do not help to distinguish PTB from other chest diseases. There may be general signs, such as fever, tachycardia (fast pulse rate) and finger clubbing. Chest signs (heard through a stethoscope) may include crackles, wheezes, bronchial breathing and amphoric breathing. There are often no abnormal signs in the chest.

PRACTICAL POINT

All PTB suspects must provide sputum samples for smear microscopy for TB case-detection.

Collection of sputum samples

A PTB suspect should submit three sputum samples for microscopy. The chances of finding TB bacilli are greater with three samples than with two samples or one sample. Secretions build up in the airways overnight. So an early morning sputum sample is more likely to contain TB bacilli than one taken later in the day. It may be difficult for an outpatient to provide three early morning sputum samples. Therefore in practice an out-patient usually provides sputum samples as follows:

- day 1 sample 1** Patient provides an "on-the-spot" sample under supervision when presenting to the health facility. Give the patient a sputum container to take home for an early morning sample the following morning.
- day 2 sample 2** Patient brings an early morning sample.
- sample 3** Patient provides another "on-the-spot" sample under supervision.

Some patients cannot produce a sputum sample. A nurse or physiotherapist may help them to give a good cough and bring up some sputum. Inpatients can follow the same method as outpatients.

Terminology

Mycobacteria are "acid- and alcohol-fast bacilli" (AAFB), often shortened to "acid-fast bacilli" (AFB). The waxy coat of mycobacteria retains an aniline dye (e.g. carbol fuchsin) even after decolorization with acid and alcohol.

Ziehl-Neelsen (Z-N) stain

This simple stain detects AFB. This is how to perform the Z-N stain:

- **Fix the smear on the slide.**
- **Cover the fixed smear with carbol fuchsin for 3 minutes.**
- **Heat, rinse with tapwater, and decolorize with acid-alcohol for 3–5 seconds.**
- **Counterstain with methylene blue for 30 seconds.**
- **Rinse again with tapwater.**
- **Observe under the microscope** (use the x100 oil immersion lens and x10 eyepiece lens).

The bacilli appear as red, beaded rods, 2–4 µm long and 0.2–0.5 µm wide.

Fluorochrome stain

Use of this stain to detect TB bacilli requires a special fluorescence microscope. The fluorochrome stain is phenolic auramine or auramine-rhodamine. After acid-alcohol decolorization and a methylene blue counterstain, the bacilli fluoresce bright yellow against a dark background. The advantage of this method is that smears can be scanned quickly under low magnification. It is important to check fluorochrome stain-positive smears using the Z-N stain.

Slide reporting

The number of bacilli seen in a smear reflects disease severity and patient infectivity. Therefore it is important to record the number of bacilli seen on each smear. The table below shows the standard method of reporting using 1000 x magnification.

Number of bacilli			Result reported
no	AFB	per 100 oil immersion fields	0
1–9	AFB	per 100 oil immersion fields	scanty (or number AFB seen)
10–99	AFB	per 100 oil immersion fields	+ (1+)
1–10	AFB	per oil immersion field	++ (2+)
> 10	AFB	per oil immersion field	+++ (3+)

Laboratory technicians should examine all three sputum samples from each TB suspect. They must record the result of each sputum sample with the laboratory reference number in the laboratory register and on the sputum request form. Results as indicated above are made available to the clinician who can then categorize the patient. Categorizing patients as smear-positive or negative requires results from more than one smear. A guide to classification of patients with pulmonary symptoms is given below.

Smear-positive	Indeterminate	Smear negative
At least 2 smears examined and both positive, i.e. reported 1–9 per 100 fields (scanty) or greater	Several possibilities, e.g. <ul style="list-style-type: none"> ◦ only one smear examined (whatever the grading) ◦ 3 smears examined but only one reported positive In either of these situations, either further sputum smears or a CXR are required before a patient can be classified.	At least two smears reported 0 (negative)

Sensitivity of sputum smear microscopy

Sputum smear microscopy for tubercle bacilli is positive when there are at least 10000 organisms present per ml of sputum.

Sputum microscopy in HIV infection

Sputum smear positivity rates in TB/HIV patients depend on the degree of immunocompromise, as shown below.

Degree of immunocompromise	Likelihood of positive sputum smear
mild	similar to HIV-negative patient
severe	decreased(decreased inflammation in lungs)

False-positive results of sputum smear microscopy

A false-positive result means that the sputum smear result is positive even though the patient does **not** really have sputum smear-positive PTB. This may arise because of the following: red stain retained by scratches on the slide; accidental transfer of AFBs from a positive slide to a negative one; contamination of the slide or smear by environmental mycobacteria; presence of various particles that are acid-fast (e.g. food particles, precipitates, other microorganisms).

False-negative results of sputum smear microscopy

A false-negative result means that the sputum smear result is negative even though the patient **really does have** sputum smear-positive PTB. This may arise because of problems in collecting, processing, or interpreting sputum smears, or because of administrative errors.

PRACTICAL POINT

A sputum smear result may be unexpectedly negative (e.g. in a patient with upper lobe cavities on CXR). Think of the possibility of a false-negative result and repeat the sputum microscopy.

Causes of false negative results of sputum smear microscopy

Type of problem	Example
sputum collection	patient provides inadequate sample inappropriate sputum container used sputum stored too long before smear microscopy
sputum processing	faulty sampling of sputum for smear faulty smear preparation and staining
sputum smear interpretation	inadequate time spent examining smear inadequate attention to smear (poor motivation)

administrative errors misidentification of patient
 incorrect labelling of sample
 mistakes in documentation

3.4 DIFFERENTIAL DIAGNOSIS OF PULMONARY TB

PRACTICAL POINT

A PTB suspect with 3 negative sputum smears may not have PTB. Reassess the patient for conditions that may be mistaken for PTB.

The table shows possible alternative diagnoses.

Diagnosis	Pointers to the correct diagnosis
bronchiectasis	coughing large amounts of purulent sputum
bronchial carcinoma (lung cancer)	risk factor (smoking, older age, previous mine-work)
other infections, e.g. bacterial pneumonia lung abscess <i>Pneumocystis carinii</i>	usually shorter history, febrile, response to antibiotic cough with large amounts of purulent sputum abscess with fluid level on CXR often dry, non-productive cough with prominent dyspnoea
congestive cardiac failure left ventricular failure	symptoms of heart failure (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, haemoptysis, oedema, epigastric discomfort from hepatic congestion) signs of heart failure
asthma	intermittent symptoms, generalized expiratory wheeze; symptoms wake the patient at night
chronic obstructive airways disease	risk factor (smoking), chronic symptoms, prominent dyspnoea, generalized wheeze, signs of right heart failure (e.g. ankle oedema)

PRACTICAL POINT

If the patient is breathless, has continuing haemoptysis, and has negative sputum smears, listen carefully for a low-pitched, rumbling, mid-diastolic murmur, indicating mitral stenosis with pulmonary oedema.

3.5 CHEST X-RAY IN DIAGNOSIS**Indications for CXR****Positive sputum smear**

The first screening test for PTB suspects is sputum smear microscopy. In most cases of sputum smear-positive PTB a CXR is not necessary. In a few cases, a CXR may be necessary; the indications are as follows:

- suspected complications in a breathless patient, needing specific treatment, e.g. pneumothorax, pericardial effusion or pleural effusion (note that a positive sputum smear is rare in pericardial effusion and pleural effusion);
- frequent or severe haemoptysis (to exclude bronchiectasis or aspergilloma);
- only 1 sputum smear positive out of 3 (in this case, an abnormal CXR is a necessary additional criterion for the diagnosis of sputum smear-positive PTB).

Negative sputum smear

Reassess patients who continue to cough despite a course of broad-spectrum antibiotic, and who have had at least two (and preferably three) negative sputum smears. If you still suspect TB despite negative sputum smears, the patient needs a CXR.

3.6 RADIOGRAPHIC ABNORMALITIES SEEN IN PULMONARY TB**PRACTICAL POINT**

No CXR pattern is absolutely typical of PTB, especially with underlying HIV infection.

The table below shows so-called "classical" and "atypical" CXR patterns. The classical pattern is more common in HIV-negative patients, and the atypical pattern in HIV-positive patients.

CLASSICAL PATTERN	ATYPICAL PATTERN
upper lobe infiltrates	interstitial infiltrates (especially lower zones)
bilateral infiltrates	
cavitation	intrathoracic lymphadenopathy
pulmonary fibrosis and shrinkage	no cavitation
	no abnormalities

PRACTICAL POINT

CXR changes in TB/HIV patients reflect the degree of immunocompromise. In mild immunocompromise, the appearance is often classical (with cavitation and upper lobe infiltrates). In severe immunocompromise, the appearance is often atypical.

3.7 DIFFERENTIAL DIAGNOSIS OF CHEST X-RAY FINDINGS

The CXR findings associated with PTB may be nonspecific. Diseases other than PTB can cause both the "classical" and the "atypical" CXR findings.

PRACTICAL POINT

The vast majority of patients with cavitary PTB (over 90%) are sputum smear-positive. Therefore, a patient with cavities on CXR and repeated negative sputum smears probably has a disease other than PTB.

The table shows the differential diagnosis of CXR findings often associated with PTB.

CXR finding	Differential diagnosis
cavitation	infections some bacterial pneumonias nocardiosis melioidosis paragonimiasis (lung fluke) lung abscess some fungal infections

cavitation	non-infectious disease bronchial carcinoma connective tissue disease occupational lung disease
unilateral infiltration	pneumonia bronchial carcinoma
bilateral infiltration	pneumonia connective tissue disease occupational lung disease sarcoidosis
mediastinal lymphadenopathy	lymphoma bronchial carcinoma sarcoidosis

3.8 THE PLACE OF MYCOBACTERIAL CULTURE IN THE DIAGNOSIS OF TB

Laboratory culture of *M. tuberculosis*

When *M. tuberculosis* is cultured from clinical specimens (e.g. sputum, lymph node aspirate, cerebrospinal fluid) this provides the gold standard for the definitive diagnosis of TB. Tubercle bacilli that have grown in culture can also be tested *in vitro* for sensitivity to anti-TB drugs. The usual culture medium is Löwenstein Jensen, although liquid culture media and automated systems (e.g. Bactec) can also be used in more sophisticated laboratories.

Limitations of mycobacterial culture for diagnosis

M. tuberculosis is a slow-growing organism, and it often takes between 6 and 8 weeks before cultures become positive. Culture results may therefore not be helpful in making a rapid individual diagnosis, although they can be helpful retrospectively. There is also the need for considerable laboratory infrastructure and laboratory skills in order to sustain a mycobacterial culture facility. Most developing countries have one or two mycobacterial reference centres where cultures and drug sensitivity analysis can be performed. However, most hospitals will not have TB culture facilities readily available.

3.9 SEPSIS AND CONCOMITANT TB

Sepsis can occur as a coinfection with TB. An inadequate clinical response after treatment of sepsis, e.g. pneumonia, may be due to the presence of concomitant HIV-related TB.

3.10 DISTINGUISHING OTHER HIV-RELATED PULMONARY DISEASES FROM PULMONARY TB

This is a common, and often difficult, diagnostic problem. Several diseases in HIV-positive individuals may present in a similar way, with cough, fever, sometimes chest signs, and CXR shadowing. Pneumonia is the most frequent and important differential diagnosis. Pneumonia can also occur as a coinfection with TB. In each case, a careful clinical assessment is needed. Send sputum samples for AFBs if the patient has had cough for 3 weeks or more.

Acute bacterial pneumonia

This is common in HIV-positive patients. The shorter history usually differentiates pneumonia from PTB. The most common pathogen is *Streptococcus pneumoniae*. Regardless of HIV status, acute bacterial pneumonia usually responds well to standard treatment with penicillin, cotrimoxazole or ampicillin.

PRACTICAL POINT

If a patient with presumed pneumonia fails to respond to a full course of standard antibiotics, consider other pathogens, e.g. *M. tuberculosis*.

Kaposi sarcoma (KS)

The clinical recognition of KS is straightforward when there are typical lesions on the skin and mucous membranes. The diagnosis of pulmonary or pleural KS is more difficult. The patient usually presents with cough, fever, haemoptysis and dyspnoea, and usually has KS lesions elsewhere. CXR shows a diffuse nodular infiltrate (with infiltrates spreading out from the hilar regions) or pleural effusion. The pleural fluid is usually blood-stained. Cytology may provide the diagnosis. It can be difficult to rule out concurrent PTB.

Pneumocystis carinii pneumonia (PCP)

Adult PCP is less commonly seen in patients with AIDS in sub-Saharan Africa than in developed countries. The patient usually presents with dry cough and progressive dyspnoea. The table below shows the clinical and CXR features that help to distinguish PCP from PTB.

Clinical and CXR features of PCP and TB

	Typical of PCP	Typical of TB
symptoms	dry cough sputum mucoid (if any) dyspnoea	productive cough purulent sputum pleuritic chest pain haemoptysis
signs	may be normal fine inspiratory crackles	signs of consolidation signs of pleural effusion
CXR	bilateral diffuse interstitial shadowing may be normal	lobar consolidation cavitation pleural effusion intrathoracic lymphadenopathy

The definitive diagnosis of PCP rests on finding the cysts in induced sputum, broncho-alveolar lavage or biopsy specimens. These investigations are often not possible in district hospitals. The diagnosis therefore depends on the clinical and CXR features, exclusion of TB and response to a trial of high-dose cotrimoxazole, combined with corticosteroids if there is severe dyspnoea.

Other conditions

Other uncommon conditions are cryptococcosis and nocardiosis. They may present in a similar way to TB. The diagnosis of pulmonary cryptococcosis rests on finding the fungal spores in sputum smears. Nocardiosis may be particularly difficult to differentiate from TB. The CXR often shows upper lobe, cavitory infiltrates. The organism may also be weakly positive on acid-fast staining. Associated soft-tissue and brain abscesses raise clinical suspicion. The diagnosis rests on finding beaded and branching Gram-positive rods on sputum smear. In South-East Asia, penicilliosis (due to a fungus called *Penicillium marneffeii*) and melioidosis can present in a similar way to PTB and may be HIV-related. The same is true for common fungal infections (paracoccidioidomycosis and histoplasmosis) in the Americas.

Crofton J, Horne N, Miller F. *Clinical tuberculosis*, second edition. London, MacMillan Press Limited, 1999.

Harries AD, Maher D, Nunn P. An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high-HIV-prevalence settings in sub-Saharan Africa. *Bulletin of the World Health Organization*, 1998, 76: 651–662.

International Union Against Tuberculosis and Lung Disease. *Technical guide. Sputum examination for tuberculosis by direct microscopy in low-income countries*. Fifth edition. Paris, 2000.

Toman K. *Tuberculosis. Case finding and chemotherapy*. Geneva, WHO, 1979.

World Health Organization. *Tuberculosis handbook*. Geneva, 1998, (WHO/TB/98.253).

4.1 EPIDEMIOLOGY OF CHILDHOOD TB

The source of transmission of TB to a child is usually an adult (often a family member) with sputum smear-positive PTB. Cases of TB in children usually represent between 10% and 20% of all TB cases. The frequency of childhood TB in a given population depends on the following: the number of infectious cases, the closeness of contact with an infectious case, the age of children when exposed to TB, and the age structure of the population. Children rarely have sputum smear-positive TB and so it is unlikely they are a powerful source of transmission. TB in children is mainly due to failure of TB control in adults. Failure of TB control in adults means failure to cure infectious cases (patients with sputum smear-positive PTB). The highest priority in TB control is to cure the infectious cases. However, it is still important to cure children with TB! Good treatment of TB in childhood will result in the following:

- improved well-being through decreased morbidity and mortality;
- improved credibility and reputation of the NTP; and
- less chance for children to have TB reactivation with cavitation in later life.

PRACTICAL POINT

A good TB control programme is the best way to prevent TB in children.

Immunization

In many countries, newborns receive BCG immunization, and yet childhood PTB still occurs. This shows that BCG is not fully effective in protecting against PTB. BCG seems to give better protection against disseminated disease, such as miliary TB or TB meningitis, than it does against PTB. The effectiveness of BCG against PTB is variable between regions, and the reasons for this are not completely understood. One problem is likely to be the timing of the vaccination. In developing countries where TB is common, children will often be exposed to TB early in life and so immunization needs to be given as early as possible, i.e. soon after birth. However, the immune system of a newborn may be too immature to be able to produce an effective immune reaction to the BCG. BCG has been more effective when given to school-aged children. However, in communities where TB is common, this would be too late to protect against most disease. Other factors that reduce the

effectiveness of BCG immunization are malnutrition and severe infections such as HIV or measles.

Risk of infection

Risk of infection depends on extent of exposure to infectious droplet nuclei. An infant whose mother has sputum smear-positive PTB, for instance, has a high chance of becoming infected. Being in very close contact with the mother, he or she is likely to inhale a larger number of infectious droplets from the air than other household contacts. The greater the exposure to infection, the greater the likelihood of disease.

Risk of progression of infection to disease

The chance of developing disease is greatest shortly after infection, and steadily decreases as time goes by. Infants and young children under 5 years of age have less-developed immune systems than school-aged children. They are therefore at particular risk (up to 20%) of developing disease following infection. Many will present with disease within one year following infection, most within 2 years. For infants particularly, the time-span between infection and disease may be quite short and the presentation of PTB is as an acute rather than chronic pneumonia. Almost always in those cases, the contact is the mother. The majority of HIV-negative children infected with *M. tuberculosis* do not develop TB disease in childhood. In these healthy, asymptomatic, but TB-infected children, the only evidence of infection may be a positive tuberculin skin test.

PRACTICAL POINT

The suspicion of TB in an infant should lead to investigation of the mother for PTB. If there is no definite history of TB in the mother, ask also about a history of chronic cough.

An infected child can develop TB disease at any time. Various illnesses or stresses may trigger progression of infection to disease. The most important trigger is weakening of immune resistance. This occurs with HIV infection, other infections (especially measles and whooping cough) and malnutrition. These conditions are also most common in infancy and early childhood.

4.2 HOW DOES TB IN CHILDREN DIFFER FROM TB IN ADULTS?

The commonest age of presentation of childhood TB disease is between 1 and 4 years. As already emphasized, young age is a risk factor for infection, for progression from infection to disease, and for spread of

disease to other parts of the body, i.e. dissemination. Most children with TB are not infectious to others.

The commonest type of TB in children is smear-negative PTB. This is because cavitating TB is infrequent in children. The majority of children with PTB are too young to provide a sputum specimen for smear microscopy. Therefore an alternative method of obtaining sputum, such as gastric aspiration, is required. If alternative diagnostic methods are not available or routinely practised, the children are registered as having “smear-negative PTB”, even though a smear has not been done. The next commonest type is extrapulmonary TB. Common forms of EPTB in children include: miliary TB and TB meningitis (usually in children less than 3 years of age); TB lymphadenopathy (all ages); TB effusions (pleural, pericardial and peritoneal); and spinal TB (often school-aged children) (see Chapter 5). Smear-positive PTB is usually diagnosed in children older than 6 years. The prevalence of PTB is normally low between 5 and 12 years and then increases in adolescents. In adolescents, PTB is generally like adult PTB, e.g. often with cavitation.

Pathogenesis

TB disease in children is usually primary TB. Post-primary TB may occur in adults following reactivation of dormant TB bacilli acquired in childhood. The age when a child is infected determines the pattern of primary disease. Pulmonary disease in young children is closely linked to pathology of the mediastinal nodes. This is lymphobronchial TB, which results in a wide spectrum of segmental lesions. These lesions may also be found in adults, but are unusual. Adults usually develop TB in the apices of the upper or lower lobes. Young children (i.e. less than 5 years of age) are particularly susceptible to severe forms of disseminated disease following primary infection. These severe forms include miliary TB and extrapulmonary forms of TB, e.g. meningitis.

PRACTICAL POINT

Malnourished and HIV-infected children may develop severe PTB at any age.

4.3 APPROACH TO DIAGNOSIS OF TB

The diagnosis of PTB in children is difficult. If you find the diagnosis of PTB in children easy, you are probably overdiagnosing. It is easy to overdiagnose PTB, but also easy to miss the diagnosis and presume the

clinical presentation is due to malnutrition or AIDS. Carefully assess all the evidence before making the diagnosis.

The diagnosis of PTB is particularly difficult in children because, under the age of 6–8 years, children with PTB rarely cough up sputum. The readily available usual test for adults and older children with PTB is sputum smear microscopy. However, there is no such “gold standard” test for the majority of children with TB. Young children usually swallow their sputum. Gastric suction and laryngeal swabs are generally not useful unless facilities are available for *M. tuberculosis* culture. This means that bacteriological confirmation is usually not possible. The diagnosis of PTB in children is therefore nearly always presumptive.

The approach to diagnosis of extrapulmonary TB in children is similar to that described for adults and is outlined in Chapter 5. In some hospitals, helpful special diagnostic investigations may be available. These may include microscopy of fluid (e.g. pleural fluid, cerebrospinal fluid, ascitic fluid) and TB culture, specialized X-rays, biopsy and histology.

Clinical assessment

There are no specific features on clinical examination that can confirm that the presenting illness is due to PTB. Respiratory symptoms and disease are extremely common in childhood, particularly before 5 years of age. In most cases of suspected PTB, the child has been treated with a broad-spectrum antibiotic, with no clinical response. Always look for three important clues to TB in children:

- (1) Contact with an adult or older child with smear-positive PTB.
It is usually possible to identify the source of infection. This is most often the child's mother or another female carer, such as an aunt, grandmother or older sister. They are the ones who spend most time with young children. Make sure you ask for a specific history of illness in each household contact. For example, do not just ask “does anyone in the home have TB?” but also “is anyone at home ill and what are the symptoms?” Remember that the contact may have occurred 6 months to 2 years ago. This is the usual time lapse between infection and developing symptoms of disease. Adult cases of PTB are occasionally diagnosed when a child presents with suspected TB.
- (2) Failure to thrive or weight loss (growth faltering).
This is a good indicator of chronic disease in children and TB may be the cause. It is not specific and may also be due to poor nutrition, persistent or recurrent diarrhoea or HIV infection.

- (3) Respiratory symptoms such as cough lasting for more than three weeks in a child who has received a course of broad-spectrum antibiotics.

PRACTICAL POINT

Ask the mother of a child with suspected TB for the child's "road to health" card (growth card). If the card is available, look for growth faltering or weight loss.

In the absence of these clues, TB is less likely. However, always take a clear history and examine the child carefully. There may be clues to other diagnoses, such as asthma or an inhaled foreign body. Note the nutritional state of the child and look for signs of HIV infection (see Chapter 7). Examine the chest. There may be unexpected findings, such as consolidation or pleural effusion. A child with these abnormalities who does not look acutely unwell (e.g. no signs of respiratory distress such as tachypnoea) and has not recently had antibiotics is more likely to have TB rather than the more common bacterial pneumonias. Finally, do not forget to examine the heart. Otherwise children with cardiac failure due to congenital heart disease, rheumatic heart disease or cardiomyopathy may be misdiagnosed as having PTB.

Investigations

If available, a tuberculin skin test should be done, as it may provide supportive evidence. A negative tuberculin test does not exclude TB. The tuberculin test is discussed in Section 4.5.

CXR is a common investigation in suspected PTB or miliary TB. The most consistent specific feature on CXR is nodal enlargement and this will be present in many children with PTB. Cavitation may be seen in older children and adolescents, who will often be sputum smear-positive. A normal CXR can be useful to exclude PTB or miliary TB in a child with suggestive symptoms, such as persistent fever, night sweats and failure to thrive. A single CXR at the time of presentation of illness has limited value. A child presenting with persistent cough should receive a course of broad-spectrum antibiotics, with a follow-up CXR at least one month later. As for clinical examination, marked abnormalities are occasionally found on CXR in a child who does not look acutely unwell. This is suggestive of PTB.

The usefulness of the tuberculin test and CXR are further reduced in malnourished or HIV-infected children (see Section 4.5). This is

unfortunate as these are common conditions that the health worker often needs to differentiate from TB. To add to the confusion, both groups are at particular risk for TB disease.

Differential diagnosis of chronic respiratory symptoms

Other conditions that present with chronic respiratory symptoms include:

- pertussis (whooping cough)
- asthma
- HIV infection (see section 4.8)
- aspirated foreign body
- bronchiectasis
- cystic fibrosis
- cardiac disease
- severe gastro-oesophageal reflux
- severe cerebral palsy

4.4 SCORE SYSTEM FOR DIAGNOSIS OF TB IN CHILDREN

There are a number of diagnostic score charts to improve diagnosis of TB in children. These score charts have rarely been evaluated. The basis of a score system is the careful and systematic collection of diagnostic information. A score system is, in fact, not diagnostic but is rather a useful screening test that helps guide your clinical judgement. A score above a certain threshold indicates a high likelihood of TB. Examples can be found in *Clinical tuberculosis* (Crofton, Horne & Miller) or in the article by van Beekhuizen in *Tropical doctor* (see “Suggestions for further reading” at the end of the chapter).

Characteristic clinical features (e.g. spinal deformity, scrofula or painless ascites) supported by simple investigations often point to the diagnosis of various forms of extrapulmonary TB. These permit a confident diagnosis of TB, even if rarely confirmed microbiologically. However, the commonest type is PTB and this is the most difficult to diagnose. Score charts are least useful for PTB because they are so nonspecific in regions where malnutrition and HIV are common. Features suggestive of TB (and commonly used in score charts) include:

- duration of illness greater than 4 weeks, particularly if the illness has not responded to other treatments, e.g. broad-spectrum antibiotics for persistent cough;

- evidence of wasting (i.e. under 60% of median weight-for-age), especially if there is a lack of weight gain in response to intensive nutritional support;
- family history of sputum-positive PTB (this is very important information);
- significant or “positive” tuberculin test.

Some score charts use response to TB treatment as a factor supporting a diagnosis of TB. This does not mean that a TB treatment trial should be used for diagnostic purposes!

4.5 TUBERCULIN SKIN TEST

Tuberculin is a purified protein derived from tubercle bacilli. Another name for tuberculin is PPD (purified protein derivative). Following infection with *M. tuberculosis*, a person develops hypersensitivity to tuberculin. Tuberculin injected into the skin of an infected person produces a delayed local reaction after 24–48 hours. This reaction is quantified by measuring the diameter of skin induration (thickening) at the site of the reaction. Various conditions can suppress this reaction. The reaction indicates **hypersensitivity**. In other words, the reaction only shows that the person has at some time been infected with *M. tuberculosis*.

PRACTICAL POINT

A tuberculin test does not measure immunity. By itself, it does not indicate the presence or extent of TB disease; it only indicates infection.

The technical details about tuberculins and how to administer and read a tuberculin test are beyond the scope of this book. *Clinical tuberculosis* (Crofton, Horne & Miller) gives a good account. The standard amount of tuberculin used is 5 units, injected as 0.1 ml into the anterior surface of the forearm at the junction of the middle and upper thirds. It is very important that the tuberculin is injected intradermally so that it is well localized. If correctly given, the injection should raise a small bump of 5 mm or more in diameter, which disappears within 1–2 hours. This is not easy in a vigorous and protesting child. Poor injection technique can cause a false-negative reaction.

Value of a negative tuberculin test

A tuberculin test is not significant, or “negative”, when the diameter of skin induration is less than 10 mm (or less than 5 mm in an HIV-infected child). This is regardless of whether the child has had BCG. A negative tuberculin skin test does not exclude TB. Thus, it is of no help in deciding that someone does not have TB. The table below shows the conditions that can suppress a tuberculin skin test in a person with active TB.

Conditions that may suppress the tuberculin skin test

HIV infection

malnutrition

severe bacterial infections, including TB itself

viral infections, e.g. measles, chickenpox, glandular fever

cancer

immunosuppressive drugs, e.g. steroids

incorrect injection of PPD

Value of a positive tuberculin skin test

The criterion for a significant or “positive” tuberculin test depends on whether a child has previously had BCG vaccination or not. This is because a reaction to tuberculin is usual after a previous BCG, at least for several years. The reaction is usually weaker (diameter often less than 10 mm) than the reaction to natural infection with *M. tuberculosis*. A tuberculin test is considered significant or positive when the diameter of skin induration is 10 mm or more. However, if the child is HIV-infected, the tuberculin test is considered positive if the induration is 5 mm or more. A positive tuberculin test is only one piece of evidence in favour of the diagnosis of TB. The younger the child and the greater the diameter of induration, the stronger is that one piece of evidence.

4.6 THE DECISION TO START TB TREATMENT IN CHILDREN

The decision to start TB treatment in a child is an active process, which involves weighing up the clinical evidence and investigation findings, careful thought, and often a period of observation. For children with confirmed TB or for whom there is a high likelihood of TB, there is no need to hesitate about starting treatment. If the diagnostic evidence is weak and the child is older and not acutely ill, there is no need for anxiety or urgency about starting treatment. Wait and see! If, however, the child is very young and acutely ill it may be necessary to start treatment on the basis of less robust evidence.

In the past, some doctors have advocated a “treatment trial” with anti-TB drugs for purposes of diagnosis. The idea is that if the child responds to the treatment, then the diagnosis is TB. There are some problems with this approach:

- some anti-TB drugs, such as rifampicin, kill other bacteria, so response to anti-TB drugs may be because the child has another (bacterial) infection;
- compliance with a “treatment trial” is often poor, because of the lack of certainty surrounding the decision to treat;
- there may be a tendency to jump too quickly to a “treatment trial” without the necessary careful and thoughtful approach to diagnosis;
- a hasty “treatment trial” may not leave enough time to give treatment for other more common infections, such as bacterial or atypical pneumonia;
- once TB treatment is started, it should be completed.

4.7 IMPACT OF HIV ON THE DIAGNOSIS OF TB IN CHILDREN

HIV makes the diagnosis and management of TB in children even more difficult than usual, for the following reasons:

- Several HIV-related diseases, including TB, may present in a similar way (see section 4.8 for differential diagnosis).
- The interpretation of tuberculin skin testing is less reliable. An immunocompromised child may have a negative tuberculin skin test despite having TB.
- In some countries HIV infection is very common in adults with TB. If there is a history of contact with an adult with smear-positive PTB and that adult is the child’s parent, then the child has an increased chance of being HIV infected as well. In addition, the child with TB, even if not HIV-infected, may come from a household where one or both parents have died. This situation makes compliance and completion of treatment more difficult.

For these reasons and those mentioned above, many of the clinical features that are used to suggest a diagnosis of childhood TB are less useful in the presence of HIV infection.

Impact of HIV infection on the usefulness of features used to diagnose PTB in children

Diagnostic feature	Impact of HIV
Chronic symptoms	less specific
Smear-positive contact (if parent)	less specific
Malnutrition or failure to thrive	less specific
Positive tuberculin test	less sensitive
“Characteristic” CXR abnormalities	less specific
Satisfactory response to TB treatment	less sensitive

4.8 DIFFERENTIAL DIAGNOSIS OF PULMONARY TB IN HIV-INFECTED CHILDREN

Bacterial pneumonia

Bacterial pneumonia is very common in all HIV-infected children and recurrent bacterial pneumonia is a feature of children with AIDS. The commonest cause is *Streptococcus pneumoniae* and response to treatment is usually satisfactory. Other causes include *Haemophilus influenzae*, *Salmonella*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Escherichia coli*. The presentation of PTB in infants can be acute, so PTB should be considered when there is a poor clinical response to standard antibiotics and the mother has TB. Pneumonia due to *Staphylococcus* or *Klebsiella* may be a problem in HIV-infected children with chronic lung disease. These bacteria can cause cystic changes and cavitation.

Lymphocytic interstitial pneumonitis (LIP)

LIP is a very common cause of lung disease in HIV-infected children over 2 years of age. LIP may be difficult to differentiate from PTB or miliary TB. Clinical features that are commonly associated with LIP include symmetrical, generalized lymphadenopathy (painless and mobile), bilateral chronic non-tender parotid enlargement, and finger clubbing. Diagnosis is clinical as it can only be confirmed by lung biopsy. Typical CXR findings are bilateral diffuse reticulonodular pattern and enlarged mediastinal/hilar lymph nodes. Note that the CXR abnormalities are often unilateral with PTB. However, LIP presents with a broad spectrum of clinical and radiological features. Bacterial pneumonia is a common complication and further confuses the CXR findings.

Bronchiectasis

This is usually a complication of LIP but may also complicate TB. A cough

productive of copious purulent and sometimes blood-stained sputum, finger clubbing, and halitosis are typical features.

Pulmonary Kaposi sarcoma

KS can involve the lungs and causes diffuse lung infiltration and lymph node enlargement. Patients may present with a large pleural effusion which is bloody on aspiration. Look for the typical KS lesions elsewhere: on the skin, palate or conjunctiva.

Pneumocystis carinii pneumonia

PCP is a common problem in HIV-infected children and usually presents as an acute, severe pneumonia in infants less than 6 months of age. Compared with TB in infants, PCP is characterized by severe hypoxia. The commonest CXR abnormalities are diffuse interstitial infiltration and hyperinflation. In developing countries, PCP is a very unlikely diagnosis of persistent respiratory disease in children after infancy. In countries where there is antenatal HIV screening and routine cotrimoxazole prophylaxis in HIV-infected infants, PCP is now unusual .

Others

Other conditions to be considered in the differential diagnosis include: fungal pneumonia, e.g. due to *Candida* or cryptococcus, nocardiosis and pulmonary lymphoma.

PRACTICAL POINT

The commonest HIV-related lung disease in children that may be confused with TB is LIP.

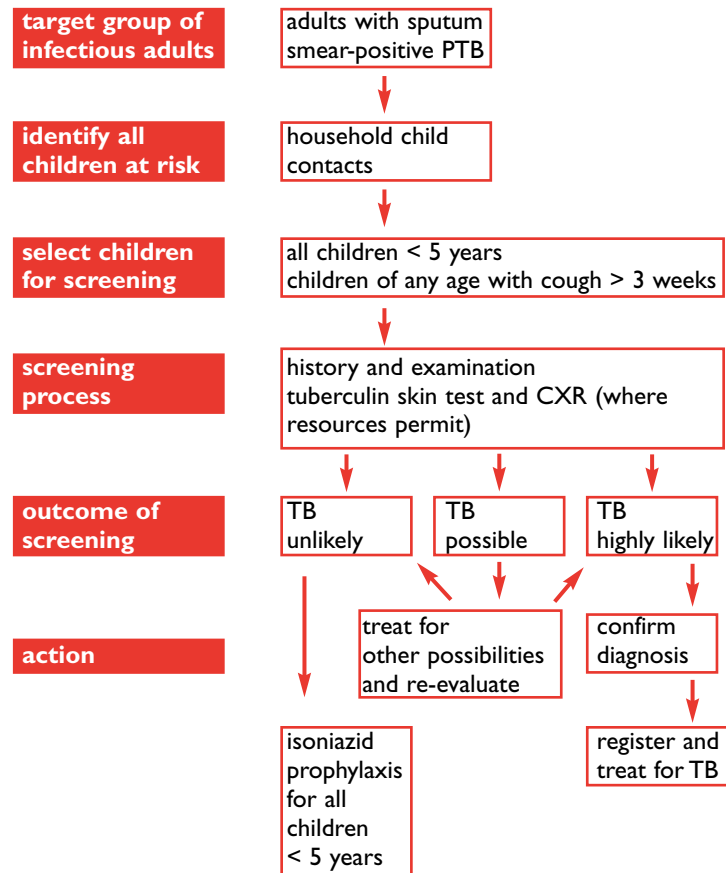
4.9 MANAGEMENT OF CHILD CONTACTS OF INFECTIOUS ADULTS

Children with TB may present to health units when they are ill. However, most national TB control programmes also recommend active contact tracing of children who are household contacts of infectious adults. In order to be effective, this screening must be systematic. If you do not have a systematic, organized process for child contact screening where you work, could you start one?

The scheme below shows how to manage child contacts of infectious adults (with sputum smear-positive PTB). Suspicion that a child contact is HIV-infected may arise because of the following: the child has clinical

evidence of HIV infection; the parent (the infectious TB patient) is known, or suspected, to be HIV-positive. If you suspect a child contact is HIV-infected, it is important to counsel the parents before HIV-testing the child.

How to identify and manage child contacts of infectious adults



A child under 5 years of age living with a sputum smear-positive PTB patient is at high risk of TB infection and developing TB disease, especially if HIV-positive. Tuberculin skin testing is not a reliable way of

distinguishing TB-infected from non-TB-infected children and is often not available. The IUATLD therefore recommends isoniazid preventive treatment for all child household contacts (under 5 years of age) of sputum smear-positive PTB patients. The preventive treatment should be based on the drug sensitivity profile of the likely source of infection, whenever this profile is available.

SUGGESTIONS FOR FURTHER READING

Chaulet P et al. *Childhood tuberculosis, still with us*. Paris, International Children's Centre, 1992.

Crofton J, Horne N, Miller F. *Clinical tuberculosis, second edition*. London, MacMillan Press Limited, 1999.

Donald PR, Fourie PB, Grange JM. *Tuberculosis in childhood*. Pretoria, JL van Schaik, 1999.

Graham SM, Coulter JBS, Gilks CF. Pulmonary disease in HIV-infected African children. *International journal of tuberculosis and lung disease*, 2001, 5: 12-23.

Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *International journal of tuberculosis and lung disease*, 2002, 6: 1038-1045.

International Union Against Tuberculosis and Lung Disease. *Tuberculosis guide for low income countries*. 5th edition, Frankfurt, pmi Verlagsgruppe, 2000.

Miller FJW. *Tuberculosis in children*. New Delhi, Churchill-Livingstone, 1986.

Mukadi YD, Wiktor SZ, Coulibaly I-M, et al. Impact of HIV infection on the development, clinical presentation, and outcome of tuberculosis among children in Abidjan, Cote d'Ivoire. *AIDS*, 1997, 11: 1151-1158.

Osborne CM. The challenge of diagnosing childhood tuberculosis in a developing country. *Archives of diseases in childhood*, 1995, 72: 369-74.

Palme IB, Gudetta B, Bruchfeld J, Muhe L, Giesecke J. Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. *The pediatric infectious disease journal*, 2002, 21: 1053-1061.

Reider HL. *Epidemiologic basis of tuberculosis control*. Paris, International Union Against Tuberculosis and Lung Disease, 1999.

Schaaf HS, Beyers N, Gie RP, et al. Respiratory tuberculosis in childhood: the diagnostic value of clinical features and special investigations. *The pediatric infectious disease journal*, 1995, 14: 189-194.

Van Beekhuizen HJ. Tuberculosis score chart in children in Aitape, Papua New Guinea. *Tropical doctor*, 1998, 28: 155-160.

Extrapulmonary TB (EPTB) can occur at any age. Young children and HIV-positive adults are particularly susceptible. Up to 25% of TB cases may present with EPTB. Children of less than 2 years of age are at risk of disseminated disease causing miliary TB or TB meningitis. The common forms of extrapulmonary TB associated with HIV are the following: lymphadenopathy, pleural effusion, pericardial disease, miliary TB, and meningitis. Many patients with extrapulmonary TB also have coexistent pulmonary TB.

PRACTICAL POINT

If a patient has extrapulmonary TB, look for pulmonary TB. If the patient has had a productive cough for more than 2 or 3 weeks, send sputum samples for AFB. If testing AFBs the test is negative, do a CXR.

5.1 DIAGNOSTIC APPROACH

Definitive diagnosis of extrapulmonary TB is often difficult. Diagnosis may be presumptive, provided you can exclude other conditions. Patients usually present with constitutional features (fever, night sweats, weight loss) and local features related to the site of disease. These local features are similar in adults and children. The degree of certainty of diagnosis depends on the availability of diagnostic tools, e.g. specialized X-rays, ultrasound, biopsy.

5.2 TUBERCULOUS LYMPHADENOPATHY

Regardless of HIV status, the lymph nodes most commonly involved are the cervical nodes. The usual course of lymph node disease is as follows:

firm, discrete nodes → fluctuant nodes → matted together → skin breakdown, abscesses, chronic sinuses → healing with scarring

PRACTICAL POINT

In severely immunocompromised patients, tuberculous lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis.

In adults, the differential diagnosis of tuberculous lymphadenopathy includes the following: persistent generalized lymphadenopathy (PGL), lymphoma, Kaposi sarcoma, carcinomatous metastases, sarcoid, and drug reactions (e.g. phenytoin).

Lymphoid interstitial pneumonitis (LIP) is often associated with PGL in HIV-infected children. LIP may be confused with TB as chronic respiratory symptoms are very common. The lymphadenopathy with LIP is characteristically generalized, symmetrical, mobile, non-tender, firm and non-fluctuant. Differential diagnoses of focal lymphadenopathy in children include bacterial or pyogenic adenitis and lymphoma (e.g. Burkitt lymphoma).

Persistent generalized lymphadenopathy (PGL)

PGL is a feature of HIV infection which develops in up to 50% of HIV-infected individuals. It is of no prognostic significance. There is no specific treatment. The diagnostic criteria for PGL are as follows: lymph nodes larger than

- 1 cm in diameter
- in 2 or more extra-inguinal sites
- for 3 or more months.

The nodes are non-tender, symmetrical, and often involve the posterior cervical and epitrochlear nodes. PGL may slowly regress during the course of HIV infection and may disappear before the onset of AIDS. In populations with a high HIV prevalence, PGL is the commonest cause of lymphadenopathy. In HIV-positive individuals PGL is a clinical diagnosis. Only investigate further if there are features of another disease. The features of lymph nodes that indicate a need for further investigation, including biopsy, are:

- large (> 4 cm diameter) or rapidly growing lymph nodes
- asymmetrical lymphadenopathy
- tender/painful lymph nodes not associated with local infection
- matted/fluctuant lymph nodes
- obvious constitutional features (e.g. fever, night sweats, weight loss)
- hilar or mediastinal lymphadenopathy on CXR.

Practical approach to investigation of lymphadenopathy
(if clinical features suggest a cause of lymphadenopathy other than PGL).

Procedure	Test	Result	Diagnosis
needle aspirate of lymph node	look at material aspirated	→ caseation	→ TB
	smear for AFB	→ AFB present	→ TB
	smear for cytology	→ malignant cells seen lymphoma, carcinoma	→ malignancy e.g. KS,
if no diagnosis after aspirate			
lymph node biopsy	look at cut surface	→ caseation	→ TB
	smear from cut surface for AFB	→ AFB seen	→ TB
	fresh node sent for TB culture	→ positive TB culture	→ TB
	node in formalin for histology	→ granuloma and AFB → malignant cells	→ TB → malignancy

Diagnosis of tuberculous lymphadenopathy is possible even without laboratory facilities for histology or TB culture. Diagnostic sensitivity of tuberculous lymphadenopathy by aspirate and smear for AFB is 70%. Diagnostic sensitivity increases to 80% if you excise a lymph node, look at the cut surface, and do a smear for AFB.

The histological appearance of tuberculous lymph nodes from HIV-positive patients depends on the degree of immunocompromise, as shown below.

Degree of immunocompromise**Histological appearance of lymph nodes**

mild

caseating lesions with few or no AFB

severe

little cellular reaction with many AFB

5.3 MILIARY (DISSEMINATED) TB

Miliary TB results from widespread bloodborne dissemination of TB bacilli. This results from either a recent primary infection or the erosion of a tuberculous lesion into a blood vessel.

Clinical features

Patients present with constitutional features rather than respiratory symptoms. They may have hepatosplenomegaly and choroidal tubercles (fundoscopy). Often the presentation is associated with fever of unknown origin and wasting may be marked. Miliary TB is an underdiagnosed cause of end-stage wasting in HIV-positive individuals. A high index of suspicion is necessary.

Diagnosis

CXR shows diffuse, uniformly distributed, small miliary shadows. "Miliary" means "like small millet seeds". The CXR can appear normal in advanced cases because of severe immunosuppression and therefore inability to mount an inflammatory response. Full blood count may show pancytopenia. Liver function tests may be abnormal. Bacteriological confirmation (smears or mycobacterial culture) is sometimes possible from sputum, cerebrospinal fluid, bone marrow, liver or blood.

Differential diagnosis

The differential diagnosis includes the following: the syndrome of HIV wasting disease (sometimes referred to as "slim disease"), bacteraemia (including typhoid fever), disseminated carcinoma, disseminated infection with "atypical" mycobacteria, trypanosomiasis (in endemic regions) and connective tissue diseases.

The typical diffuse CXR abnormalities can be confused with those of LIP in children. The table below lists features that help to differentiate miliary TB from LIP. However, there is clinical overlap as LIP presents with a broad range of clinical and radiographic features, which vary depending on the stage of HIV disease.

Clinical differentiation of miliary TB from LIP in children

	Miliary TB	LIP
Clinical features:		
Respiratory symptoms	-/+	+++
Persistent fever	++	++
Wasting	+++	-/+
Generalized lymphadenopathy	-/+	+++
Parotid enlargement	-	++
Clubbing	-	+
Hepatomegaly	++	++
CXR features:		
Diffuse micronodular	++	+
Diffuse reticular	-	++
Lymphadenopathy	-/+	++

5.4 TUBERCULOUS SEROUS EFFUSIONS (PLEURAL, PERICARDIAL, ASCITES)

Inflammatory tuberculous effusions may occur in any of the serous cavities of the body, i.e. pleural, pericardial or peritoneal cavities. They are more common in HIV-positive than in HIV-negative adults, and also occur in school-aged children with or without HIV infection. Serous effusions are often indicative of primary disease or reinfection.

Approach to diagnosis

The presentation is usually with constitutional and local features. Microscopy of the aspirate from tuberculous serous effusions rarely shows AFB because the fluid forms as an inflammatory reaction to TB lesions in the serous membrane. TB culture, even if available, is of no immediate help. A culture result usually takes 4-6 weeks. The white cell content is variable, usually with predominant lymphocytes and monocytes. The aspirate is an exudate (i.e. protein content is more than 30 g/l).

PRACTICAL POINT

A biochemistry laboratory is not essential to diagnose an exudate. Simply leave the aspirate standing: if “spider clots” develop in the specimen, it is an exudate.

In populations in sub-Saharan Africa with high HIV prevalence, TB is the commonest cause of an exudative serous effusion. The diagnosis is usually presumptive (i.e. without microbiological or histological confirmation). It is important to exclude other causes of an exudate.

PRACTICAL POINT

Interpret with caution the laboratory result of protein concentration in any aspirated fluid. If there has been a delay in laboratory analysis, a protein clot may have formed in the sample. The laboratory result may then be falsely low.

Tuberculous pleural effusion

The clinical and CXR diagnosis of a pleural effusion is straightforward. The typical clinical features are constitutional and local (chest pain; breathlessness; tracheal and mediastinal shift away from the side of the effusion; decreased chest movement, dull percussion note and decreased breath sounds on the side of the effusion). CXR shows unilateral, uniform white opacity, often with a concave upper border. If available, ultrasound can confirm the presence of fluid in the pleural space in case of doubt.

Always perform diagnostic pleural aspiration if a patient has a pleural effusion. The fluid is usually straw-coloured. The white cell count is usually high (about 1000–2500 per mm³) with predominant lymphocytes. Occasionally the fluid is blood-stained. The presence of pus on aspiration indicates an empyema (purulent effusion).

PRACTICAL POINT

In a hospital with limited facilities serving a population with high TB prevalence, patients with a unilateral exudative pleural effusion that has not responded to a full course of antibiotics should be treated with anti-TB drugs.

If facilities are available, closed pleural biopsy using an Abrams needle is useful for histological diagnosis. Since the distribution of TB lesions in the pleura is patchy, the diagnostic yield of closed pleural biopsy is about 75%. Multiple biopsies increase the diagnostic yield. A small open pleural biopsy increases the yield even further but is not usually necessary.

Differential diagnosis

The differential diagnosis of an exudative pleural effusion includes

malignancy, post-pneumonic effusion, pulmonary embolism and amoebic liver abscess (extending on the right).

Tuberculous empyema

This usually arises when a tuberculous cavity in the lung ruptures into the pleural space. The physical signs are those of a pleural effusion, but aspiration reveals thick white or yellow pus. If the pus is too thick to remove using a needle and syringe, use an intercostal drain. Send the pus to the laboratory for examination for TB and also for Gram stain and bacterial culture. If facilities are available, closed pleural biopsy is useful for histological diagnosis.

The main differential diagnosis is bacterial empyema, when the patient is usually more acutely ill and toxic. It may be possible to confirm bacterial empyema by Gram stain or culture of the aspirated pus.

A succussion splash is a splashing sound heard with the stethoscope while shaking the patient's chest. A succussion splash indicates a pyopneumothorax (pus and air in the pleural space). After CXR confirmation, insert a chest drain with underwater seal.

PRACTICAL POINT

Always test a patient with signs of a pleural effusion for a succussion splash.

Tuberculous pericardial effusion

Diagnosis

The diagnosis usually rests on suggestive constitutional and cardiovascular features and investigation findings (ECG, CXR and echocardiography). It is important to exclude uraemia and Kaposi sarcoma.

Cardiovascular symptoms

- chest pain
- shortness of breath
- cough
- dizziness and weakness (low cardiac output)
- leg swelling
- right hypochondrial pain (liver congestion)
- abdominal swelling (ascites)

Cardiovascular signs

- tachycardia
- low blood pressure
- pulsus paradoxus
- raised jugular venous pressure (JVP) with small amplitude "a" and "v" waves
- impalpable apex beat
- quiet heart sounds
- pericardial friction rub
- signs of right-sided heart failure (e.g. hepatomegaly, ascites, oedema)

PRACTICAL POINT

The signs may be subtle. Assess carefully any patient with oedema or ascites with the possibility of pericardial effusion in mind.

CXR

- large globular heart
- clear lung fields
- pleural fluid

ECG

- tachycardia
- ST and T wave changes
- low voltage QRS complexes
- sometimes electrical alternans (alternating positive and negative R waves, reflecting a heart that moves with each beat within the pericardial fluid)

Echocardiography

- pericardial fluid
- strands crossing between visceral and parietal pericardium

Pitfalls in diagnosis of pericardial effusion

Clinicians have misdiagnosed pericardial effusion as the following:

- congestive cardiac failure;
- hepatoma or amoebic liver abscess (enlarged liver);
- bilateral pleural effusions.

Pericardiocentesis

This is only safe under the following conditions:

- a) echocardiography has confirmed a moderate to large pericardial effusion;
- b) the operator is experienced.

Therapeutic pericardiocentesis is necessary if there is cardiac tamponade (acute life-threatening cardiac impairment).

PRACTICAL POINT

In populations with high TB/HIV prevalence, TB is the most likely treatable cause of pericardial effusion. It may be safer for the patient to start presumptive anti-TB treatment than to undergo diagnostic pericardiocentesis.

Treatment with steroids and anti-TB drugs, without pericardiocentesis, usually results in satisfactory resolution of tuberculous pericardial effusion.

Outcome

A possible complication despite TB cure is the development of pericardial constriction. Medical management of heart failure due to pericardial constriction helps in some cases. A surgeon may weigh up the possible benefit to the patient of pericardiectomy, set against the operative risks.

Differential diagnosis

Apart from TB, the differential diagnosis of pericardial effusion includes the following:

transudates: uraemia, heart failure, liver failure, hypothyroidism;

exudates: malignancy, bacterial pericardial empyema, inflammatory diseases.

Tuberculous ascites

Ascites results from peritoneal TB. Routes of spread of TB to the peritoneum include the following:

- from tuberculous mesenteric lymph nodes;
- from intestinal TB (pulmonary TB patients may develop intestinal ulcers and fistulae as a result of swallowing infected sputum);
- bloodborne.

Clinical features

Patients present with constitutional features and ascites. Marked wasting is common in children. Signs of other causes of ascites such as nephrotic syndrome (peripheral and periorbital oedema) or portal hypertension (marked splenomegaly) are usually absent. There may be palpable abdominal masses (mesenteric lymph nodes). Adhesion of nodes to

bowel may cause bowel obstruction. Fistulae may develop between bowel, bladder and abdominal wall.

Investigations

Do a CXR to look for associated PTB. Always do a diagnostic ascitic tap. The aspirated fluid is usually straw-coloured, but occasionally turbid or blood-stained. The fluid is an exudate, usually with more than 300 white cells per mm^3 and predominantly lymphocytes. Ultrasound, if available, may show features consistent with TB, including enlarged mesenteric or retroperitoneal lymph nodes.

PRACTICAL POINT

An ill, wasted patient with TB ascites may have a low serum albumin concentration. In this case, the usual threshold of 30 g/l albumin concentration for diagnosing an exudate is too high. Instead, calculate the difference between the albumin concentrations in serum and ascites. A serum–ascites albumin difference of less than 11 g/l means that the ascites is an exudate.

Diagnosis

The diagnosis is usually presumptive. Definitive diagnosis rests on a peritoneal biopsy, available in some hospitals. Blind percutaneous needle biopsy of the peritoneum has a low pick-up rate and a high complication rate. In experienced hands, laparoscopy under local anaesthetic has a high pick-up rate. Laparoscopy enables direct visualization and biopsy of peritoneal TB lesions. Laparotomy will confirm the diagnosis in nearly every case but is too invasive for routine use.

Differential diagnosis

Apart from TB, the differential diagnosis of ascites includes the following:

transudates: heart failure, renal failure, nephrotic syndrome, chronic liver disease due to cirrhosis, hepatosplenic schistosomiasis, hypoproteinaemia;

exudates: malignancy, other infections causing peritonitis.

5.5 TUBERCULOUS MENINGITIS

Routes of spread of TB to the meninges include the following:

- from rupture of a cerebral tuberculoma into the subarachnoid space;
- bloodborne.

Clinical features

The patient may present with constitutional features and chronic meningitis. There is gradual onset and progression of headache and decreased consciousness. Examination often reveals neck stiffness and a positive Kernig's sign. Cranial nerve palsies result from exudate around the base of the brain. Tuberculomas and vascular occlusion may cause focal neurological deficits and seizures. Obstructive hydrocephalus may develop. Spinal meningeal involvement causes paraplegia (spastic or flaccid).

Diagnosis

The diagnosis usually rests on clinical grounds and cerebrospinal fluid (CSF) examination. In most cases of clinically suspected TB meningitis, lumbar puncture is safe.

PRACTICAL POINT

Lumbar puncture is hazardous if the patient has a focal neurological deficit (cerebral space-occupying lesion) or if fundoscopy shows papilloedema (raised intracranial pressure). In these circumstances, a CT brain scan is helpful, if available. Otherwise, it may be safer to start presumptive treatment with anti-TB drugs rather than risk lumbar puncture.

The CSF opening pressure is high. The CSF may look clear or occasionally cloudy. The white cell count is usually less than 500 per mm³ with predominantly lymphocytes (or early in the course of infection, predominantly polymorphs). Usually the protein level is high and the glucose low. CSF microscopy shows AFBs in a minority of cases. It is possible to increase the diagnostic pick-up rate by the following:

- examine the deposit on centrifugation of a 10 ml CSF sample;
- examine the deposit for at least half an hour before reporting it as negative;
- examine several CSF samples obtained over a few days.

PRACTICAL POINT

Lumbar puncture is important for differentiating purulent from TB meningitis. Always exclude cryptococcal meningitis by CSF microscopy (India ink stain) and, if available, fungal culture.

Difficulties in interpreting CSF findings

Some of the CSF findings may be normal, especially in HIV-positive patients. The percentages of HIV-positive TB meningitis patients with normal CSF findings are as follows: glucose 15%, protein 40%, white cell count 10%.

Differential diagnosis

The table below shows the differential diagnosis of TB meningitis, with typical CSF abnormalities.

Differential diagnosis of tuberculous meningitis

Disease	CSF abnormalities			
	White cells	Protein	Glucose	Microscopy
tuberculous meningitis	Elevated L > PMN	Increased	Decreased	AFB (in some cases)
cryptococcal meningitis*	Elevated L > PMN	Increased	Decreased	Positive India ink staining
partially treated bacterial meningitis*	Elevated	Increased	Decreased	Bacteria on Gram stain (rarely)
viral meningitis	Elevated L > PMN	Increased	Normal (low in mumps or <i>H. simplex</i>)	
acute syphilis	Elevated L > PMN	Increased	Normal	
late stage trypanosomiasis	Elevated L > PMN	Increased	Decreased	Motile trypanosomes
tumour (carcinoma/lymphoma)	Elevated L > PMN	Increased	Decreased	Cytology shows malignant cells
leptospirosis	Elevated L > PMN	Increased	Decreased	Leptospire
amoebic meningitis	Elevated L > PMN	Increased	Decreased	Amoebae

PMN = polymorphonuclear leukocytes; L = lymphocytes

* common differential diagnosis

Other forms of extrapulmonary TB are less common. There is no information as to whether they occur any more frequently in HIV-positive than in HIV-negative individuals. The table below shows the usual clinical features and diagnostic tests.

Site of disease	Clinical features	Diagnosis
Spine	Back pain Gibbus Psoas abscess Radicular pain Spinal cord compression	Plain X-ray Tissue biopsy
Bone	Chronic osteomyelitis	Tissue biopsy
Peripheral joints	Usually monoarthritis especially hip or knee	Plain X-ray Synovial biopsy
Gastrointestinal	Abdominal mass Diarrhoea	Barium X-ray
Liver	Right upper quadrant pain and mass	Ultrasound and biopsy
Renal and urinary tract	Urinary frequency Dysuria Haematuria Loin pain/swelling	Sterile pyuria Urine culture Intravenous pyelogram Ultrasound
Adrenal gland	Features of hypoadrenalism (hypotension, low serum sodium, normal/high potassium, raised urea, low glucose)	Plain X-ray (calcification) Ultrasound
Upper respiratory tract	Hoarseness and stridor Pain in ear Pain on swallowing	Usually complication of pulmonary disease
Female genital tract	Infertility Pelvic inflammatory disease Ectopic pregnancy	Pelvic examination X-ray genital tract Ultrasound pelvis Tissue biopsy
Male genital tract	Epididymitis	Often evidence of renal/urinary tract TB

Spinal TB

TB of the spine is important. The disastrous consequence for the patient of a missed diagnosis of thoracic or cervical spinal TB is paralysis. TB starts in an intervertebral disc and spreads along the anterior and longitudinal ligaments, before involving the adjacent vertebral bodies. Where TB is common, plain X-ray of the spine is usually diagnostic. The typical appearance is erosion of the anterior edges of the superior and inferior borders of adjacent vertebral bodies. The disc space is narrowed. The sites most commonly involved are the lower thoracic, lumbar and lumbosacral areas.

The main differential diagnoses are malignancy and pyogenic spinal infections. Malignant deposits in the spine tend to erode the pedicles and spinal bodies, leaving the disc intact. Pyogenic infection tends to be more acute than TB, with more severe pain.

Gastrointestinal TB

Ileocaecal TB may present with constitutional features, chronic diarrhoea, subacute obstruction, or a right iliac fossa mass. Diagnosis rests on barium examination of the small and large bowel, or on colonoscopy, if available. The differential diagnosis includes ileocaecal Crohn disease, carcinoma of the caecum, appendix abscess, lymphoma, amoeboma and tubo-ovarian abscess.

Hepatic TB

Miliary TB may involve the liver. Hepatic TB can cause diagnostic confusion. Solitary or multiple TB abscess formation can mimic amoebic liver abscess. Nodular hepatic TB can mimic hepatoma. In these situations, ultrasound examination is useful. Liver biopsy, available in some hospitals, is diagnostic.

Crofton J, Horne N, Miller F. *Clinical tuberculosis*. second edition. London, MacMillan Press Limited, 1999.

Donald PR, Fourie PB, Grange JM. *Tuberculosis in childhood*. Pretoria, JL van Schaik, 1999.

Harries AD, Maher D, Nunn P. An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high HIV prevalence settings in sub-Saharan Africa. *Bulletin of the World Health Organization*, 1998, 76, (6): 651-662.

Maher D, Harries AD. Tuberculous pericardial effusion: a prospective clinical study in a low-resource setting – Blantyre, Malawi. *International Journal of Tuberculosis lung Disease*, 1997, 1 (4): 358-364.

Miller FJW. *Tuberculosis in children*. New Delhi, Churchill-Livingstone, 1986.

Toman's tuberculosis case detection, treatment and monitoring: questions and answers. Edited by T Frieden, second edition. World Health Organization, Geneva, 2004. ISBN 92 4 154603 4. (WHO/HTM/TB/2004.334).

6.1 CLINICAL RECOGNITION OF HIV INFECTION IN TB PATIENTS

In many TB/HIV patients in sub-Saharan Africa, the only HIV-related illness present is TB. However, certain clinical features are more common in HIV-positive TB patients than in HIV-negative TB patients. The table below shows the clinical features that suggest possible HIV infection.

Clinical features suggestive of HIV coinfection in TB patients

Past history	<ul style="list-style-type: none"> ◦ sexually transmitted infection (STI) ◦ herpes zoster (shingles), which often leaves a scar ◦ recent or recurrent pneumonia ◦ severe bacterial infections (sinusitis, bacteraemia, pyomyositis) ◦ recent treated TB
Symptoms	<ul style="list-style-type: none"> ◦ weight loss (> 10 kg or > 20% of original weight) ◦ diarrhoea (> 1 month) ◦ retrosternal pain on swallowing (suggests oesophageal candidiasis) ◦ burning sensation of feet (peripheral sensory neuropathy)
Signs	<ul style="list-style-type: none"> ◦ scar of herpes zoster ◦ pruritic (itchy) papular skin rash ◦ Kaposi sarcoma ◦ symmetrical generalized lymphadenopathy ◦ oral candidiasis ◦ angular cheilitis ◦ oral hairy leukoplakia ◦ necrotizing gingivitis ◦ giant apthous ulceration ◦ persistent painful genital ulceration

PRACTICAL POINT

Always look in the mouth of any patient. Many mouth lesions are highly suggestive of HIV infection, and others are pathognomonic.

PRACTICAL POINT

Full blood count (FBC) findings suggestive of HIV infection are unexplained anaemia, leukopenia or thrombocytopenia.

The definitive diagnosis of HIV infection rests on a positive HIV test.

6.2 HIV TESTING

HIV infection is usually diagnosed through detection of antibodies to the virus. Production of these antibodies usually begins 3–8 weeks after infection. The period following infection but before antibodies become detectable is known as the “window period”. Diagnosis of HIV infection is also possible through detection of the virus (p24 antigen, nucleic-acid based tests or culture).

6.2.1 HIV antibody tests

The most widely available way of identifying HIV-infected individuals is the detection of HIV antibodies in serum or plasma samples. The table below shows the two main methods of testing for HIV antibodies. Serological tests are available that test for both HIV-1 and HIV-2. The technical details of these tests are beyond the scope of this manual. HIV diagnostic tests are extremely reliable, and are highly sensitive and specific. The reliability of test results depends on proper sample collection and testing. The staff taking the sample must label the specimen bottle and the form accurately. High quality performance of tests by laboratory staff is crucial.

Advantages and disadvantages of HIV antibody tests

HIV testing method	Advantages	Disadvantages
EIA (formerly known as ELISA)	<ul style="list-style-type: none"> ◦ less expensive than immunoblot ◦ large numbers of sera can be tested daily ◦ sensitive and specific 	<ul style="list-style-type: none"> ◦ some specialized laboratory equipment necessary ◦ skilled technical staff ◦ steady power supply ◦ a whole kit (90–100 samples) has to be used

Simple/rapid (e.g. rapid immunobinding assay)	<ul style="list-style-type: none"> ◦ simple, rapid ◦ less expensive than immunoblot ◦ no specialized equipment necessary ◦ supplied as single-use tests so individual specimens can be tested 	
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EIA

The usual type of test for HIV antibodies is the enzyme immunoassay (EIA). EIAs are probably the most efficient tests for testing large numbers of samples per day, as in large blood banks or for surveillance studies. The cost per individual EIA is about US\$ 0.75–1.75.

Simple/rapid tests

Several antibody tests can equal the performance of EIA and do not need special equipment or highly trained staff. These tests are considered rapid if they take less than 10 minutes and simple if they take longer. There are four types of assay: agglutination, comb/dipstick, flow-through membrane and lateral flow membrane. In most formats, the appearance of a clearly visible dot or line indicates a positive result. Many of the tests have an internal control sample, which validates each test run. Test kits are relatively expensive at US\$ 1–2 per test.

Tests not using plasma or serum

Tests are available that can use whole blood, dried blood spots, saliva or urine. They are much more user-friendly than those that require traditional blood sampling by venepuncture. The level of antibodies in these specimens is much lower than in serum or plasma. While useful for surveillance, a positive result needs to be confirmed for an individual diagnosis.

6.2.2 Tests to detect the virus itself

The first assays capable of detecting free circulating HIV particles were the HIV p24 antigen EIAs. Quantitative measurement of plasma HIV RNA (viral load) have now superseded these EIAs. Measurement of viral load is based on amplification of viral nucleic acids or of the probe-binding signal (e.g. branched DNA tests). Results are reported as copies of virus per ml, and the new generation tests can detect 20–50 copies per ml. Measurement of viral load is now standard in industrialized

countries for staging and monitoring response to antiretroviral therapy. However, several factors have limited their use so far in developing countries. These include the expense of the complex equipment necessary and the need for rigorous laboratory conditions, quality control and highly trained staff.

6.2.3 Objectives of HIV antibody testing in TB patients

There are three possible main objectives in performing HIV antibody tests in TB patients:

- individual patient management (HIV testing in individual TB patients);
- surveillance (anonymous testing to monitor epidemiological trends);
- research (voluntary testing for epidemiological, clinical, or virological studies).

6.2.4 Strategy for HIV antibody testing in TB patients (which tests to use and when to use them)

In general, WHO recommends different HIV testing strategies, depending on the objective of testing. The aim is to maximize accuracy and minimize cost. The table below shows the strategy appropriate for each objective of testing.

Objectives, strategies and interpretation of HIV tests

Objective	Testing strategy	Interpretation of result
Individual patient management	Test sample with EIA or simple/rapid assay	1st assay negative = patient HIV negative or test to be repeated
		1st assay positive + 2nd assay positive = patient HIV-positive
		1st assay positive and 2nd assay negative → repeat both assays
		Results remain discordant → repeat sample and testing
Surveillance (in population with HIV prevalence > 10%)	Test sample with EIA or simple/rapid assay	Assay negative = patient HIV-negative
		Assay positive = patient HIV-positive

6.2.5 Diagnosis of HIV infection in individual TB patients

The link between HIV and TB is well known to many members of the public. Patients with TB may therefore be well aware of the possibility of HIV coinfection. It is important to offer counselling and voluntary HIV testing, if available, to TB patients. Possible benefits include:

- a) patients may want the chance to know their HIV status;
- b) better diagnosis and management of other HIV-related illnesses;
- c) avoidance of drugs associated with a high risk of side-effects;
- d) increased condom use and decreased HIV transmission;
- e) possible use of chemoprophylaxis with cotrimoxazole to prevent opportunistic infections and reduce mortality;
- f) possible use of ART for HIV;
- g) the opportunity to counsel patients and relatives about HIV infection and about the prognosis;
- h) the opportunity to advise patients and relatives about measures to prevent further HIV transmission.

It is preferable to have same-day HIV testing using rapid test kits as this minimizes the number of visits to counselling and testing centres. The other important issue for clients is confidentiality.

PRACTICAL POINT

Anti-TB drug treatment is the same for HIV-positive and HIV-negative TB patients, with one exception: do not give thioacetazone to HIV-positive TB patients (increased risk of severe and sometimes fatal skin reactions).

A policy of compulsory HIV testing of TB patients (even if this were legal) would be counterproductive. This type of policy would have the following results:

- a) patients would be deterred from seeking care;
- b) there would be decreased case-finding in at-risk groups;
- c) the credibility of health services would be reduced.

6.3 HIV COUNSELLING

HIV voluntary counselling and testing (VCT) starts with counselling of individuals to enable them to make an informed choice about HIV testing. This decision is entirely the choice of the individual, who must be assured that the process will be confidential. Confidential counselling is essential before and after HIV antibody testing. Individuals give explicit informed consent to have the test. This means that they understand what the test involves and the implications of testing. The counsellor

provides support. Counselling is a dialogue between the individual and the counsellor.

Counsellors

With suitable training, anyone who works with patients and families can be a counsellor. Counsellors may be members of the community or health workers. For sustainability of VCT services, counsellors need support and supervision. Many health workers have had counselling training. In the course of their duties they have the opportunity to counsel patients for HIV testing. Doctors and other clinicians are often in a good position to counsel patients for HIV testing. This is because clinicians have already established a relationship with the patient, who usually trusts the clinician.

Pretest counselling

The aim is to enable people to make an informed decision to have the test or not. People need to know what the test involves and what are the implications of the result. Together the counsellor and the person considering being tested assess the person's: a) likelihood of having acquired HIV infection, b) knowledge about HIV, and c) ability to cope with a positive result.

PRACTICAL POINT

In high HIV-prevalence regions, anyone with TB is in a high-risk group for HIV.

- | | |
|---|---|
| a) Assessment of risk of having acquired HIV infection | <ul style="list-style-type: none"> ◦ multiple sex partners ◦ sex with commercial sex workers ◦ for men, sex with other men ◦ nonsterile skin piercing, e.g. scarification, tattooing ◦ previous blood transfusion ◦ intravenous drug use ◦ sexual partner/spouse of person at risk |
| b) Assessment of knowledge about HIV | <ul style="list-style-type: none"> ◦ what does the test involve and mean? ◦ how does HIV transmission occur? ◦ what is high-risk behaviour? |
| c) Assessment of ability to cope with result | <ul style="list-style-type: none"> ◦ person's expected reaction to result ◦ who will provide emotional support? ◦ impact of a positive result on <ul style="list-style-type: none"> - relationships - social issues, e.g. employment - future health |

Post-test counselling

The content of post-test counselling depends on the HIV test result. The aims are to discuss the result, share information, provide support, and encourage future safe sexual behaviour. Always ensure confidentiality. Break the news openly and sympathetically. When someone has a positive HIV test result, common reactions at different times may include shock, anger, guilt, grief and depression. People will need continuing support.

Issues for discussion when the HIV test result is negative

- If the person has recently indulged in high-risk behaviours, then he or she could still be incubating HIV (i.e. the test could be in the "window period").
- Avoidance of unsafe sexual behaviour.
- Promotion of healthy behaviour.

Issues for discussion when the HIV test result is positive

- General health (good diet, balance of rest and exercise, avoiding infections, when to seek advice about symptoms of other HIV-related illnesses).
- Avoidance of pregnancy.
- Awareness of possible anti-TB drug side-effects.
- A positive result is an entry point to medical care of HIV-related diseases, to chemoprophylaxis for opportunistic infections and possibly to ART.
- Safe sexual behaviour.
- Avoidance of blood or organ donation.
- The person's reaction to the test result.
- Emotional and psychological support for the person.
- How to tell friends, family and sexual partners.
- Counselling of partner(s) if possible.
- Referral to local community services and support groups, if available.
- Social implications, e.g. employment, life assurance.

UNAIDS *policy on HIV testing and counselling*. Geneva, Joint UN Programme on HIV/AIDS, 1997.

UNAIDS *Technical Update. HIV testing methods*. Joint UN Programme on HIV/AIDS, Geneva, 1997, UNAIDS Best Practice Collection.

Joint UN Programme on HIV/AIDS, World Health Organization. *Operational characteristics of commercially available assays to determine antibodies to HIV-1 and/or HIV-2 in human sera. Report 11*. Geneva, 1999. WHO/BTS/99.1; UNAIDS/99.5.

UNAIDS *Technical Update. Voluntary counselling and testing (VCT)*. Geneva, 2000, Joint UN Programme on HIV/AIDS, Best Practice Collection.

Volberding PA. HIV quantification: clinical applications. *Lancet*, 1996, 347: 71-73.

World Health Organization. Revised recommendations for the selection and use of HIV antibody tests. *Weekly epidemiological record*, 1997, 72: 81-83.

World Health Organization. The importance of simple and rapid tests in HIV diagnostics: WHO recommendations. *Weekly epidemiological record*, 1998, 73: 321-328.

World Health Organization. *Increasing access to knowledge of HIV status: conclusions of a WHO consultation*, 3-4 December 2001, WHO/HIV/2002.09.

World Health Organization. *Testing and counselling*. Geneva, 2002 <http://www.who.int/hiv/topics/vct/testing> (accessed 8 May 2003).

7.1 CLINICAL RECOGNITION OF HIV INFECTION IN CHILDREN WITH TB

HIV infection in children may show in many ways. The clinical signs are often not specific for HIV infection. For example, weight loss, fever and cough are common in TB, with or without HIV infection. The clinical definition of HIV infection is therefore difficult.

PRACTICAL POINT

Parents provide important clues to possible HIV infection in their children. Ask the parents about their health. Sometimes parents may reveal their own HIV status.

WHO has developed a clinical staging system for HIV infection and HIV-related disease (see Chapter 1). The main uses are for prognosis and for deciding when to start antiretroviral therapy. The features of paediatric HIV/AIDS are not very specific in developing countries where childhood malnutrition is common and TB is endemic. Severe malnutrition or wasting in a school-aged child or in a child from a well-nourished family is unlikely to be due simply to poor intake. This should raise the suspicion of underlying disease, e.g. HIV or TB or both. The table below lists clinical signs suggestive of HIV infection. Many are more specific than those in the WHO clinical staging system but are less sensitive. In other words, the presence of a particular sign strongly suggests HIV infection, but many children have HIV infection without that sign. The interpretation of clinical signs also depends on local patterns of disease. For example, splenomegaly is commonly caused by malaria in sub-Saharan Africa, where its specificity as a sign of HIV-related disease is therefore low.

Clinical signs suggestive of HIV infection in children

Common	failure to thrive in a breastfed infant before 6 months of age
	recurrent bacterial infections
	generalized symmetrical lymph node enlargement
	extensive oropharyngeal candidiasis
	suppurative otitis media in a breastfed infant
	generalized rash e.g. itchy papular rash, extensive molluscum contagiosum

	extensive fungal skin, nail and scalp infections
	bilateral non-tender parotid gland enlargement
	finger clubbing
	enlarged non-tender liver with no apparent cause
	splenomegaly (in non-malarious areas)
	persistent severe anaemia
Less common	recurrent abscesses or deep tissue necrosis
	recurrent herpes simplex
	KS lesions
	shingles in more than one dermatome
	developmental regression
	acquired rectovaginal fistula

Many of these signs are strongly suggestive of HIV. However, no particular sign is diagnostic and confirmation is necessary by HIV testing.

7.2 HIV TESTING

The usual HIV test is one that detects antibodies to HIV in the blood. Rarely, a single HIV test for an individual person may not be reliable. The usual recommendation in diagnosing HIV infection is therefore to perform two tests. Both tests should be positive for a diagnosis of HIV infection.

A positive HIV antibody test is not a reliable indicator of HIV infection in infants. During the pregnancy of a woman with HIV infection, antibodies to HIV cross the placenta. Therefore almost all children born to HIV-positive mothers have HIV antibodies in their blood at birth. However, only about one-third of children born to HIV-infected mothers are infected. Initially, therefore, HIV antibody testing cannot distinguish uninfected from infected children. In uninfected children, these maternal antibodies usually become undetectable by 9 months of age, but occasionally they remain detectable until 15 months. Most infected children make their own antibodies, so the HIV antibody test will still be positive after 15 months.

PRACTICAL POINT

In children under 15 months of age, the diagnosis of HIV infection rests on clinical features and a positive HIV test in the mother.

A child with suspected HIV generally means a family with suspected HIV. Counselling therefore has to take into consideration the mother and, if possible, the father. Until recently there have been few specific treatment options to offer the child and family when a child tests HIV-positive. This has made raising the issue of testing difficult. However, the increasing availability of antiretroviral treatment is likely to encourage HIV testing. Also, parents often want to know the cause of their child's illness. See Chapter 6 for the issues for discussion with adults with suspected HIV.

Pretest counselling

It is important to counsel the mother before testing her child for HIV. Her consent is necessary before testing her blood (if the child is under 18 months) or the child's blood (if the child is over 18 months) for HIV. If her child tests HIV-positive, then it is extremely likely that she is the source of infection and is HIV-positive.

Consider the implications for the mother when she hears that her child may have HIV infection:

- her child may have an incurable and fatal disease;
- she herself may have HIV;
- her husband may have HIV;
- any future children may have HIV.

Her decision to have a test or not is difficult. She will need time and support while she considers the advantages and disadvantages of a test. If she knows she is HIV-positive, the main advantage is that she can plan for the future. On the other hand, she may be fearful that her husband will beat her or leave her if she tells him that she is HIV-positive. She may also be concerned that if her child tests positive, the health workers will no longer provide good care for her child.

PRACTICAL POINT

The mother may like to bring her husband for joint pretest counselling. It is usually easier for a woman to tell her husband she may be HIV-positive than to tell him afterwards that she is HIV-positive.

Post-test counselling

Chapter 6 lists the issues for discussion relevant to anyone who tests HIV-positive. There are other issues specific to a mother who tests HIV-

positive. These include the poor outlook for the child and the risk of future babies being HIV-infected. About one-third of children born to HIV-positive women are also HIV-infected (in the absence of interventions to prevent mother-to-child transmission).

When counselling women who are breastfeeding or who have delivered recently, it is important to discuss breastfeeding. There is risk of HIV transmission by breastfeeding. However, in many low-income countries, breastfeeding is still a safer alternative to bottle-feeding. For example, a child whose mother is HIV-positive and who lives in an environment where there is no clean water is probably at higher risk of dying from diarrhoea if bottle-fed than from AIDS if breastfed.

It is also important to consider PCP prophylaxis with cotrimoxazole for infants born to an HIV-infected mother. PCP is a very common cause of death in HIV-infected infants especially before 6 months of age. The recommended cotrimoxazole dosage for PCP prophylaxis is 150 mg TMP/750 mg SMX per m²/day given 3 times per week. Thus, appropriate dosage for infants 2–6 months (usually 3–6 kg) would be 40 mg TMP/200 mg SMX once a day three times per week. If only cotrimoxazole tablets are available, then give half a crushed tablet (80 mg TMP/400 mg SMX) on Monday, Wednesday and Friday.

Lepage P, Spira R, Kalibala S, et al. Care of human immunodeficiency virus-infected children in developing countries. *The pediatric infectious disease journal*, 1998, 17: 581–586.

Marum LH, Tindyebwa D, Gibb D. Care of children with HIV infection and AIDS in Africa. *AIDS*, 1997, 11 (Supplement B): S125-S134.

Joint UN Programme on HIV/AIDS. *Provisional WHO/UNAIDS Secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa*. Geneva, 2000. (Available at <http://www.unaids.org>).

Temmerman M, Ndirya-Achola J, Ambani J, Piot P. The right not to know HIV-test results. *Lancet*, 1995, 345: 969–970.

Joint United Nations Programme on HIV/AIDS, *AIDS epidemic update: December 2002*. Geneva.

World Health Organization, *Counselling for HIV/AIDS: a key to caring*. Geneva, 1995.

World Health Organization, *Scaling up antiretroviral therapy in resource-limited settings. Guidelines for a public health approach*. Geneva, 2002 (includes a clinical staging system for HIV and HIV-related disease).

8.1 STANDARDIZED CASE DEFINITIONS

8.1.1 Introduction

The diagnosis of TB means that a patient has symptomatic disease due to lesions caused by *M. tuberculosis*. What type of TB? It is important to answer this question before starting treatment. A case definition tells us the type of TB. We define TB cases in a standardized way. This means that when we talk about a certain type of TB, we are all talking about the same thing.

A TB suspect is any person who presents with symptoms and signs suggestive of TB, in particular cough of long duration.

A case of TB is a patient in whom TB has been bacteriologically confirmed, or who has been diagnosed by a clinician.

Note: any person given treatment for TB should be recorded.

A definite TB case is a patient who is culture-positive for the *M. tuberculosis* complex. (In countries where culture is not routinely available, a patient with two sputum smears positive for AFB is also considered a “definite case”.)

8.1.2 Questions and answers about case definitions

Why make case definitions? There are 2 purposes:

- to determine treatment;
- for recording and reporting (see Chapter 2).

Why do case definitions determine treatment? There are 3 reasons:

- to identify priority cases;
- to make the most cost-effective use of resources (by targeting resources on priority cases);
- to minimize side-effects for patients (by using the most intensive regimens only for certain cases).

What determines a case definition? There are 4 determinants:

- site of TB;

- b) result of sputum smear;
- c) previous TB treatment;
- d) severity of TB.

PRACTICAL POINT

Always ask "new" TB patients if they have ever had TB treatment before.

The table below shows the determinants of the case definition and their importance.

Determinant of case definition	Importance
site of TB	recording and reporting
result of sputum smear for AFBs	<ul style="list-style-type: none"> ◦ priority is to identify sputum smear-positive cases (since these are the infectious cases) ◦ in a good NTP, at least 50% of total cases will be smear-positive PTB ◦ recording and reporting (monitoring of bacteriological cure is readily available only in this group)
previous TB treatment	previously treated patients who are still sputum smear-positive have a high risk of drug-resistant TB and so need a different and more powerful regimen
severity of TB	most authorities recommend a less intensive regimen for patients with non-cavitary, smear-negative PTB (who are known to be HIV-negative)

8.1.3 Case definitions by site and result of sputum smear

Pulmonary TB – sputum smear-positive (PTB+)

Two or more initial sputum smear examinations positive for AFB

or

1 sputum smear positive for AFB, and CXR abnormalities consistent with active pulmonary TB as determined by a clinician

or

1 sputum smear positive for AFB, which is also culture positive for *M. tuberculosis*

Pulmonary TB – sputum smear-negative (PTB-)

A case of pulmonary TB that does not meet the above definition for smear-positive TB.

In keeping with good clinical and public health practices, diagnostic criteria should include:

at least three sputum smears negative for AFB

and

no response to a course of broad-spectrum antibiotics

and

CXR abnormalities consistent with active TB

and

decision by a clinician to treat with a full course of anti-TB treatment

Extrapulmonary TB

TB of organs other than the lungs: e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, meninges. Diagnosis is based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extrapulmonary TB, followed by a decision by a clinician to treat with a full course of anti-TB treatment. A patient diagnosed with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

PRACTICAL POINT

**The following are forms of extrapulmonary TB:
pleural effusion (the pleurae are outside the lungs);
miliary (TB is widespread throughout the body and not limited to the lungs).**

8.1.4 Category of TB patient for registration on diagnosis**New**

A patient who has definitely never taken anti-TB drugs or who has taken anti-TB drugs for less than one month.

Relapse

A TB patient who:

a) previously received treatment and was declared cured or treatment completed;

and

b) has once again developed bacteriologically positive (by smear or culture) TB.

Treatment after failure

A patient who is started on a re-treatment regimen after having failed previous treatment.

Treatment after default

A TB patient who returns to treatment, bacteriologically positive, following interruption of treatment for 2 months or more.

Transfer in

A TB patient who has been transferred from another TB register to continue treatment.

Other

All TB patients who do not fit the above definitions. This group includes chronic cases (TB patients who are sputum smear-positive at the end of a re-treatment regimen).

8.2 STANDARDIZED DIAGNOSTIC CATEGORIES

Based on case definition, all TB patients (adults and children) fall into one of four diagnostic categories for treatment. Patients are categorized in order to match each diagnostic category with an effective treatment regimen. The table below shows the patients belonging to each category.

TB diagnostic category	Patients
Category I	<ul style="list-style-type: none"> ◦ new sputum smear-positive PTB ◦ new sputum smear-negative PTB with extensive parenchymal involvement ◦ new cases of extrapulmonary TB (more severe forms) ◦ severely ill TB patients with concomitant HIV infection
Category II	<ul style="list-style-type: none"> ◦ previously treated sputum smear-positive PTB: relapse, treatment after default, treatment after failure
Category III	<ul style="list-style-type: none"> ◦ new sputum smear-negative PTB with limited parenchymal involvement and known HIV-negative ◦ extrapulmonary TB (less severe forms) and known HIV-negative
Category IV	<ul style="list-style-type: none"> ◦ chronic and MDR-TB cases

The table below shows the severe and less severe forms of extrapulmonary TB.

Severe extrapulmonary TB	Less severe extrapulmonary TB
meningitis	lymph node
miliary	pleural effusion (unilateral)
pericarditis	bone (excluding spine)
peritonitis	peripheral joint
bilateral or extensive pleural effusion	adrenal gland
spinal	
intestinal	
genitourinary	

Children

Children often fall into Category III. PTB in children is almost always "smear-negative" (actually a smear is often not done, since children rarely cough up sputum). Young people infected during adolescence may develop primary TB. This usually presents as pleural effusion or small parenchymal lesions in the lungs. In one series of adolescents with pleural effusion, without treatment about 25% went on to develop PTB.

SUGGESTIONS FOR FURTHER READING

World Health Organization. *Treatment of tuberculosis. Guidelines for national programmes*. Third edition. Geneva, 2003 (WHO/CDS/TB/2003.313).

International Union Against Tuberculosis and Lung Disease. *Management of tuberculosis. A guide for low-income countries*. Fifth edition. Paris, 2000.

World Health Organization. *Tuberculosis handbook*. Geneva, 1998 (WHO/TB/98.253).

World Health Organization. International Union Against Tuberculosis and Lung Disease, Royal Netherlands Tuberculosis Association. Revised international definitions in tuberculosis control. *International journal of tuberculosis and lung disease*, 2001, 5 (3): 213–215.

9.1 INTRODUCTION

Aims of anti-TB drug treatment

1. To cure the patient of TB.
2. To prevent death from active TB or its late effects.
3. To prevent TB relapse or recurrent disease.
4. To prevent the development of drug resistance.
5. To decrease TB transmission to others.

PRACTICAL POINT

Properly applied anti-TB drug treatment will achieve these aims.

Effective anti-TB drug treatment = properly applied short-course chemotherapy

We have known for over 100 years that *M. tuberculosis* causes TB. We have had effective anti-TB drugs for nearly 50 years. Yet the world's TB problem is now bigger than ever. Why? The problem is not the lack of an effective treatment. Properly applied short-course chemotherapy (SCC) fulfils the above aims of anti-TB drug treatment. The problem is organizational: how to apply SCC properly? The answer is a well managed TB control programme. Chapter 2 describes the organizational framework of an effective national TB programme (NTP).

Standardized TB treatment regimens

There are many different possible anti-TB treatment regimens. WHO and the IUATLD recommend standardized TB treatment regimens. The NTP in your country will recommend which regimens to use. When properly applied, these standardized regimens fulfil the above aims of anti-TB drug treatment. The regimens are affordable. The World Bank recognises SCC as one of the most cost-effective of all health interventions. The Global Drug Facility (GDF) is a mechanism to ensure uninterrupted access to quality anti-TB drugs at low cost (<http://stoptb.org/GDF>).

The first-line anti-TB drugs

The table below shows the first-line anti-TB drugs and their mode of action, potency, and recommended dose. The doses are the same for adults and children.

First-line anti-TB drugs (abbreviation)	Mode of action	Potency	Recommended dose (mg/kg of body weight)	
			daily	intermittent (3 times a week)
isoniazid (H)	bactericidal	high	5	10
rifampicin (R)	bactericidal	high	10	10
pyrazinamide (Z)	bactericidal	low	25	35
streptomycin (S)	bactericidal	low	15	15
ethambutol (E)	bacteriostatic	low	15	(30)
thioacetazone (T)	bacteriostatic	low	2.5	not applicable

The available formulations and combinations of these drugs vary from country to country. Follow the recommendations in your NTP manual.

Intermittent use

Thioacetazone is the only essential anti-TB drug **not** effective when given intermittently. In any case, patients known or suspected to be HIV-positive should not receive thioacetazone. The efficacy of intermittent ethambutol is not proven.

Thioacetazone

Some countries still use thioacetazone (usually in combination with isoniazid in the continuation phase). WHO discourages the use of thioacetazone because of the risk of severe toxicity, especially in HIV-infected individuals. Ethambutol should replace thioacetazone, especially in areas where HIV is common. It is becoming easier to mobilize the resources to replace it with ethambutol. The price of rifampicin is falling. Also, the GDF is now making low-cost, quality-assured anti-TB drugs available to more countries.

Where thioacetazone is still in use, it is essential to warn patients about the risk of severe skin reactions. Advise the patient to stop thioacetazone at once and report to a health unit if itching or a skin reaction occurs.

9.2 MODES OF ACTION OF ANTI-TB DRUGS

A population of TB bacilli in a TB patient consists of the following groups:

- metabolically active, continuously growing bacilli inside cavities;
- bacilli inside cells, e.g. macrophages;

- c) semidormant bacilli (persisters), which undergo occasional spurts of metabolic activity;
- d) dormant bacilli, which fade away and die on their own.

Different anti-TB drugs act against different groups of bacilli.

PRACTICAL POINT

Anti-TB drug treatment takes a long time because it is difficult to kill the semidormant TB bacilli.

Bactericidal drugs

Isoniazid kills 90% of the total population of bacilli during the first few days of treatment. It is most effective against the metabolically active, continuously growing bacilli.

Rifampicin can kill the semidormant bacilli that isoniazid cannot.

Pyrazinamide kills bacilli in an acid environment inside cells, e.g. macrophages.

Sterilizing action

This means killing all the bacilli. The persisters are hardest to kill. The aim of killing all the bacilli is to prevent relapse. Rifampicin is the most effective sterilizing drug. Its effectiveness makes **short-course** chemotherapy possible. Pyrazinamide is also a good sterilizing drug, since it kills the bacilli protected inside cells.

Preventing drug resistance

A population of TB bacilli never previously exposed to anti-TB drugs will include a few naturally occurring drug-resistant mutant bacilli. Faced with anti-TB drugs, these drug-resistant mutant bacilli will grow and replace the drug-sensitive bacilli under the following circumstances:

- a) inadequate anti-TB drug combinations;
- b) inadequate application of anti-TB drug treatment.

Isoniazid and rifampicin are most effective in preventing resistance to other drugs. Streptomycin and ethambutol are slightly less effective.

9.3 TB TREATMENT REGIMENS

Treatment regimens have an initial (intensive) phase and a continuation phase. The initial phase is designed for the rapid killing of actively

growing bacilli and the killing of semidormant bacilli. This means a shorter duration of infectiousness. The continuation phase eliminates bacilli that are still multiplying and reduces failures and relapses. The principles of treatment are the same in all TB patients (adults and children).

9.3.1 New cases

Initial phase (2 months)

During the initial phase, there is rapid killing of TB bacilli. Infectious patients become non-infectious within about 2 weeks. Patients improve and symptoms lessen. The vast majority of patients with sputum smear-positive PTB become sputum smear-negative within 2 months. Directly observed treatment (DOT) is essential in the initial phase to ensure that the patient takes every single dose. This protects rifampicin against the development of drug resistance. The risk of drug resistance is higher during the early stages of anti-TB drug treatment when there are more TB bacilli.

Continuation phase (4–6 months)

At the time of starting the continuation phase there are low numbers of bacilli and hence less chance of selecting drug-resistant mutants. Thus, fewer drugs are necessary, but they are needed for a longer time in order to eliminate the remaining TB bacilli. Killing the persisters prevents relapse after completion of treatment. DOT is the ideal when the patient receives rifampicin in the continuation phase. If local conditions do not allow DOT, the next best option is as close supervision as possible, for example weekly supervision.

The patient usually receives monthly drug supplies for self-administered treatment during a continuation phase that does not include rifampicin.

9.3.2 Re-treatment cases

The initial phase lasts 3 months, with DOT. The continuation phase lasts 5 months, with close supervision.

9.3.3 Standard code for TB treatment regimens

There is a standard code for TB treatment regimens. Each anti-TB drug has an abbreviation (shown in the table on page 112). A regimen consists of 2 phases. The number before a phase is the duration of that phase in months. A number in subscript (e.g. ₃) after a letter is the

number of doses of that drug per week. If there is no number in subscript after a letter, then treatment with that drug is daily. An alternative drug (or drugs) appears as a letter (or letters) in brackets.

Examples

2SHRZ/6HE. This is a common regimen.

The **initial phase** is **2SHRZ**. The duration of the phase is 2 months. Drug treatment is daily (no subscript number after the letters), with streptomycin (S), isoniazid (H), rifampicin (R) and pyrazinamide (Z).

The **continuation phase** is **6HE**. The duration of the phase is 6 months. Drug treatment is daily, with isoniazid (H) and ethambutol (E).

2SHRZ/4H₃R₃. In some countries, resources are available to provide rifampicin in the continuation phase as well as in the initial phase.

The **initial phase** is **2SHRZ**, the same as in the first example.

The **continuation phase** is **4H₃R₃**. The duration is 4 months, with isoniazid and rifampicin three times per week (subscript number 3 after the letters).

9.3.4 Recommended treatment regimens

There are several possible regimens. The regimen recommended depends on the patients diagnostic category (see Chapter 8). The table below shows possible alternative regimens for each diagnostic category. Follow the regimens recommended by the NTP in your country. Look in your NTP manual.

Recommended treatment regimens for each diagnostic category
(World Health Organization. *Treatment of tuberculosis. Guidelines for national programmes. Third edition.* Geneva, 2003) (WHO/CDS/TB/2003.313)

TB diagnostic category	TB patients	TB treatment regimens	
		Initial phase (daily or 3 times weekly) ^a	Continuation phase (daily or 3 times weekly) ^a
I	New smear-positive patients. New smear-negative pulmonary TB with extensive parenchymal involvement. Severe concomitant HIV disease or severe forms of extrapulmonary TB.	2HRZE^b	4HR (or 6HE daily^c)
II	Previously treated sputum smear-positive pulmonary TB: - relapse - treatment after default - treatment failure ^d .	2 HRZES/1HRZE	5HRE
III	New smear-negative pulmonary TB (other than in Category I). Less severe forms of extrapulmonary TB.	2HRZE^e	4HR (or 6HE daily^c)
IV	Chronic and MDR-TB cases (still sputum-positive after supervised re-treatment) ^f .	Specially designed individualized or standardized regimens are suggested for this category (refer to the current WHO TB treatment guidelines, Chapter 5)	

^a Direct observation of drug intake is required during the initial phase of treatment in smear-positive cases, and always in treatment including rifampicin.

^b Streptomycin may be used instead of ethambutol. In TB meningitis, ethambutol should be replaced by streptomycin.

^c This regimen may be associated with a higher rate of treatment failure and relapse compared with the 6-month regimen with rifampicin in the continuation phase (refer to the current WHO TB treatment guidelines, section 4.8)

^d Whenever possible, drug sensitivity testing is recommended before prescribing Category II treatment in failure cases. It is recommended that patients with proven MDR-TB use Category IV regimens (refer to the current WHO TB treatment guidelines, Chapter 5).

^e Ethambutol may be omitted during the initial phase of treatment for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli, and young children with primary TB.

^f Contacts of patients with culture-proven MDR-TB should be considered for early culture and sensitivity testing.

Some authorities recommend a 7 month continuation phase with daily isoniazid and rifampicin (7HR) for Category I patients with particular forms of TB. These are TB meningitis, miliary TB and spinal TB with neurological signs.

Fixed-dose combination drugs (FDC) should be recommended wherever they are available, especially for regimens containing rifampicin in the continuation phase or when direct observation is not fully guaranteed.

9.3.5 Use of streptomycin in areas of high HIV prevalence

- In populations with high TB/HIV prevalence, overcrowding is common in TB wards. The staff workload is high, motivation may be poor and resources may be insufficient. This may result in inadequate sterilization of needles and syringes used for streptomycin injections. Without rigorous sterilization, there is a risk of transmission of HIV and other bloodborne pathogens between patients.
- Streptomycin injections are very painful in wasted HIV-infected TB patients.
- Many NTPs now recommend the use of ethambutol in place of streptomycin.

9.3.6 Use of TB drugs in children

The treatment regimens and drug dosages in mg/kg of body weight are the same for children as for adults. Children usually tolerate TB drugs very well and serious side-effects are unusual. Do not give thioacetazone to HIV-infected children. Ethambutol is safe even in children too young to report early visual side-effects provided that the recommended dose is not exceeded. Since TB drugs are often not available in syrup form, give children portions of tablets according to weight.

Health service staff must identify a guardian responsible for the child's treatment. This is usually but not always the child's mother. If a child has HIV infection, often the parent is also sick. If the parent dies before the child has completed treatment, this commonly causes some social dislocation. For example, the family may send a child from the town to stay with other family members in a rural village. This may lead to poor compliance and an adverse treatment outcome. Health service staff need to be aware of a child's family and social circumstances and arrange transfer of TB treatment as necessary.

9.4 TB TREATMENT REGIMENS: QUESTIONS AND ANSWERS

Why use 4 drugs in the initial phase?

- * There is a high degree of initial resistance in some populations.
- * Use of a 3-drug regimen runs the risk of selecting drug-resistant mutants. This may happen especially in patients with high bacillary loads, e.g. cavitary pulmonary TB, HIV-positive TB patients.
- * A 4-drug regimen decreases the risks of drug resistance, treatment failure, and relapse.

Why use pyrazinamide only in the initial phase?

- * Pyrazinamide has its maximum sterilizing effect within the first 2 months.
- * There is less benefit from longer use.

Is a 4-month continuation phase possible?

- * A 4-month continuation phase is possible with rifampicin throughout (e.g. 2SHRZ/4HR). This is because isoniazid and rifampicin are both potent bactericidal drugs. In the usual 6 month continuation phase (6HE or 6HT), the only potent bactericidal drug is isoniazid.

When should regimens containing rifampicin throughout be used?

- * Although the high cost of rifampicin has prevented some countries from using these regimens, falling costs make them increasingly affordable.
- * Since rifampicin administration should be under direct observation, TB programmes need to mobilize the resources to ensure this.

Why is it so important to prevent rifampicin resistance?

- * Rifampicin is the most effective anti-TB drug. It is unlikely that a new anti-TB drug will become widely available in the near future. If rifampicin resistance becomes widespread, TB will be effectively untreatable.

How do we prevent rifampicin resistance?

- * Acquired drug resistance develops for several reasons. These include poorly performing TB control programmes, lack of supervision of anti-TB treatment, poor prescribing by clinicians, poor absorption in HIV-positive patients, and the use of rifampicin alone. The best way to prevent rifampicin resistance is to strengthen NTPs and ensure DOT when and where possible. It is important to use methods of drug

administration that avoid the danger of the use of rifampicin alone. These include the use whenever possible of FDC tablets and of anti-TB drugs supplied in blister packs.

What are the advantages of FDC tablets?

- * Dosage recommendations are more straightforward. Adjustment of dosage according to patient weight is easier. Thus prescription errors are likely to be less frequent.
- * There is a smaller number of tablets to ingest, which should encourage adherence to treatment.
- * Patients cannot be selective about which drugs they ingest. Thus monotherapy is impossible and risk of drug resistance is reduced.

When does multidrug-resistant (MDR) TB arise?

- * MDR-TB arises from failure to deliver anti-TB drug treatment properly.

What is the treatment of MDR-TB?

- * MDR-TB treatment consists of second-line drugs, e.g. ethionamide, cycloserine, kanamycin, capreomycin and quinolones. These are unavailable in many countries with high TB prevalence and often prohibitively expensive.

What should we do when faced with MDR-TB?

- * The cause of the problem is usually a poorly performing NTP. The answer is to spend time, effort and resources to improve the NTP. In some countries, one or two specialist centres may have the expertise and second-line drugs available to treat patients with MDR-TB.
- * NTPs are establishing “DOTS-Plus” pilot projects in areas where MDR-TB is common. A global DOTS-Plus Working Group coordinates these pilot projects. DOTS-Plus aims to assess the feasibility and cost-effectiveness of the use of second-line drugs within the DOTS strategy. In negotiation with the Working Group, the pharmaceutical industry has agreed to provide second-line drugs at preferential prices to DOTS-Plus pilot projects. Part of the Working Group is the Green Light Committee. This assesses applications from TB programmes for inclusion among the projects supported by the Working Group. You should refer to the guidelines for establishing DOTS-Plus pilot projects (see “Suggestions for further reading”).

Pregnancy

- * Streptomycin during pregnancy can cause permanent deafness in the baby.
- * **Do not give streptomycin in pregnancy.** Use ethambutol instead.
- * Isoniazid, rifampicin, pyrazinamide and ethambutol are safe to use.
- * Second-line drugs such as fluoroquinolones, ethionamide and prothionamide are teratogenic, and should not be used.

Breastfeeding women

- * All anti-TB drugs are compatible with breastfeeding.

Renal failure

- * Rifampicin, isoniazid and pyrazinamide are safe and can be given in normal dosages. Patients with severe renal failure should receive pyridoxine with isoniazid to prevent peripheral neuropathy.
- * Ethionamide and prothionamide are also safe.
- * The excretion of streptomycin is renal. The excretion of ethambutol and thioacetazone is partly renal.
- * Avoid streptomycin and ethambutol if there are alternatives. Otherwise give in reduced doses at less frequent intervals.
- * **Do not give thioacetazone.** The margin between the therapeutic and toxic dose is too narrow.
- * The safest regimen to give to patients in renal failure is 2HRZ/4HR.

Liver disease

- * Most anti-TB drugs can cause liver damage and therefore care is needed.
- * **Do not give pyrazinamide because this is the most hepatotoxic anti-TB drug.**
- * Isoniazid and rifampicin plus one or two non-hepatotoxic drugs, such as streptomycin and ethambutol, can be used for a total treatment duration of eight months.
- * If the patient has severe liver damage, an alternative regimen is streptomycin plus isoniazid plus ethambutol in the initial phase followed by isoniazid and ethambutol in the continuation phase with a total duration of 12 months.
- * Recommended regimens are 2SRHE/6HE or 2SHE/10HE.

What is adjuvant steroid treatment?

Adjuvant steroid treatment is steroid treatment given in addition to anti-TB drug treatment. Studies in the pre-HIV era confirmed the benefit of steroids for TB meningitis and pleural and pericardial TB. Steroids are also of benefit in HIV-positive patients with pericardial TB.

What are the indications for treatment with steroids?

- * TB meningitis (decreased consciousness, neurological defects, or spinal block).
- * TB pericarditis (with effusion or constriction).
- * TB pleural effusion (when large with severe symptoms).
- * Hypoadrenalism (TB of adrenal glands).
- * TB laryngitis (with life-threatening airway obstruction).
- * Severe hypersensitivity reactions to anti-TB drugs.
- * Renal tract TB (to prevent ureteric scarring).
- * Massive lymph node enlargement with pressure effects.

What are the recommended treatment doses of prednisolone?

Rifampicin is a potent inducer of hepatic enzymes that metabolize steroids. The effective dose of prednisolone is therefore half the prescribed treatment dose given to the patient. The table below shows suggested treatment doses of prednisolone.

Indication	Prednisolone treatment (dose for children in brackets)
TB meningitis	60 mg (1–2 mg/kg) daily for weeks 1–4, then decrease over several weeks
TB pericarditis	60 mg (1–2 mg/kg) daily for weeks 1–4 30 mg (0.5–1 mg/kg) daily for weeks 5–8, then decrease over several weeks
TB pleural effusion	30 mg (0.5–1 mg/kg) daily for 1–2 weeks

Is steroid treatment safe in TB/HIV patients?

Steroids are immunosuppressants. Steroids may further depress immunity and increase risk of opportunistic infections in HIV-positive patients. However, on balance, TB/HIV patients are still likely to benefit from the use of steroids for the above indications.

PRACTICAL POINT

Recording treatment results in sputum smear-positive PTB patients is vital to monitor patient cure and NTP effectiveness (see Chapter 2).

9.7 MONITORING OF TB PATIENTS DURING TREATMENT

It is important to monitor all TB patients, adults and children, during treatment. This is in order to assess the progress of individual TB patients and to evaluate NTP performance.

Bacteriological monitoring is readily available only for patients with sputum smear-positive PTB. These are usually adults and sometimes older children. Routine monitoring of treatment response by CXR is unnecessary and wasteful of resources.

Clinical monitoring is the usual guide to treatment response for other TB patients. These include adults with sputum smear-negative PTB and extrapulmonary TB and most children.

9.7.1 Monitoring of patients with sputum smear-positive PTB

When to monitor	8-month treatment regimen	6-month treatment regimen
At time of diagnosis	sputum smear	sputum smear
At end of initial phase	sputum smear	sputum smear
In continuation phase	sputum smear (month 5)	sputum smear (month 5)
During last month of treatment	sputum smear (month 8)	sputum smear (month 6)

Sputum smear at end of initial phase

The vast majority of patients have a negative sputum smear at the end of the initial phase. If the sputum smear is still positive at the end of the initial phase, continue initial phase treatment with the same 4 drugs for 4 more weeks. If you check the sputum smear again at this point, it is unlikely still to be positive. Go on to the continuation phase (even if the sputum smear after the extra 4 weeks of initial phase treatment is still positive).

Sputum smear in continuation phase

In 8-month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. In 6-month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. A common cause of treatment failure is the failure of the programme to ensure patient adherence to treatment. The patient's treatment category changes to Category 2 and the re-treatment regimen starts.

Sputum smear on completion of treatment

Negative sputum smears in the last month of treatment and on at least one previous occasion mean bacteriological cure.

9.7.2 Recording treatment outcome**Sputum smear-positive PTB patients**

At the end of the treatment course in each individual patient, the district TB officer (DTO) should record the treatment outcome as follows:

Cure	patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion
Treatment completed	patient who has completed treatment but does not meet the criteria to be classified as a cure or a failure
Treatment failure	patient who is sputum smear-positive at 5 months or later during treatment
Died	patient who dies for any reason during the course of treatment
Defaulted (treatment interrupted)	patient whose treatment was interrupted for 2 consecutive months or more
Transferred out	patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known

- Treatment success** is the sum of patients cured and those who have completed treatment.
- In countries where culture is the current practice, patients can be classified as cure or failure on the basis of culture results.

Sputum smear-negative PTB and extrapulmonary TB patients

Four of the above standard outcome indicators are applicable to adults and children with smear-negative PTB or extrapulmonary TB. These

indicators are treatment completion, death, default and transfer out, which the DTO should record in the district TB register.

Record as a treatment failure a patient who was initially smear-negative before starting treatment and became smear-positive after completing the initial phase of treatment.

9.7.3 Cohort analysis: questions and answers

What is cohort analysis?

A cohort is a group of patients diagnosed and registered for treatment during a specific time period (usually one quarter of the year). For example, all the sputum smear-positive PTB patients registered from 1 January to 31 March in any year form the cohort for that quarter-year. Cohort analysis refers to the statistical breakdown of the cohort according to certain indicators. These indicators are the standardized case definitions and treatment categories (see Chapter 8) and the treatment outcomes. New and previously treated patients form separate cohorts.

Who performs cohort analysis and how often?

Cohort analysis is a continuous process. The DTO performs cohort analysis on TB patients registered in the district every quarter-year and at the end of every year. The regional TB officer performs cohort analysis on all TB patients registered in the region. The NTP central unit performs cohort analysis on all TB patients registered nationally.

What is cohort analysis for?

Cohort analysis is the key management tool used to evaluate the effectiveness of NTP performance. It enables district and regional NTP staff and the NTP directorate to identify districts with problems. Examples of problems identified include the following: low cure rate, high default rate, higher than expected proportions of sputum smear-negative PTB or extrapulmonary TB, lower than expected case detection rate. Identification of problems enables the NTP to overcome them and improve programme delivery.

9.8 RESPONSE OF HIV-POSITIVE TB PATIENTS TO ANTI-TB TREATMENT

Response in patients who complete treatment

Patients who complete treatment show the same clinical, radiographic and microbiological response to SCC whether HIV-positive or HIV-

negative. The only exception is that on average weight gain is less in HIV-positive than HIV-negative TB patients.

Case-fatality

Case-fatality is the percentage of TB patients who die within a given period (e.g. during treatment). HIV-positive TB patients have a much higher case-fatality during and after anti-TB treatment compared with HIV-negative patients. In sub-Saharan Africa, up to 30% of HIV-positive smear-positive PTB patients die before the end of treatment. Evidence is also accumulating that HIV-positive smear-negative PTB patients have a worse prognosis than those who have HIV-positive smear-positive PTB. Excess deaths in TB/HIV patients during and after treatment are partly due to TB itself and partly due to other HIV-related problems. These include septicaemia, diarrhoea, pneumonia, anaemia, Kaposi sarcoma, and cryptococcal meningitis.

Case-fatality is lower in TB/HIV patients treated with SCC than with the old standard regimen (ISHT or SHE/IIHT or HE). This is partly because SCC is a more effective anti-TB treatment. Also, as well as anti-TB activity, rifampicin has broad-spectrum antimicrobial activity. This may reduce deaths due to HIV-related bacterial infections during TB treatment.

Two studies suggest the importance of DOT in reducing deaths. Self-administered treatment was associated with a higher mortality among HIV-positive TB patients compared with DOT. This association remained even after controlling for all other factors in a multivariate analysis. Adjunctive treatments may be needed with anti-TB treatment to reduce deaths.

Recurrence of TB after completion of anti-TB treatment

Old standard treatment (initial phase ISHT or SHE; continuation phase IIHT or HE)

The recurrence rate is higher in HIV-positive than in HIV-negative TB patients. In one study of TB/HIV patients, there was an association between recurrence and cutaneous reaction to thioacetazone. A severe thioacetazone reaction necessitated interruption of treatment and a change to ethambutol. There are several possible explanations for the link between increased risk of recurrence and thioacetazone reaction. These include treatment interruption, subsequent poor compliance, more advanced immunocompromise, and change to the combination of isoniazid and ethambutol in the 11-month continuation phase.

SCC

Among TB patients who complete SCC, the recurrence rate may be higher in HIV-positive than in HIV-negative patients. Studies suggest two ways of reducing this higher recurrence rate, although they do not prolong survival. One way is to extend the duration of the treatment regimen from 6 to 12 months. Another way is to give post-treatment prophylaxis (for example with isoniazid). Further studies are needed before these treatments can be widely recommended. Studies are still needed to confirm the benefit, establish the optimum regimen (drugs and duration) and assess operational feasibility.

Recurrence: relapse or reinfection?

When TB recurs after previous cure, there are 2 possibilities:

- a) true relapse (reactivation of persisters not killed by anti-TB drugs);
- b) reinfection (due to re-exposure to another source of infection).

The risk of re-infection depends on the intensity of exposure to TB transmission.

Alzeer AH, Fitzgerald JM. Corticosteroids and tuberculosis: risks and use as adjunct therapy. *Tubercle and lung disease* 1993; 74: 6–11.

Graham SM, Daley HM, Banerjee A, Salaniponi FM, Harries AD. Ethambutol usage in tuberculosis - time to reconsider? *Archives of diseases in childhood*, 1998, 79: 274–278

Horne NW. *Modern drug treatment of tuberculosis*. 7th edition. London, Chest, Heart and Stroke Association, 1990.

Reider HL. *Interventions for tuberculosis control and elimination*. Paris, International Union Against Tuberculosis and Lung Disease, 2002.

Stop TB Partnership. *Global TB Drug Facility prospectus*. Geneva, World Health Organization, 2001 (WHO/CDS/TB/2001.10a)

World Health Organization. *Tuberculosis handbook*. Geneva, 1998 (WHO/TB/98.253).

World Health Organization. *Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis*. Geneva, 2003 (WHO/CDS/TB/2000.279).

World Health Organization. *Treatment of tuberculosis. Guidelines for national programmes*. Third edition, Geneva, 2003 (WHO/CDS/TB/2003.313).

World Health Organization, International Union Against Tuberculosis and Lung Disease, Royal Netherlands Tuberculosis Association. Revised international definitions in tuberculosis control. *International journal of tuberculosis and lung disease*, 2001, 5 (3): 213–215.

Ya Diul M, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS*, 2001, 15: 143–152.

10.1 INTRODUCTION

Most TB patients complete their treatment without any significant drug side-effects. However, a few patients do develop side-effects. So clinical monitoring of all TB patients for side-effects is important during TB treatment. Routine laboratory monitoring is not necessary.

Health personnel monitor patients for drug side-effects by:

- teaching patients and their family members how to recognise symptoms of common side-effects, and to report if patients develop such symptoms;
- asking specifically about these symptoms when they see all patients at least monthly during treatment.

10.2 PREVENTION OF SIDE-EFFECTS

Health personnel should be aware of the special situations that influence the choice and dose of anti-TB drugs (see Chapter 9).

It is possible to prevent the peripheral neuropathy caused by isoniazid. This neuropathy usually shows as a burning sensation of the feet. It occurs more commonly in HIV-positive individuals and in people who drink alcohol. These patients should receive preventive treatment with pyridoxine 10 mg daily. Ideally, where possible, pyridoxine 10 mg daily should routinely accompany isoniazid.

10.3 WHERE TO MANAGE DRUG REACTIONS

Reaction	Where to manage reaction
minor, e.g. gastrointestinal, joint pains	outpatient setting
major, e.g. jaundice, severe rash	refer to district or central hospital

10.4 WHEN TO STOP ANTI-TB DRUGS

When patients have minor drug side-effects, explain the situation, offer symptomatic treatment, and encourage them to continue treatment.

When a patient has a major reaction, stop the suspected responsible drug(s) at once. A patient who develops one of the following reactions must never receive that drug again:

Reaction	Drug responsible
severe rash, agranulocytosis	thioacetazone
hearing loss or disturbed balance	streptomycin
visual disturbance (poor vision and colour perception)	ethambutol
renal failure, shock, or thrombocytopenia	rifampicin
hepatitis	pyrazinamide

10.5 SIDE-EFFECTS OF ANTI-TB DRUGS

Drug	Common side-effects	Rare side-effects
isoniazid	<ul style="list-style-type: none"> ◦ peripheral neuropathy ◦ hepatitis if age > 40 ◦ sleepiness/lethargy 	convulsions, pellagra, joint pains, agranulocytosis, lupoid reactions, skin rash, acute psychosis
rifampicin	<ul style="list-style-type: none"> ◦ gastrointestinal: anorexia, nausea, vomiting, abdominal pain ◦ hepatitis ◦ reduced effectiveness of oral contraceptive pill 	acute renal failure, shock, thrombocytopenia, skin rash, "flu syndrome" (intermittent doses), pseudomembranous colitis, pseudoadrenal crisis, osteomalacia, haemolytic anaemia
pyrazinamide	<ul style="list-style-type: none"> ◦ joint pains ◦ hepatitis 	gastrointestinal symptoms, skin rash, sideroblastic anaemia
streptomycin	<ul style="list-style-type: none"> ◦ auditory and vestibular nerve damage (also to fetus) ◦ renal damage 	skin rash
ethambutol	<ul style="list-style-type: none"> ◦ optic neuritis 	skin rash, joint pains, peripheral neuropathy
thiacetazone	<ul style="list-style-type: none"> ◦ skin rash, often with mucous membrane involvement and sometimes blistering 	hepatitis, agranulocytosis

PRACTICAL POINT

Rifampicin reduces the effectiveness of the oral contraceptive pill. Advise women to use another form of contraception.

PRACTICAL POINT

Warn patients that rifampicin colours all body secretions (urine, tears, semen and sweat) red or orange.

10.5.1 Side-effects of anti-TB drugs in HIV-positive TB patients

Adverse drug reactions are more common in HIV-positive than in HIV-negative TB patients. Risk of drug reaction increases with increased immunocompromise. Most reactions occur in the first 2 months of treatment.

Skin rash

This is the commonest reaction. Fever often precedes and accompanies the rash. Mucous membrane involvement is common. The usual drug responsible is thioacetazone. Streptomycin and rifampicin are sometimes to blame. Severe skin reactions, which may be fatal, include exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Other reactions

The commonest reactions necessitating change in treatment include gastrointestinal disturbance and hepatitis. There may be an increased risk of rifampicin-associated anaphylactic shock and thrombocytopenia.

10.6 Symptom-based approach to management of drug side-effects

Side-effects	Drug(s) probably responsible	Management
Minor		Continue anti-TB drugs
anorexia, nausea, abdominal pain	rifampicin	give tablets last thing at night
joint pains	pyrazinamide	give aspirin or nonsteroidal anti-inflammatory drug
burning sensation in feet	isoniazid	give pyridoxine 50–75 mg daily
orange/red urine	rifampicin	reassurance
Major		Stop drug(s) responsible
skin itching/rash	thioacetazone (streptomycin)	stop anti-TB drugs (see below)
deafness (no wax on auroscopy)	streptomycin	stop streptomycin, give ethambutol instead
dizziness (vertigo and nystagmus)	streptomycin	stop streptomycin, give ethambutol instead
jaundice (other causes excluded)	most anti-TB drugs	stop all anti-TB drugs until jaundice resolves (see below)
vomiting and confusion (suspected drug-induced pre-icteric hepatitis)	most anti-TB drugs	stop anti-TB drugs, urgent liver function tests
visual impairment	ethambutol	stop ethambutol
generalized, including shock and purpura	rifampicin	stop rifampicin

10.7 MANAGEMENT OF SKIN ITCHING AND RASH

The approach depends on whether the patient is receiving thioacetazone. In populations with a high TB/HIV prevalence, thioacetazone is the drug most likely to cause skin reactions.

PRACTICAL POINT

Try to determine if the skin reaction was present before anti-TB drugs were started, as many HIV-positive patients have itchy skin lesions as a result of HIV infection.

10.7.1 Treatment regimen includes thioacetazone

If a patient starts to itch, and there is no other obvious cause (e.g. scabies), stop the anti-TB drugs at once. The itching may be a warning sign of severe skin reaction. Stopping thioacetazone at once may avert, or decrease the severity of, the skin reaction.

Give the patient intravenous fluids if the skin reaction is severe and accompanied by any of the following:

- exfoliative dermatitis or toxic epidermal necrolysis,
- mucous membrane involvement,
- hypotension.

Many physicians give steroid treatment, although there is no firm evidence that this helps. A typical dose schedule consists of 60 mg daily of oral prednisolone until there is some improvement. A gradual reduction in dose over the next few days depends on the patient's response. Initially, if a patient is unable to swallow, give intravenous hydrocortisone 100–200 mg daily (instead of oral prednisolone). Patients with exfoliation should also receive antibiotics to safeguard against life-threatening infection of lesions. On recovery, restart anti-TB drugs, replacing thioacetazone with ethambutol.

PRACTICAL POINT

Never give a patient thioacetazone again after any thioacetazone reaction.

A severe reaction may mean stopping anti-TB treatment for 3–4 weeks. A severely ill TB patient may die without anti-TB treatment. In this case, give the patient 2 or more previously unused drugs until the reaction has resolved. Then reintroduce the initial regimen (with ethambutol instead of thioacetazone).

10.7.2 Treatment regimen does not include thioacetazone

If a patient starts to itch, exclude other obvious causes. Try treatment with antihistamines, continue anti-TB treatment and observe closely. In some cases, the itching resolves. In other cases, a rash develops. In this case, stop the anti-TB drugs. Wait for the rash to resolve. If the reaction is severe, the patient may need supportive treatment as above.

The problem now is to reintroduce TB treatment when it is not known

which anti-TB drug was responsible for the reaction. The table below shows the standard approach to reintroducing anti-TB drugs after a drug reaction.

Reintroduction of anti-TB drugs following drug reaction

Drug	Likelihood of causing a reaction	Challenge doses		
		Day 1	Day 2	Day 3
Isoniazid	least likely	50 mg	300 mg	300 mg
Rifampicin	↓	75 mg	300 mg	Full dose
Pyrazinamide		250 mg	1 gr	Full dose
Ethambutol		100 mg	500 mg	Full dose
Streptomycin	most likely	125 mg	500 mg	Full dose

If possible, while a patient is undergoing drug challenge, give two anti-TB drugs that the patient has not had before. The idea of drug challenge is to identify the drug responsible for the reaction. Drug challenge starts with the anti-TB drug least likely to be responsible for the reaction (i.e. isoniazid). Start with a small challenge dose. If a reaction occurs to a small challenge dose, it will not be such a bad reaction as to a full dose. Gradually increase the dose over 3 days. Repeat the procedure, adding in one drug at a time. A reaction after a particular drug is added identifies that drug as the one responsible for the reaction.

If the drug responsible for the reaction is pyrazinamide, ethambutol, or streptomycin, resume anti-TB treatment without the offending drug. If possible, replace it with another drug. It may be necessary to extend the treatment regimen. Consider the start of the resumed regimen as a new start of treatment. This prolongs the total time of TB treatment, but decreases the risk of recurrence.

PRACTICAL POINT

Refer patients with severe drug reactions to a specialist centre.

10.8 DESENSITIZATION

Rarely, patients develop hypersensitivity reactions to the two most potent anti-TB drugs, isoniazid and rifampicin. These drugs form the cornerstone of SCC. If an HIV-negative patient has had a reaction (but

not a severe reaction) to isoniazid or rifampicin, it may be possible to desensitize the patient to the drug. However, desensitization in TB/HIV patients needs very careful consideration because of the high risk of serious toxicity.

The following method may be used for desensitization. Start desensitization with a tenth of the normal dose. Then increase the dose by a tenth of a normal dose each day, until the patient has the full dose on the tenth day. Once drug sensitization is over, give the drug as part of the usual treatment regimen. If possible, while carrying out desensitization, give the patient two anti-TB drugs that he or she has not had before. This is to avoid the risk of drug resistance developing during desensitization.

10.9 MANAGEMENT OF HEPATITIS

Most anti-TB drugs can damage the liver. Isoniazid and pyrazinamide are most commonly responsible. Ethambutol is rarely responsible. When a patient develops hepatitis during anti-TB treatment, the cause may be the anti-TB treatment or something else. It is often difficult to find out. Try to rule out other possible causes before deciding that the hepatitis is drug-induced. Hepatitis presents with anorexia, jaundice and often liver enlargement.

If you diagnose drug-induced hepatitis, stop the anti-TB drugs. Wait until the jaundice or hepatic symptoms have resolved and the liver enzymes have returned to baseline. If liver enzymes cannot be measured, then it is advisable to wait two weeks after the jaundice has disappeared before recommencing anti-TB treatment.

It is strange, but fortunate, that in most cases the patient can restart the same anti-TB drugs without hepatitis returning. This can be done either gradually or all at once (if the hepatitis was mild). If the hepatitis has been life-threatening, it is probably safer to use the standard regimen of streptomycin, isoniazid and ethambutol.

A severely ill TB patient may die without anti-TB drugs. In this case, treat the patient with 2 of the least hepatotoxic drugs, streptomycin and ethambutol. When the hepatitis resolves, restart usual anti-TB treatment. In the face of extensive TB, the fluoroquinolones, especially ofloxacin, can be considered in conjunction with streptomycin and ethambutol as an interim non-hepatotoxic regimen.

SUGGESTIONS FOR FURTHER READING

Crofton J, Horne N, Miller F. *Clinical tuberculosis*. Second edition. MacMillan Press Limited, London, 1999.

Horne NW. *Modern drug treatment of tuberculosis*. Seventh edition, London, The Chest, Heart and Stroke Association, 1990.

Mitchell I, Wendon J, Fitt S, et al. Anti-tuberculosis therapy and acute liver failure. *Lancet*, 1995, 345: 555–556.

Reider HL. *Interventions for tuberculosis control and elimination*. Paris, International Union Against Tuberculosis and Lung Disease, 2002.

II.1 INTRODUCTION

Rapid progress in developing antiretroviral therapy (ART) led in 1996 to the introduction of highly active antiretroviral therapy (HAART). This revolutionized the treatment of HIV infection. HAART is a combination of at least three antiretroviral (ARV) drugs. As with anti-TB treatment, a combination of ARV drugs provides efficacy and decreases risk of drug resistance. HAART is the global standard of care in the treatment of HIV infection. Although not a cure for HIV infection, HAART usually results in near-complete suppression of HIV replication. Treatment has to be lifelong.

ART results in dramatic reductions in morbidity and mortality in HIV-infected people. There are several requirements for successful use of ART. These include considerable efforts to maintain adherence to lifelong treatment and to monitor response to treatment, drug toxicities and drug interactions.

Although the benefits of ART are considerable, administration is not easy. Many HIV-infected persons cannot tolerate the toxic effects of the drugs. Adherence is difficult because of often large numbers of pills and complicated treatment regimens. Poor adherence to treatment leads to the emergence of drug-resistant viral strains, which are very difficult to treat. Careful monitoring of patients is necessary to evaluate response to treatment.

HAART is the global standard of care. However, access is limited to very few HIV-infected people where the burden of HIV is greatest (in sub-Saharan Africa and Asia). WHO estimated that in 2002 there were 6 million people in developing countries in need of ART. Of these, only 230000 had access to ART (and half of those were in one country, Brazil). There are increasing international efforts to improve access to ART in resource-limited settings. Drug costs (one of the major barriers to access in poor countries) are rapidly declining. Modification of drug patent laws is under discussion to allow resource-poor countries to import cheap generic versions of the drugs. Pilot schemes are under development to ensure proper and safe drug administration and distribution at district level. The WHO Model List of Essential Drugs includes eight ARV drugs. WHO has published guidelines for a public health approach to scaling up ART in resource-limited settings. These

developments will facilitate the achievement of the target to have 3 million people in developing countries on ART by 2005.

ART will become increasingly available in resource-poor countries. Clinicians treating TB patients need to be familiar with the principles and practice of ART. This chapter therefore provides a brief guide to ART, including the specific treatment of HIV infection in TB/HIV patients. You should consult the suggestions for further reading for more comprehensive guidance on ART. In this rapidly evolving field, you should also consult national and international authorities for regularly updated guidance. The WHO website is a useful source of up-to-date guidance (<http://www.who.int/HIV>).

11.2 ANTIRETROVIRAL DRUGS

ARV drugs belong to two main classes:

- reverse transcriptase inhibitors (RTIs);
- protease inhibitors (PIs).

RTIs are further divided into three groups:

- nucleoside reverse transcriptase inhibitors (NsRTIs);
- non-nucleoside reverse transcriptase inhibitors (NNRTIs);
- nucleotide reverse transcriptase inhibitors (NtRTIs).

The table shows the ARV drugs (abbreviation in brackets) approved for inclusion in WHO's Model List of Essential Drugs (EDL) from April 2002.

NsRTIs	NNRTIs	PIs
Zidovudine (AZT, ZDV)	Nevirapine (NVP)	Saquinavir (SQV)
Didanosine (ddI)	Efavirenz (EFV)	Ritonavir (RTV) (as pharmacoenhancer)
Stavudine (d4T)		Indinavir (IDV)
Lamivudine (3TC)		Nelfinavir (NFV)
Abacavir (ABC)		Lopinavir/ritonavir (LPV/r)

Examples of other drugs not included in the EDL are give below:

NsRTIs	zalcitabine (ddC)
NtRTI	tenofovir (TDF)
NNRTIs	delavirdine (DLV)
PIs	aprenavir (APV)

11.3 PRINCIPLES OF ART

ARV drugs act by blocking the action of enzymes that are important for

replication and functioning of HIV. The drugs must be used in standardized combinations (usually three drugs together). Monotherapy is not recommended because of the inevitable development of drug resistance. However, for the specific indication of prevention of mother-to-child transmission of HIV infection, short course monotherapy is still recommended. Dual nucleoside therapy is also not recommended because it does not reduce HIV-related mortality at a population level.

11.4 PRINCIPLES OF A PUBLIC HEALTH APPROACH TO ART

WHO recommends a standardized approach to overall TB control and a standardized approach to TB treatment regimens. Similarly with HIV, WHO recommends a standardized approach to care, which includes standardized ART regimens. Standardization and simplification of ART regimens facilitate the effective implementation of HIV treatment programmes. Effective implementation means maximized benefit for individual patients with minimised risk of drug resistance. Although experience with ART in resource-limited district settings is limited, countries are now scaling up ART. Further experience gained in providing standardized first- and second-line regimens will inform future WHO guidelines.

PRACTICAL POINT

For effective and safe prescribing, consult guidelines for information on regimens, doses, side-effects and drug interactions. See “Scaling up antiretroviral therapy in resource-limited settings”, Geneva, WHO, Revision 2003.

The same public health principles underpin the approaches to TB treatment and to ART. In both cases, success requires the following: political commitment; diagnosis and registration of patients; standardized drug treatment regimens under proper case management conditions; secure drug supply; programme monitoring and evaluation through recording and reporting of patients registered and their outcomes.

11.5 INITIATION OF ART

There is some controversy about the best time to start ART. Clinicians in industrialized countries use plasma HIV RNA levels and CD4+ T-lymphocyte counts in guiding this decision. For example, a high viral load (i.e. above 30000 RNA copies/ml by RT-PCR) is an indication to start

ART. These expensive laboratory tests are used for staging HIV infection and for monitoring therapy. WHO guidelines apply in resource-limited settings where these tests may not be available. Clinical stage (see Section 1.2.7) is important as a criterion for starting ART.

11.5.1 Adults and adolescents with documented HIV infection

Recommendations for initiating ART

CD4 testing available	WHO stage 4 irrespective of CD4 cell count WHO stage 1, 2 or 3 with CD4 cell counts less than 200/mm ³
CD4 testing not available	WHO stage 3 or 4 irrespective of total lymphocyte count WHO stage 2 with total lymphocyte count less than 1200/mm ³

Contraindications to starting treatment include severe renal or hepatic insufficiency, and concomitant incurable disease.

11.5.2 Infants and children

Recommendations for initiating ART

CD4 testing	Age	HIV Diagnostic testing	Treatment recommendation
If CD4 testing is available	< 18 months	Positive HIV virological test ¹ HIV virological testing not available but infant HIV-seropositive or born to known HIV-infected mother (Note: HIV antibody test <i>must</i> be repeated at age 18 months to obtain definitive diagnosis of HIV infection)	<ul style="list-style-type: none"> ◦ WHO Paediatric Stage 3 (AIDS), irrespective of CD4 cell percentage² ◦ WHO Paediatric Stage 1 disease (asymptomatic) or Stage 2 disease with CD4 percentage < 20%³ ◦ WHO Paediatric Stage 3 disease (AIDS) with CD4 cell percentage < 20%

	> 18 months	HIV antibody seropositive	<ul style="list-style-type: none"> ◦ WHO Paediatric Stage 3 disease (AIDS) irrespective of CD4 cell percentage² ◦ WHO Paediatric Stage I (asymptomatic) or Stage 2 disease, with CD4 percentage <15%³
If CD4 testing is not available	< 18 months	Positive HIV virological test ¹	◦ WHO Paediatric Stage 3 ²
		HIV virological testing not available but infant HIV-seropositive or born to known HIV-infected mother	◦ Treatment not recommended ⁴
	> 18 months	HIV antibody seropositive	◦ WHO Paediatric Stage 3 ²

- ¹ HIV DNA PCR or HIV RNA or immune complex dissociated p24 antigen assays, or HIV culture.
- ² Initiation of ARV can also be considered for children who have advanced WHO Paediatric Stage II disease including e.g. severe recurrent or persistent oral candidiasis outside the neonatal period, weight loss, fevers, or recurrent severe bacterial infections, irrespective of CD4 count.
- ³ The rate of decline in CD4 percentage (if measurement available) should be factored into the decision-making.
- ⁴ Many of the clinical symptoms in the WHO Paediatric Stage II and III disease classification are not specific for HIV infection and significantly overlap those seen in children without HIV infection in resource-limited settings; thus, in the absence of virological testing and CD4 cell assay availability, HIV-exposed infants <18 months of age should generally not be considered for ART regardless of symptoms.

11.6 RECOMMENDED DOSES OF ARV DRUGS

11.6.1 Adults and adolescents¹

The field of ARV drug treatment is rapidly evolving. Clinicians need to keep up to date with the latest guidance on drug doses and treatment. The WHO website is a useful source of such guidance (www.who.int/HIV).

Drug	Dose ¹
Nucleoside RTIs (NsRTIs)	
Zidovudine (ZDV)	300 mg twice daily
Stavudine (d4T)	40 mg twice daily (30 mg twice daily if < 60 kg)
Lamivudine (3TC)	150 mg twice daily
Didanosine (ddl)	400 mg once daily (250 mg once daily if < 60 kg)
Abacavir (ABC)	300 mg twice daily
Nucleotide RTI (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside RTIs (NNRTIs)	
Efavirenz (EFZ)	600 mg once daily
Nevirapine (NVP)	200 mg once daily for 14 days, then 200 mg twice daily
Protease inhibitors (PIs)	
Nelfinavir (NFV)	1250 mg twice daily
Indinavir/ritonavir (IDV/r)	800 mg/100 mg twice daily ^{2,4}
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily (533 mg/133 mg twice daily when combined with EFZ or NVP)
Saquinavir/ritonavir (SQV/r)	1000 mg/100 mg twice daily ^{3,4}

¹ These dosages are in common clinical use. The dosages in this table were selected on the basis of the best available clinical evidence, and dosages that can be given on a once or twice daily basis were preferred in order to enhance adherence to therapy. The doses listed are those for individuals with normal renal and hepatic function. Product-specific information should be consulted for dose adjustments that may be indicated with renal or hepatic dysfunction or for potential drug interactions with other HIV and non-HIV medications.

² This dosage regimen is in common clinical use. Other IDV/r dosage regimens that range from 800 mg/200 mg twice daily to 400 mg/100 mg twice daily are also in clinical usage.

³ Both the hard-gel and soft-gel capsule formulations can be used when SQV is combined with RTV.

⁴ Dosage adjustment when combined with an NNRTI is indicated but a formal recommendation cannot be made at this time. One consideration is to increase the RTV component to 200 mg twice daily when EFZ or NVP is used concomitantly. More drug interaction data are needed.

11.6.2 Children

The following table indicates the recommended doses of ARV drugs for children.

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose* and dose frequency	Other comments
Nucleoside reverse transcriptase inhibitors (NRTIs) Zidovudine (ZDV)	Syrup: 10 mg/ml Capsules: 100 mg; 250 mg Tablet: 300 mg	All ages	< 4 weeks: 4 mg/kg twice daily 4 weeks to 13 years: 180 mg/m ² twice daily Maximum dose: >13 yrs: 300 mg twice daily	Large volume of syrup not well tolerated in older children Needs storage in glass jars and is light-sensitive Can give with food Doses of 600 mg/m ² twice daily required for HIV encephalopathy Do not use with d4T (antagonistic antiretroviral effect) Well tolerated Can give with food Store solution at room temperature (use within one month of opening) Tablet can be washed, mixed with a small amount of water or food, and taken immediately
Lamivudine (3TC)	Oral solution: 10 mg/ml Tablet: 150 mg	All ages	< 30 days: 2 mg/kg twice daily >30 days and < 60 kg: 4 mg/kg twice daily Maximum dose: > 60 kg: 150 mg twice daily	Well tolerated Can give with food Store solution at room temperature (use within one month of opening) Tablet can be washed, mixed with a small amount of water or food, and taken immediately

Fixed-dose combination of ZDV plus 3TC	No liquid available Tablet: 300 mg ZDV plus 150 mg 3TC	Adolescents and adults	Maximum dose: > 13 years or > 60 kg: 1 tablet twice daily	Tablet should not be split Tablet can be washed, mixed with a small amount of water or food, and taken immediately For children <30 kg, ZDV+3TC cannot be dosed accurately in tablet form
Didanosine (ddl, dideoxyinosine)	Oral suspension paediatric powder/ water: 10 mg/ml. In many countries needs to be made up with additional antacid Chewable tablets: 25 mg; 50 mg; 100 mg; 150 mg; 200 mg Enteric-coated beadlets in capsules: 125 mg; 200 mg; 250 mg; 400 mg	All ages	< 3 months: 50mg/m ² twice daily 3 months to 13 years: 90 mg/m ² twice daily or 240 mg/m ² once daily Maximum dose: >13 years or > 60 kg: 200 mg twice daily or 400 mg once daily	Keeps suspension refrigerated; stable for 30 days; must shake well Should be taken on an empty stomach, at least 30 minutes before or 2 hours after eating
Stavudine (d4T)	Oral solution: 1 mg/ml Capsules: 15 mg, 20 mg, 30 mg, 40 mg	All ages	< 30 kg: 1 mg/kg twice daily 30 to 60 kg: 30 mg twice daily	Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food Large volume of solution Keep solution refrigerated; stable for 30 days; must shake well

Stavudine (d4T) (continued)			Maximum dose: > 60 kg: 40 mg twice daily	Needs to be stored in glass bottles Capsules opened up and mixed with small amount of food are well tolerated (stable in solution for 24 hours if kept refrigerated) Do not use with AZT (antagonistic antiretroviral effect)
Abacavir (ABC)	Oral solution: 20 mg/ml Tablet: 300 mg	Over age 3 months	< 16 years or < 37.5 kg: 8 mg/kg twice daily Maximum dose: > 16 years or > 37.5 kg: 300 mg twice daily	Syrup well tolerated or can crush tablet Can give with food MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION. ABC should be stopped permanently if hypersensitivity reaction
Fixed-dose combination of ZDV plus 3TC plus ABC (trizavir)	No liquid available Tablet: ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg	Adolescents and adults	Maximum dose: > 40 kg: 1 tablet twice daily	Tablet cannot be split. MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION. Trizavir should be stopped permanently if hypersensitivity reaction For children <30 kg, trizavir cannot be dosed accurately in tablet form

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

<p>Nevirapine (NVP)</p>	<p>Oral suspension: All ages 10 mg/ml</p> <p>Tablet: 200 mg</p>		<p>15 to 30 days: 5 mg/kg once daily for 2 weeks, then</p> <p>120 mg/m² twice daily for 2 weeks, then 200 mg/m² twice daily</p> <p>> 30 days to 13 yrs: 120 mg/m² once daily for 2 weeks, then 120–200 mg/m² twice daily</p> <p>Maximum dose: > 13 years: 200 mg once daily for first 2 weeks, then 200 mg/ twice daily</p>	<p>If rifampicin coadministration, avoid use</p> <p>Store suspension at room temperature; must shake well</p> <p>Can give with food</p> <p>MUST WARN PARENTS ABOUT RASH. Do not escalate dose if rash occurs (if mild/moderate rash, hold drug; when rash cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug)</p> <p>Drug interactions</p>
<p>Efavirenz (EFZ)</p>	<p>Syrup: 30 mg/ml (note: syrup requires higher doses than capsules, see dosing chart)</p> <p>Capsules: 50 mg, 100 mg, 200 mg</p>	<p>Only for children over 3 years</p>	<p>Capsule (liquid) dose for > 3 years: 10 to 15 kg: 200 mg (270 mg = 9 ml) once daily 15 to 20 kg: 250 mg (300 mg = 10 ml) once daily 20 to 25 kg: 300 mg (360 mg = 12 ml) once daily</p>	<p>Capsules may be opened and added to food but have very peppery taste; however, can mix with sweet foods or jam to disguise taste</p> <p>Can give with food (but avoid after high-fat meals which increase absorption by 50%).</p>

<p>Efavirenz (EFZ) (continued)</p>			<p>2.5 to 33 kg: 350 mg (450 mg = 15 ml) once daily 33 to 40 kg: 400 mg (510 mg = 17 ml) once daily Maximum dose: >40 kg: 600 mg once daily</p>	<p>Best given at bedtime, especially first 2 weeks, to reduce central nervous system side-effects. Drug interactions</p>
<p>Protease inhibitors (PIs)</p>				
<p>Nelfinavir (NFV)</p>	<p>Powder for oral suspension (mix with liquid): 200 mg per level 5 ml teaspoon (50 mg per 1.25 ml scoop) Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)</p>	<p>All ages However, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants < 1 yr</p>	<p>< 1 yr: 40–50 mg/kg three times daily or 75 mg/kg twice daily > 1 year to < 13 years: 55 to 65 mg/kg twice daily Maximum dose: > 13 yrs: 1250 mg twice daily</p>	<p>Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc. – do not use acidic food or juice (increases bitter taste) Because of difficulties with use of powder, crushed tablets preferred (even for infants) if appropriate dose can be given Powder and tablets can be stored at room temperature</p>

Nelfinavir (NFV) (continued)				Take with food Drug interactions (less than ritonavir-containing protease inhibitors)
Lopinavir/ritonavir (LPV/r)	6 months of age or older	Oral solution: 80 mg/ml lopinavir plus 20 mg/ml ritonavir Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir	> 6 months to 13 years: 225 mg/m ² LPV/57.5 mg/m ² ritonavir twice daily or weight-based dosing: 7–15 kg: 12 mg/kg LPV 3 mg/kg ritonavir twice daily 15–40 kg: 10 mg/kg lopinavir 2–5 mg/kg ritonavir twice daily Maximum dose: > 40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 ml) twice daily	Preferably oral solution and capsules should be refrigerated; however, can store at room temperature up to 25°C (77°F) for 2 months Liquid formulation has low volume but bitter taste Capsules large Should be taken with food Drug interactions

* **Body surface area calculation (m²): square root of (height in cm multiplied by weight in kg divided by 3600)**

11.7 CHOICE OF ART REGIMEN

WHO recommends standardized and simplified ART regimens in support of effective large-scale ART programmes. Countries should select a single first-line, and a limited number of second-line, regimens for large-scale use. This clinical manual provides guidance on recommended first-line regimens. The WHO guidelines *Scaling up antiretroviral therapy in resource-limited settings* provide full details, including guidance on second-line regimens. The results of clinical studies and of surveillance for drug resistance should inform policies for recommended first-line and second-line regimens.

11.7.1 Adults

Recommended combination regimens without a PI

Two NsRTIs (e.g. zidovudine/lamivudine) + one NNRTI (either nevirapine or efavirenz)

or

three NsRTIs (including abacavir), e.g. zidovudine/lamivudine/abacavir

Alternative NsRTI combinations (not in preferred order):

zidovudine + didanosine

stavudine + lamivudine or didanosine

Zidovudine and stavudine should not be used together because of their mutually antagonistic effect. Didanosine and zalcitabine may lead to additive neurotoxicity and should not be combined.

Recommended combination regimens containing a PI

Two NsRTIs + one PI, e.g. zidovudine/lamivudine/indinavir

These are effective regimens. However, there are some disadvantages, such as complex dosing schedules, drug interactions with rifampicin, and concern over long-term toxicity of PIs.

Recommended first-line ARV combination regimens in adults and adolescents with documented HIV infection

Regimen*	Pregnancy Considerations	Major toxicities
ZDV/3TC/EFZ or ZDV/3TC/NVP	Substitute NVP for EFZ in pregnant women or women for whom effective contraception cannot be assured	ZDV-related anaemia EFZ-associated CNS symptoms Possible teratogenicity of EFZ NVP-associated hepatotoxicity and severe rash
ZDV/3TC/ABC	ABC safety data limited	ZDV-related anaemia ABC hypersensitivity
ZDV/3TC/ PI** or ZDV/3TC/NFV	LPV safety data limited NFV: most supportive safety data	ZDV-related anaemia NFV-associated diarrhoea IDV-related nephrolithiasis PI-related metabolic side-effects

*ZDV/3TC is listed as the initial recommendation for dual NsRTI component based on efficacy, toxicity, clinical experience and availability of fixed-dose formulation. Other dual NsRTI components can be substituted including d4T/3TC, d4T/ddl and ZDV/ddl depending upon country-specific preferences. ZDV/d4T should never be used together because of proven antagonism.

** PIs include IDV, LPV, and SQV.

11.7.2 Children

There have been a limited number of studies of ART in children. They suggest that many different ARV regimens result in broadly similar improvements in surrogate markers. Most ARVs available for adults are also available for children in specific formulations, including dosages based on either body surface area or weight. First-line treatment options for children include ZDV/3TC plus either a non-nucleoside (NVP or EFZ) or ABC. Children under the age of 3 years should not receive EFZ because of lack of appropriate dosing information. In children over three years, EFZ is the NNRTI of choice when starting ART before completion of rifampicin-containing anti-TB therapy.

Recommended first-line ARV combination regimens for children¹

Regimen	Comments
ZDV/3TC ² plus ABC	Preferred if child receiving concomitant anti-TB therapy
ZDV/3TC ² plus NNRTI	NNRTI choice: <ul style="list-style-type: none">◦ if < 3 years or < 10 kg, NVP◦ if >3 years or >10 kg, NVP or EFV

¹ Country-specific considerations and preferences should determine which regimen or regimens to make available.

² The greatest clinical experience is with ZDV/3TC, which is therefore the first choice dual NsRTI regimen. Other dual NsRTI components can be substituted, including ZDV/ddI, d4T/3TC, d4T/ddI, and ddI/3TC. ZDV/d4T should never be used because of proven antagonism.

11.8 MONITORING THE EFFICACY OF ART

Efficacy is monitored by:

clinical improvement

- gain in body weight,
- decrease in occurrence and severity of HIV-related diseases (infections and malignancies),

increase in total lymphocyte count,

improvement in biological markers of HIV (when available)

- CD4+ T-lymphocyte counts,
- plasma HIV RNA levels.

11.9 ADVERSE EFFECTS

All ARV drugs have class-specific adverse effects.

- NsRTIs: fatty changes in the liver
lactic acidosis
lipodystrophy syndrome with prolonged use
- PIs: lipodystrophy syndrome
elevated serum cholesterol and triglycerides
elevated blood glucose
bleeding episodes in patients with haemophilia
- NNRTIs: skin rash
abnormal liver enzymes/hepatitis

Lactic acidosis is due to toxicity of NsRTIs on cellular mitochondria. If unrecognized, it is potentially fatal. If patients develop pronounced fatigue, nausea, vomiting and abdominal pain, lactic acidosis should be considered.

Lipodystrophy syndrome has distinctive features. There is peripheral fat loss around the face, limbs and buttocks. Fat accumulates centrally around the abdomen and breasts and over the back of the neck (so-called “buffalo hump”). Often associated with lipodystrophy are raised blood levels of cholesterol, triglycerides and glucose.

Other specific drug side-effects include:

NsRTIs

zidovudine	nausea, headache, fatigue, muscle pains, myopathy, anaemia, agranulocytosis,
didanosine	nausea, diarrhoea, neuropathy, pancreatitis
zalcitabine	neuropathy, pancreatitis, oral ulcers
stavudine	neuropathy, pancreatitis
lamivudine	nausea, headache, fatigue, muscle pains, anaemia, agranulocytosis,
abacavir	nausea, fatigue, sleep disturbance, hypersensitivity reaction

NNRTIs

nevirapine	rash, hepatitis
efavirenz	neuropsychiatric disturbances
delavirdine	headaches

PIs

saquinavir	nausea, diarrhoea
ritonavir	nausea, diarrhoea, weakness, skin sensitivity, abnormal taste, perioral numbness
indinavir	nausea, abdominal pain, headache, kidney stones
nelfinavir	diarrhoea, nausea, skin rash
amprenavir	nausea, vomiting, diarrhoea, abnormal taste, mood disorder, perioral numbness
lopinavir/ritonavir	abdominal pain, diarrhoea, fatigue, headache, nausea, vomiting, pancreatitis

Monitoring the safety of ART and tolerance depends on clinical assessment and laboratory tests. Laboratory tests include measurements of full blood count, liver enzymes, serum amylase (pancreatitis), glucose, triglycerides and creatine phosphokinase (myopathy). Different ART regimens require different laboratory tests.

11.10 INTERACTIONS BETWEEN ARV DRUGS AND DRUGS USED TO PREVENT OR TREAT OPPORTUNISTIC INFECTIONS

There are many interactions between ARV and other drugs. Two examples of common interactions are between: i) zidovudine and cotrimoxazole; and ii) PIs and ketoconazole or fluconazole.

- Trimethoprim-sulfamethoxazole can give additive haematological toxicity when given with zidovudine.
- Antifungal drugs such as ketoconazole and fluconazole may inhibit the metabolism of PIs. This may result in increased serum levels of PI and increased risk of toxicity.

11.11 ANTIRETROVIRAL DRUGS AND TB TREATMENT

11.11.1 Drug interactions

Rifampicin stimulates the activity of the cytochrome P450 liver enzyme system, which metabolizes PIs and NNRTIs. This can lead to decreased 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 ARV drugs, ineffective treatment of TB or an increased risk of drug toxicity.

Isoniazid can cause peripheral neuropathy. The NsRTIs (didanosine, zalcitabine and stavudine) may also cause peripheral neuropathy. There is a potential added toxicity if isoniazid is added. Isoniazid also has a theoretical interaction with abacavir.

11.11.2 Treating TB and HIV together

In patients with HIV-related TB, the priority is to treat TB, especially smear-positive PTB (on account of the need to stop TB transmission). However, patients with HIV-related TB can have ART and anti-TB treatment at the same time, if managed carefully. Careful evaluation is necessary in judging when to start ART. In the case, for example, of a patient with a high risk of death during the period of TB treatment (i.e. disseminated TB and/or CD4 count $<200/\text{mm}^3$), it may be necessary to start ART concomitantly with TB treatment. On the other hand, for a patient with smear-positive PTB as the first manifestation of HIV

infection, who does not appear to be at high risk of dying, it may be safer to defer ART until the initial phase of TB treatment has been completed. This decreases the risk of immune reconstitution syndrome and avoids the risk of drug interaction between rifampicin and a PI.

11.11.3 Immune reconstitution syndrome

Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs or radiographic manifestations of TB after beginning anti-TB treatment. This paradoxical reaction in HIV-infected patients with TB is thought to be a result of immune reconstitution. This occurs as a result of the simultaneous administration of ART and anti-TB drugs. Symptoms and signs may include high fever, lymphadenopathy, expanding central nervous system lesions and worsening of CXR findings. A thorough evaluation is necessary to exclude other causes, particularly TB treatment failure, before diagnosing a paradoxical reaction. For severe paradoxical reactions, prednisone (1–2 mg/kg for 1–2 weeks, then gradually decreasing doses) may help, although there is no evidence for this.

11.11.4 Options for ART in patients with TB

Possible options for ART in patients with TB include the following:

- Defer ART until completion of TB treatment.
- Defer ART until the completion of the initial phase of TB treatment and then use ethambutol and isoniazid in the continuation phase.
- Treat TB with a rifampicin-containing regimen and use efavirenz + two NsRTIs.

SUGGESTIONS FOR FURTHER READING

Bartlett JG, Gallant JE. *Medical management of HIV infection*. Baltimore, MD, Johns Hopkins University School of Medicine, 2000–2001.

Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet*, 2000, 356: 1423–1430.

Harrington M, Carpenter CCJ. World AIDS Series: Hit HIV-1 hard, but only when necessary. *Lancet*, 2000, 355: 2147–2152.

Pozniak AL, Miller R, Ormerod LP. The treatment of tuberculosis in HIV-infected persons. *AIDS*, 1999; 13: 435–445.

World Health Organization. *Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach*. 2003 revision. Geneva, (www.who.int/hiv).

Harries AD, Nyangulu DS, Hargreaves NJ, Kaluwa O, Salaniponi FM. Preventing antiretroviral anarchy in sub-Saharan Africa. *Lancet*, 2001, 358: 410–14.

Harries AD, Hargreaves NJ, Chimzizi R, Salaniponi FM. Highly active antiretroviral therapy and tuberculosis control in Africa: synergies and potential. *Bulletin of the World Health Organization*, 2002, 80: 464–469.

12.1 INTRODUCTION

Whether or not TB/HIV patients have access to ART, they may have, or will develop, other HIV-related diseases. This chapter is a brief guide to their management at district hospital level. At the end of the chapter is a guide to prevention of HIV-related diseases. Therapies in **bold** are available in most district hospitals. The WHO publications, *Guidelines for the clinical management of HIV Infection for adults and for children and Management of sexually transmitted infections*, give a fuller account. Clinicians should always check drug dosages.

12.2 CLINICAL SPECTRUM OF HIV-RELATED DISEASE

In general, pathogens may be high-grade or low-grade. High-grade pathogens may be pathogenic in healthy individuals with normal immune status. Low-grade pathogens are usually pathogenic in persons with immunodeficiency. The pathogens that cause disease and the type of clinical disease they cause depend on the degree of progression of HIV infection and the associated extent of immunosuppression. High-grade pathogens (e.g. the pneumococcus, non-typhoid salmonellae and *M. tuberculosis*) can cause disease at any stage in the course of HIV infection. Low-grade pathogens (e.g. *Candida*, *Cryptococcus neoformans*, toxoplasma, cytomegalovirus, *Pneumocystis carinii* and atypical mycobacteria) cause disease in the more advanced stages. Disseminated infections become increasingly common in advanced stages of HIV infection with more severe immunosuppression. The WHO clinical staging system for HIV infection and disease reflects these features. Diseases caused by low-grade pathogens and disseminated infections characterize stage 4 in adults and adolescents and stage 3 in children. Infections caused by the high-grade pathogens tend to be easier to diagnose and treat than those caused by the low-grade pathogens.

The spectrum of disease in HIV-positive persons varies among regions. Dominating the picture in sub-Saharan Africa are the high-grade pathogens (bacterial and mycobacterial) such as the pneumococcus, non-typhoid salmonellae and *M. tuberculosis*, which are endemic, highly associated with poverty, and intensely transmitted in overcrowded unsanitary environments. TB has become a leading cause of death among people with HIV infection, accounting for up to a third of AIDS deaths

worldwide. There has also been recent recognition of the association between HIV infection and increased frequency of clinical malaria. In this region, some low-grade opportunistic pathogens are important (particularly cryptococcus and toxoplasma), but those that dominate the picture in the industrialized countries, such as *Pneumocystis carinii* and atypical mycobacteria, are relatively rare. Although the spectrum of disease in HIV-positive persons has not been as fully characterized in other regions, a similar pattern is likely to be seen throughout the developing world.

Nearly 90% of all HIV-positive persons live in developing countries in Africa and South-East Asia. Thus, worldwide, the main burden of disease in HIV-infected individuals arises from a limited number of common infectious agents, namely *M. tuberculosis*, pneumococcus and non-typhoid salmonellae. Diagnosis of these infections is usually possible at health centres or district hospitals. They are generally amenable to treatment with cheap, affordable and effective antimicrobials. For example, a course of TB treatment may cost as little as US\$10 in some countries (although more in sub-Saharan Africa). Thus diagnosis and treatment of common HIV-related diseases due to high-grade pathogens are feasible and affordable. There is a need to strengthen the ability of general health care providers to diagnose and treat these diseases. This has the potential to dramatically decrease their contribution to HIV-related morbidity and mortality. WHO has developed an essential drugs list for the treatment of common HIV-related diseases. In many parts of the world the treatments for a variety of HIV-related infections (including herpes simplex virus, cytomegalovirus and atypical mycobacteria) and cancers (including Kaposi sarcoma and non-Hodgkin lymphoma) are more expensive and not yet widely available.

12.3 SEXUALLY TRANSMITTED INFECTIONS

A person who has unsafe sex is at risk of several sexually transmitted infections (STIs). So a patient with one STI is at increased risk of having another STI. HIV is usually sexually transmitted. STIs other than HIV are common in TB/HIV patients. This section gives a brief account of the drug treatment of STIs. When you treat a patient with STI, also remember patient education, counselling, condom provision and partner management.

12.3.1 Syndromic management

Accurate STI diagnosis is often not feasible. WHO has developed a

syndromic management approach based on the recognition of consistent groups of symptoms and signs (syndromes). The treatment recommended for each syndrome cures the majority of infections responsible for causing the syndrome. The table below shows the recommended plans of treatment for the common STI-associated syndromes where laboratory investigations are not available.

Syndrome	Plan of treatment
Men	
urethral discharge	treat for gonorrhoea and chlamydia
Women	
cervicitis	treat for uncomplicated gonorrhoea and chlamydia
vaginal discharge	treat for vaginitis (candidiasis and <i>Trichomonas vaginalis</i> /bacterial vaginosis) treat for cervicitis (in high gonorrhoea and chlamydia prevalence settings)
Men and women	
genital ulcers	treat for syphilis and chancroid (and herpes in high HSV-2 prevalence settings)
inguinal bubo	
- with ulcers	treat for syphilis and chancroid
- without ulcers	treat for lymphogranuloma venereum

12.3.2 Treatment regimens for common STIs

The table below shows treatment regimens for the common STIs.

Do not use ciprofloxacin or tetracyclines in pregnancy. Avoid tetracyclines in childhood.

STI	Treatment regimen
gonorrhoea (uncomplicated)	ciprofloxacin 500 mg orally as a single dose OR ceftriaxone 250 mg by i.m. injection as a single dose OR cefixime 400 mg orally as a single dose OR spectinomycin 2 g by i.m. injection as a single dose OR trimethoprim 80mg/sulfamethoxazole 400 mg (TMP-SMX) 10 tablets orally as a single dose OR gentamicin 240 mg by i.m. injection as a single dose

chlamydia	doxycycline 100 mg orally twice daily for 7 days OR tetracycline 500 mg orally 4 times daily for 7 days OR erythromycin 500 mg orally 4 times daily for 7 days
primary syphilis (chancres)	benzathine penicillin G 2.4 million IU, by i.m. injection at a single session (often split into 2 doses at separate sites) OR procaine penicillin G 1.2 million IU by i.m. injection daily for 10 consecutive days OR (if allergic to penicillin) tetracycline 500 mg orally 4 times daily for 15 days OR doxycycline 100 mg orally twice daily for 15 days OR erythromycin 500 mg orally 4 times daily for 15 days
chancroid	erythromycin 500 mg orally 3 times daily for 7 days OR ciprofloxacin 500 mg orally twice daily for 3 days OR ceftriaxone 250 mg by i.m. injection as a single dose OR azithromycin 1 g orally as a single dose OR TMP-SMX 2 tablets orally twice daily for 7 days
lymphogranuloma venereum	doxycycline 100 mg orally twice daily for 14 days OR tetracycline 500 mg orally 4 times daily for 14 days OR erythromycin 500 mg orally daily for 14 days OR sulfadiazine 1 g orally 4 times daily for 14 days
candidiasis	nystatin 100000 IU intravaginally once daily for 14 days OR miconazole or clotrimazole 200 mg intravaginally once daily for 3 days OR clotrimazole 500 mg intravaginally as a single dose
<i>Trichomonas vaginalis</i>	metronidazole 2 g orally as a single dose OR metronidazole 400–500 mg orally twice daily for 7 days
bacterial vaginosis	metronidazole 2 g orally as a single dose OR metronidazole 400–500 mg orally 2x daily for 7 days

The diagnosis of these HIV-related skin and mouth problems usually rests on characteristic clinical features. The tables below show diagnoses and treatments.

Skin problems

- Virus infections

Infection	Local treatment	Drug treatment	
		Adults	Children
Herpes simplex (oral and genital)	Local lesion care (i.e. regular cleaning and avoiding secondary bacterial infection)	Acyclovir orally 5 times/daily until healed	
		200 mg	<2 years 100 mg > 2 years 200 mg
Varicella zoster	Local lesion care (i.e. regular cleaning and avoiding secondary bacterial infection)	Analgesia	
		Acyclovir	
		800 mg orally 5 times/daily for at least 7 days	20 mg/kg (max. 800 mg) 4 times/daily for 5 days
Anal/genital warts (human papilloma virus)	Topical 20% podophyllin 1-2 times per week until healed Trichloroacetic acid Cryotherapy		
Molluscum contagiosum	Leave the lesions alone OR prick each lesion with a needle or sharpened orange stick and touch with phenol. Trichloroacetic acid Cryotherapy		

◦ Fungal infections

Infection	Local treatment	Drug treatment	
		Adults	Children
Tinea (pedis/ corporis/ cruri)	Whitfield's ointment or Castellani's paint Topical antifungals 1% clotrimazole 2% miconazole	In resistant cases griseofulvin	
		500 mg orally twice daily	10 mg/kg orally daily in divided doses or as a single dose
Candidiasis	1% aqueous gentian violet or nystatin ointment twice daily until lesions are cleared Topical antifungals		
Cutaneous cryptococcosis/histoplasmosis		Systemic antifungal therapy	

◦ Bacterial infections

Infection	Local treatment	Drug treatment	
		Adults	Children
Impetigo, furunculosis		Penicillin V orally 4 times daily for 1–2 weeks	
		500 mg	Up to 1 year 62.5 mg, 1–5 years 125 mg, 6–12 years 250 mg
		OR flucloxacillin orally 4 times daily for 1–2 weeks	
		500 mg	< 2 years quarter adult dose 2–10 years half adult dose
		OR Erythromycin orally 4 x daily for 1 - 2 weeks	
		500 mg	< 2 years 125 mg 2-8 years 250 mg > 8 years 250–500 mg

Pyomyositis	Surgical drainage	Plus antibiotics (as for impetigo)	
Bacillary angiomatosis (due to <i>Bartonella henselae</i>) (lesions may resemble Kaposi Sarcoma –definitive diagnosis by biopsy)		Erythromycin orally 4 times daily for 8 weeks	
		500 mg	< 2 years 25 mg 2–8 years 250 mg > 8 years 250–500 mg
		Doxycycline orally twice a day for 8 weeks	
		100 mg (Not to be given to pregnant or breast-feeding women)	Not to be given to children < 12 years

◦ Other

Condition	Local treatment	Drug treatment	
		Adults	Children
Pruritus without skin lesions	Calamine lotion Antihistamines		
Papular folliculitis (pruritic papular dermatosis; eosinophilic folliculitis)	Calamine lotion Topical antifungals with 1% hydrocortisone Strong topical corticosteroids	Antihistamines	
		Metronidazole twice a day for 7–14 days	
Seborrhoeic dermatitis	Antifungal shampoos OR topical antifungals with steroids OR topical 1% hydrocortisone Strong topical corticosteroids	If severe, ketoconazole orally	
		200 mg twice daily	7.5 mg/kg every 8 hours 3 mg/kg daily

Ichthyosis (dry scaly skin)	Emollients (e.g. aqueous cream)	
Psoriasis	Conventional antipsoriasis treatment, e.g. coal tar in salicylate ointment twice daily	
Scabies	Topical benzyl benzoate 25% Topical lindane lotion	Ivermectin 200 µg/kg as a single dose with topical drugs
Kaposi sarcoma	Local lesion care. Radiotherapy	Chemotherapy

◦ Mouth problems

Condition	Local treatment	Drug treatment	
		Adults	Children
Oral candidiasis	Topical antifungals such as amphotericin lozenges, nystatin pastilles/pessaries: nystatin drops 100000 units 3 times daily OR nystatin pessaries one every 4 hours OR nystatin tabs 500000 units 4 times daily. If nystatin not available, use gentian violet 0.25–0.5% In all cases treat for 7–14 days. Recurrence is common without prophylaxis.	In resistant cases oral ketoconazole for 14 days	
		200 mg twice daily	3 mg/kg daily
		As an alternative in resistant cases (except in children under 1 year) fluconazole for 14 days	
		100 mg daily	2 mg/kg daily
Hairy leukoplakia	No treatment		
Angular cheilitis	Topical antifungals e.g. 1% clotrimazole		

Gingivitis/ dental abscesses		Metronidazole orally for 7 days	
		400 mg 3 times daily	7.5 mg/kg every 8 hours
		AND/OR penicillin V for 7 days	
Aphthous ulcers	Mouth rinses with steroid and tetracycline Topical corticosteroids	500 mg 4 times daily	Up to 1 year 62.5 mg 1–5 years 125 mg, 6–12 years 250 mg
		Oral prednisolone	
		Oral acyclovir (Oral thalidomide 200 mg daily in refractory cases)	

12.5 RESPIRATORY PROBLEMS

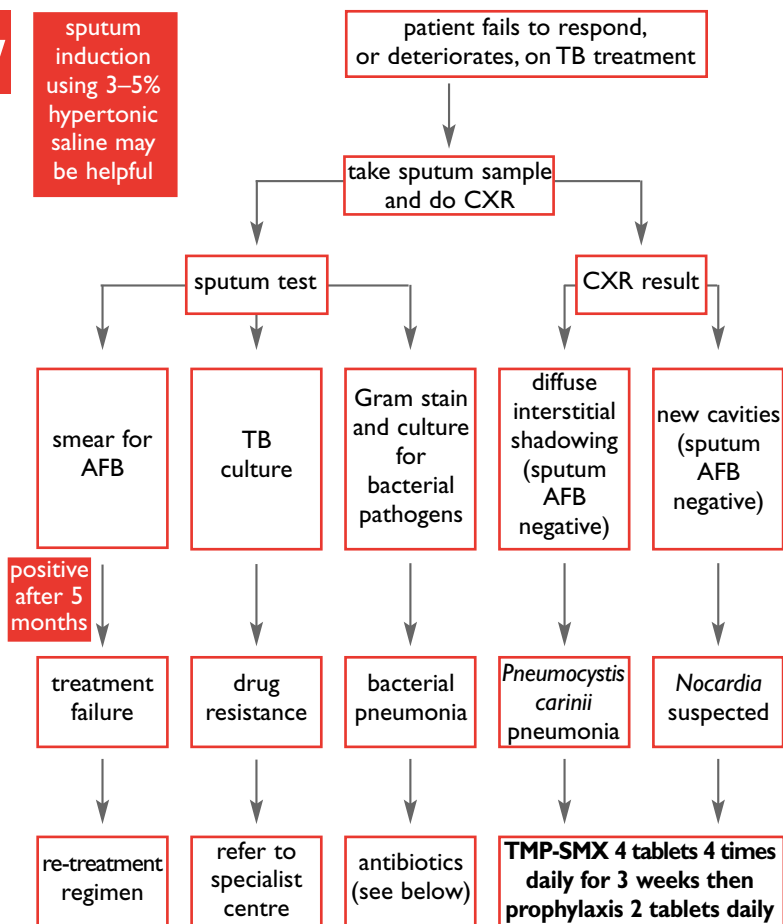
12.5.1 Respiratory problems in adults

Some TB/HIV patients fail to improve, or even deteriorate, during anti-TB treatment. They continue to have, or develop new, respiratory problems, e.g. cough, breathlessness, chest pain. First check that they have taken their anti-TB drugs. Then consider the following possibilities.

Original diagnosis	Possibilities
sputum smear-negative PTB	incorrect diagnosis e.g. other pathogens, heart failure, chronic obstructive airways disease
sputum smear-positive PTB	patient not adherent to anti-TB treatment; drug-resistant TB; superimposed infection with other pathogens.

The flow chart shows the management approach in HIV-positive PTB patients who fail to respond or deteriorate while on anti-TB treatment.

sputum induction using 3–5% hypertonic saline may be helpful



The table below shows the main bacterial pathogens responsible for superimposed pneumonia in smear-positive PTB patients and the treatment.

Pathogen	Treatment
<i>Streptococcus pneumoniae</i>	penicillin or TMP-SMX
<i>Haemophilus influenzae</i>	amoxycillin or TMP-SMX
<i>Staphylococcus aureus</i>	flucloxacillin or chloramphenicol
Gram-negative bacilli	chloramphenicol (and gentamicin if necessary)

12.5.2 Respiratory problems in children

HIV-infected children with TB are also more susceptible to other respiratory diseases and more likely to die despite TB treatment. An important reason for a poor response to TB treatment is that the child does not have PTB. The difficulties in diagnosing PTB in children mean that it may be confused with other causes of HIV-related lung disease (see Chapter 4). Most children who receive treatment for PTB are smear-negative cases. If they do not improve on TB treatment, consider other diagnoses, e.g. LIP or cardiac disease. In all cases, consider poor treatment adherence as a cause of poor treatment response.

Mixed respiratory infections are a particular feature of HIV-infected children. It is common for children with TB to develop bacterial pneumonia as a complication. The main bacterial pathogens are those listed above. Treatment should follow Integrated Management of Childhood Illness (IMCI) guidelines. If the child has severe pneumonia, admit to hospital and give chloramphenicol 25 mg/kg intramuscularly or intravenously three times a day (and oxygen if necessary). If the child does not improve within 48 hours, switch to gentamicin 7.5 mg/kg IM once a day and cloxacillin 50 mg/kg IM or IV every 6 hours.

HIV-infected children with presumed TB may have lymphocytic interstitial pneumonitis (LIP) either as an alternative diagnosis or occasionally as a mixed infection. LIP is also often complicated by acute bacterial pneumonia. Clinical features that suggest LIP are generalized symmetrical lymphadenopathy, non-tender parotid enlargement and finger clubbing. Typical CXR features are a bilateral reticulonodular interstitial pattern and adenopathy. If the child with LIP has persistent respiratory distress, then give prednisolone 1–2 mg/kg daily for 2–4 weeks and then reduce gradually over 2 weeks.

12.6 GASTROINTESTINAL PROBLEMS

12.6.1 Dysphagia

There are various HIV-related causes of oesophageal inflammation. They present in a similar way with pain on swallowing. Oesophageal candidiasis is the commonest HIV-related cause of dysphagia. The diagnosis of other causes needs endoscopy, biopsy and a good laboratory.

Where there are no facilities for investigation of a known HIV-positive patient with dysphagia, treat empirically with an oral antifungal agent.

Where available, barium swallow shows characteristic appearances of fine mucosal ulceration. Upper gastrointestinal endoscopy shows white plaques and biopsy allows confirmation.

The table below shows the treatment of the causes of dysphagia.

Cause of dysphagia	Treatment	
	Adults	Children
Candidal oesophagitis	Nystatin 4 times daily for 1–14 days	
	500000 units (OR Nystatin pessaries 100,000 units every 4 hours)	100000 units
	Ketoconazole for 7–14 days	
	200 mg twice daily	3 mg/kg daily
	OR fluconazole for 7–14 days	
	100 mg once daily	Not recommended under one year 1–2mg/kg daily
	Prophylaxis with nystatin pastilles OR fluconazole for life	
Herpes simplex	Acyclovir	
	800 mg orally five times daily for 7–10 days.	20 mg/kg (max. 800 mg) 4 times daily for 5 days
Cytomegalovirus	Treatment usually not available (intravenous ganciclovir or foscarnet) on account of expense.	
Ulcers of unknown cause	Prednisolone for 2 weeks, then slowly taper to zero	
	40 mg daily	

12.6.2 Diarrhoea in adults

Introduction

Episodes of acute diarrhoea, recurrent diarrhoea or chronic diarrhoea are very common, affecting up to 60% of HIV-positive individuals at some time in their illness. Common accompanying features include nausea, vomiting, abdominal cramps, flatulence, weight loss and dehydration.

Rehydration

Always assess the state of hydration of any patient with diarrhoea. Most

patients with mild to moderate dehydration should receive oral rehydration solution. A few patients, with severe dehydration, need intravenous fluids.

Investigation

Where facilities are available, send multiple stool samples for microscopy and culture. With appropriate stains it is possible on microscopy to diagnose the following pathogens: *Cryptosporidium*, *Isoospora belli*, *Microsporidia*. Stool culture can permit the diagnosis of *Salmonella*, *Shigella*, and *Clostridium difficile*.

Treatment

In most cases, the cause is not known. So treatment in these cases is empirical. Some cases (probably due to *Isoospora belli*) respond to treatment with trimethoprim-sulfamethoxazole (TMP-SMX). Other cases (probably due to *Microsporidia*) respond to treatment with metronidazole or albendazole.

Sometimes you do find a specific cause of diarrhoea. Many of the treatable causative pathogens are common in unsanitary environments. The table shows specific causes with the appropriate treatment.

Diagnosis	Treatment
Bacterial infections	
<i>Salmonella</i>	trimethoprim 80 mg/sulfamethoxazole 400 mg (TMP-SMX) 2 tablets twice daily for 7 days OR chloramphenicol 500 mg 4 times daily for 7 days. ciprofloxacin 500 mg twice daily for 7 days
<i>Shigella</i>	trimethoprim 80 mg/sulfamethoxazole 400 mg (TMP-SMX) 2 tablets twice daily for 7 days OR nalidixic acid 1g 4 times daily for 7 days ciprofloxacin 500 mg twice daily for 3–7 days
<i>Campylobacter jejuni</i>	erythromycin 500 mg 4 times daily for 7 days ciprofloxacin 500 mg twice daily for 3–7 days
<i>Clostridium difficile</i>	metronidazole 400 mg 3 times daily for 7–14 days vancomycin 250 mg twice daily for 7–14 days
Protozoal infections	
<i>Cryptosporidium</i>	symptomatic treatment only paramomycin (efficacy is marginal)

<i>Isospora belli</i>	trimethoprim 80 mg/sulfamethoxazole 400mg (TMP-SMX) 2 tablets twice daily for 7–14 days
<i>Microsporidia</i> (<i>Enterocytozoon bieneusi</i> or <i>Septata intestinalis</i>)	metronidazole 400 mg 3 times daily for 7 days albendazole 800 mg twice daily for 4 weeks
<i>Giardia lamblia</i>	metronidazole 2 gr daily for 3 days tinidazole 2 gr as a single dose
<i>Entamoeba histolytica</i>	metronidazole 800 mg 3 times daily for 7 days, then diloxanide furoate 500 mg 3 times daily for 10 days or tetracycline 500 mg 4 times daily for 10 days
<i>Cyclospora cayetanensis</i>	trimethoprim 80 mg/sulfamethoxazole 400 mg (TMP-SMX) 2 tablets twice daily for 3–7 days

Persistent diarrhoea

Give symptomatic treatment if diarrhoea persists, the cause is not known, and there is no response to TMP-SMX then metronidazole then albendazole. Antidiarrhoeal agents for symptomatic treatment include codeine and loperamide but these should be avoided in children.

12.6.3 Diarrhoea in children

Acute diarrhoea

Management of acute watery diarrhoea in HIV-infected children is similar to that in HIV-uninfected children with an emphasis on prevention of dehydration or rehydration of the dehydrated child. State of hydration is more difficult to assess if the patient is severely malnourished and rehydration needs to be more careful.

Do not restrict intake of food but rather advise small frequent meals of nutritious food. If the child is breastfed, then this should be continued. Restricting the intake of food increases the chance of the child developing persistent diarrhoea.

Dysentery

If a child has dysentery, i.e. acute bloody diarrhoea usually with fever and abdominal pain, treat with an antibiotic for 5 days. Antibiotic choice will depend on local sensitivity patterns for *Shigella*. This might be TMP

4 mg/SMX 20 mg twice daily, nalidixic acid 15 mg/kg 4 times a day or ciprofloxacin 10–15 mg/kg twice a day for 5 days.

Persistent diarrhoea

This is diarrhoea that lasts for two weeks or longer. Occasionally it is due to gut parasites such as *Entamoeba histolytica* or *Giardia lamblia*. If so, give oral metronidazole 10 mg/kg, 3 times a day for 5 days. The most important aspect of management (and the most neglected) is nutritional rehabilitation. Micronutrients such as zinc, vitamin A and folic acid are important and should be given. Feeds should be more frequent than usual and should contain adequate calories and protein. Milk-based or egg-based diets are useful. Yoghurt is also effective.

12.7 NEUROLOGICAL PROBLEMS IN ADULTS

A wide variety of neurological problems may occur in TB/HIV patients. The common presentations are the following:

- 1) acute confusion,
- 2) chronic behaviour change,
- 3) persistent headache,
- 4) difficulty in walking,
- 5) poor vision,
- 6) burning sensation in the feet.

Neurological problems are often thought to be difficult to diagnose. In fact, they are no more difficult to diagnose than other problems, **provided that you take time and care**. You have to take time and care to obtain a detailed history and perform a proper neurological examination. It is usually necessary to obtain some, if not all, of the history from the patient's relatives or friends. Some simple district-level laboratory tests on blood and cerebrospinal fluid (CSF) are often helpful.

12.7.1 Acute confusion

The differential diagnosis when a TB/HIV patient becomes acutely confused includes the following:

- a) acute superimposed infection, e.g. septicaemia, meningitis, malaria;
- b) hypoxaemia, e.g. pneumothorax, pneumonia, heart failure, anaemia;
- c) metabolic disturbance, e.g. secondary to diarrhoea, hypoadrenalism;
- d) adverse drug reaction, e.g. acute confusion may be the first sign of drug-induced acute fulminant liver failure (a useful test, if available, is the prothrombin time).

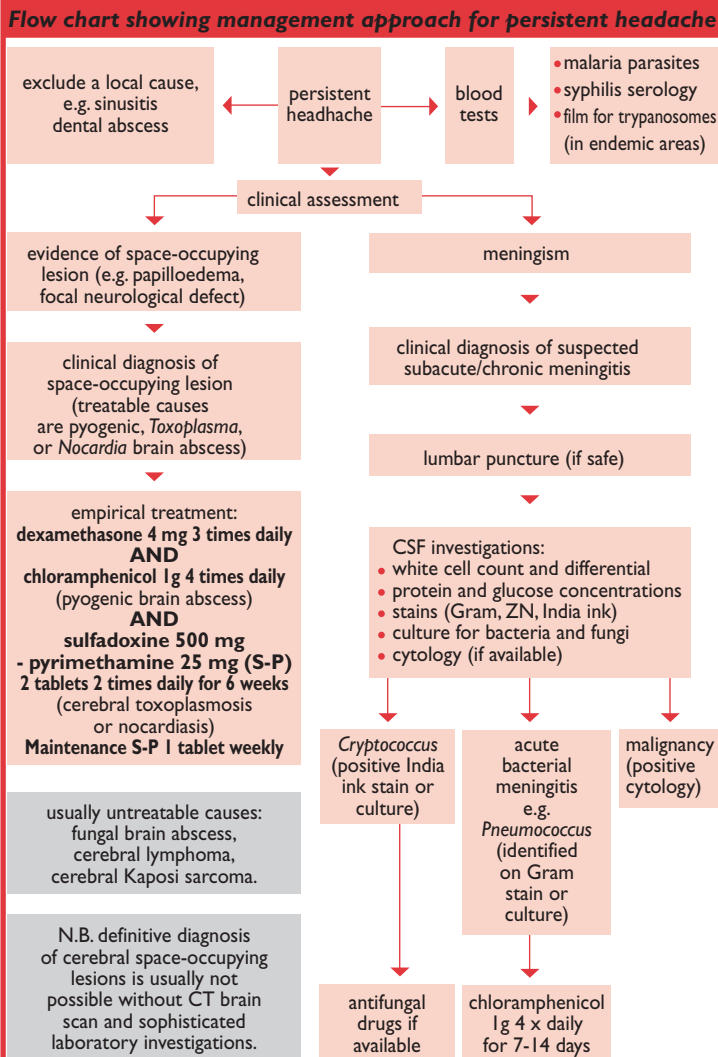
Always check a blood film for malaria. Do a lumbar puncture if the patient has meningism and it is safe to do a lumbar puncture. Other investigations depend on the laboratory facilities available and clinical clues to the diagnosis.

12.7.2 Chronic behaviour change

Chronic behaviour change, i.e. over a period of month is usually due to AIDS dementia or progressive multifocal leukoencephalopathy. These are untreatable, unless there is access to ART. Since the diagnoses are clinical, you must rule out other treatable possibilities. Send blood for syphilis serology and (in endemic areas) microscopy for trypanosomes. If lumbar puncture is safe, send CSF to the laboratory to exclude chronic meningitis (e.g. cryptococcal, TB).

12.7.3 Persistent headache

The flow chart below shows the management approach to the TB/HIV patient with headache. The following features may accompany headache: reduced level of consciousness, confusion, convulsions.



It is possible, but rare, for TB meningitis to develop after a TB patient has already started anti-TB treatment. For example, a cerebral tuberculoma could rupture into the subarachnoid space releasing TB bacilli not yet killed by anti-TB drugs. A commonly recommended treatment regimen for TB meningitis is as follows: 2SHRZ/7HR.

It is unlikely, but possible, that a patient already on TB treatment could develop acute bacterial meningitis. The diagnosis rests on CSF examination.

Cryptococcal meningitis

The outcome is fatal without treatment and often very poor with treatment. In many countries the drugs for treating cryptococcal meningitis are expensive, and are not often available in routine settings. The treatment for many patients is therefore symptomatic with analgesia and sedation. Patients who can afford specific antifungal drug treatment should receive fluconazole 400 mg daily initially for 10 weeks. Alternative regimens are i) intravenous amphotericin B (0.5 mg/kg per day) for 14 days followed by fluconazole 400 mg daily for 8 weeks or ii) intravenous amphotericin B (0.5 mg/kg per day) for 14 days followed by intraconazole 400 mg daily for 8 weeks. Lifelong maintenance treatment with fluconazole 200 mg daily is then necessary to prevent relapse.

12.7.4 Difficulty in walking

Spinal TB may cause difficulty in walking. So first make sure (by clinical examination and spine X-ray) that the patient does not also have spinal TB.

The cause of difficulty walking in a TB/HIV patient may be HIV-related (spinal cord myelopathy and occasionally peripheral neuropathy) or unrelated to HIV. A patient with difficulty walking and HIV myelopathy usually has a spastic paraparesis. It is only possible to make this diagnosis by excluding the causes of spinal cord disease unrelated to HIV. The table below shows the main causes of spinal cord disease unrelated to HIV, and the diagnostic tests. In HIV-related peripheral neuropathy, sensory disturbance tends to predominate over motor weakness.

Cause of spinal cord disease	Diagnostic tests
cervical spondylosis	cervical spine X-ray, myelography
prolapsed intervertebral disc	myelography
epidural abscess	myelography
treatable tumours (neurofibroma, meningioma)	myelography
schistosomiasis	identification of eggs in stool, urine, or rectal snips myelography
neurosyphilis	syphilis serology, CSF findings
subacute combined degeneration of the cord	anaemia with raised MCV, low serum vitamin B12 level

Spinal cord schistosomiasis is difficult to diagnose, but schistosomiasis is easy to treat. If a patient with a spinal cord problem lives in an area endemic for schistosomiasis, give empirical treatment with a single dose of praziquantel (40 mg/kg) while pursuing further management.

12.7.5 Poor vision

PRACTICAL POINT

If a patient receiving ethambutol develops difficulty seeing clearly, or has problems perceiving colours, stop ethambutol.

Cytomegalovirus retinitis can cause poor vision but is rare in African AIDS patients. The diagnosis rests on the characteristic appearance on fundoscopy of a necrotizing retinitis with perivascular haemorrhages and exudates. The treatment with ganciclovir or foscarnet is prohibitively expensive in many countries.

12.7.6 Burning sensation in the feet

HIV may cause a peripheral neuropathy, often worse when a TB patient starts isoniazid. The main symptom is a painful burning sensation in the feet. The signs include distal weakness and atrophy with absent ankle jerks.

Prevention

If resources allow, all TB patients should receive pyridoxine 10 mg daily as prophylaxis against isoniazid neuropathy. Otherwise reserve pyridoxine prophylaxis for HIV-positive TB patients and TB patients who drink alcohol.

Treatment

Treat patients with established isoniazid neuropathy with pyridoxine 50–75 mg daily. Amitriptyline (25–75 mg at night), phenytoin (100–300 mg at night), or carbamazepine (100–200 mg twice daily) may relieve symptoms in HIV neuropathy.

12.8 NEUROLOGICAL PROBLEMS COMMON IN CHILDREN

Developmental delay or even developmental regression are the most common neurological problems. Developmental delay is common in any child who is chronically ill and malnourished, both common in HIV-infected children with TB. HIV can also infect the brain. This may lead to

a variety of neurological problems including developmental regression, behaviour change, confusion and seizure disorders.

Much of the same applies for children as for adults (see above). It is important to consider other diagnoses such as cerebral malaria or meningitis. Cryptococcal meningitis does occur in HIV-infected children but bacterial meningitis is more common. Occasionally very wasted HIV-infected children have an acute psychotic reaction with confusion, aggressive behaviour and hallucinations one to two weeks after starting TB treatment. It is likely that this is due to isoniazid and treatment is to withhold isoniazid and give pyridoxine. The condition usually settles over a week and then isoniazid can be reintroduced.

12.9 FEVER

12.9.1 Approach to management

Fever usually settles within 2–3 weeks of starting anti-TB treatment. Further fever may signal a drug reaction or a disseminated infection. The table below shows the approach to management of further or persistent fever.

Features accompanying fever	Likely cause	Action
rash	drug reaction	Stop anti-TB drugs
weight loss progressive anaemia or pancytopenia	disseminated infection	Examine patient Investigations: <ul style="list-style-type: none"> ◦ blood film for malaria ◦ blood film for trypanosomes ◦ blood cultures ◦ consider lumbar puncture Consider empirical treatment for malaria— if no response start antibiotics for suspected septicaemia

12.9.2 Disseminated infection

Disseminated infection carries a high mortality. The table below shows the wide variety of pathogens that can cause disseminated infection in TB/HIV patients.

Pathogens causing disseminated infection in TB/HIV patients

Bacteria	Mycobacteria	Viruses	Others
Non-typhoidal <i>Salmonella</i>	<i>M. tuberculosis</i>	<i>Cytomegalovirus</i>	<i>Cryptococcus</i>
<i>Streptococcus pneumoniae</i>	<i>M. avium complex (MAC)</i>		<i>Histoplasma</i>
<i>Pseudomonas aeruginosa</i>			<i>Leishmania</i>
<i>Staphylococcus aureus</i>			<i>Penicillium marneffeii</i>
Other Gram-negative bacteria			

Bacterial septicaemia

Non-typhoidal *Salmonella* such as *S. typhimurium* or *S. enteritidis* and *Pneumococcus* are the commonest identified causes of septicaemia in HIV-positive adults and children in sub-Saharan Africa. Many strains of *S. typhimurium* are resistant to several antibiotics. If you suspect septicaemia, treat the patient with **chloramphenicol** or **ampicillin and gentamicin**.

Disseminated *M. avium complex (MAC)*

MAC is less frequent in AIDS patients in sub-Saharan Africa than elsewhere. Diagnostic facilities and treatment (e.g. clarithromycin + ethambutol + rifabutin) are generally not available in district hospitals and many central hospitals.

12.10 OTHER HIV-RELATED PROBLEMS

Tumours

Kaposi sarcoma (KS)

KS can affect many parts of the body, but usually the skin and mouth, and sometimes the lung and pleura, gastrointestinal tract, and pericardium. The clinical appearance is usually distinctive. There is often oedema with KS on the face and legs. Diagnostic confusion can arise with keloids, leprosy, sarcoidosis, melanoma and bacillary angiomatosis due to *Bartonella henselae*. In case of doubt, particularly with bacillary angiomatosis which is treatable with erythromycin or doxycycline (see

section 12.4 on skin problems), a biopsy is diagnostic. Histology shows typical proliferation of spindle cells and small blood vessels.

In a TB/HIV patient with KS, development of a pleural effusion or progressive lung infiltrations during anti-TB treatment is probably due to KS.

Many countries have limited resources for treating KS. Treatment is often unsatisfactory. Nonsteroidal anti-inflammatory drugs (NSAIDs) may help relieve pain. Cytotoxic chemotherapy (e.g. vincristine) and radiotherapy may be available in some central hospitals but treatment response is unsatisfactory.

Lymphoma

AIDS patients are at increased risk of developing atypical aggressive lymphomas. Prognosis is poor even with cytotoxic chemotherapy.

Anaemia

Anaemia in TB/HIV patients may be due to any of the following: TB, HIV-induced marrow suppression, concurrent infections, drug side-effects. Treatment is supportive: iron and folic acid; blood transfusion if essential. In malaria-endemic regions, check a blood film for malaria parasites.

Thrombocytopenia

The main causes are HIV-induced autoimmune thrombocytopenia and drug side-effects. High-dose steroids may help if there is bleeding and the platelet count is low (less than 20×10^9 per litre).

Renal disease

HIV-related nephropathy causes nephrotic syndrome and progressive renal damage. There is no specific treatment. Treat urinary tract infections in the usual way.

Congestive cardiomyopathy

Consider HIV-related congestive cardiomyopathy in the differential diagnosis of heart failure. Treat heart failure in the usual way.

Arthropathy

Pyrazinamide often causes joint pains but rarely arthritis. HIV-related arthropathy usually affects small joints. NSAIDs may help relieve pain.

Hypoadrenalism

Cytomegalovirus can cause necrotizing adrenalitis. This is difficult to

distinguish from TB of the adrenal glands or pseudoadrenal crisis (rifampicin). Treatment is with steroid supplements.

Soft-tissue infections, e.g. pyomyositis, and sinusitis

These are common in HIV-positive patients. They are diagnosed and treated in the usual way.

12.11 PREVENTION OF HIV-RELATED OPPORTUNISTIC INFECTIONS

12.11.1 General measures

There are some general measures that may help in reducing exposure to selected pathogens in HIV-positive patients.

Pathogen	Suggested intervention
<i>Pneumocystis carinii</i>	Avoid close contact with patients who have known <i>Pneumocystis carinii</i> pneumonia
<i>Toxoplasma gondii</i>	Avoid eating undercooked red meat Avoid exposure to cats
Cryptosporidium	Avoid drinking ground water (difficult for rural communities) Avoid young household pets
<i>Histoplasma capsulatum</i>	In endemic areas avoid caves (bats) or cleaning chicken coops

12.11.2 Immunizations

Killed or inactivated vaccines pose no danger to immunosuppressed individuals.

Adults

In general, adult HIV-positive patients should **not** receive live bacteria or live virus vaccines (e.g. oral poliovirus, measles, varicella, mumps and yellow fever vaccines). It is often recommended that pneumococcal, hepatitis B and influenza vaccines be given to HIV-positive persons. However, this is rarely done in resource-poor countries within the public health sector because of cost. Also, a study in Uganda showed no benefit to using a 23-valent pneumococcal polysaccharide vaccine in HIV-1 infected adults.

Children

In children with known or suspected asymptomatic HIV infection, all EPI vaccines should be given (see section 14.4).

12.11.3 Primary chemoprophylaxis in adults

Industrialized countries

The table shows the opportunistic infections, the indications and the drug regimens commonly recommended for primary prophylaxis in industrialized countries. Primary prophylaxis refers to preventing a first episode of disease in an HIV-positive individual. Primary prophylaxis is not routinely recommended against herpes viruses (herpes simplex, varicellazoster and cytomegalovirus) or fungi.

Primary prophylaxis recommended in industrialized countries

Pathogen	Indications	Drug regimen (First Choice)
<i>Pneumocystis carinii</i>	CD4+ lymphocyte count < 200/mm ³ history of oral candidiasis unexplained weight loss AIDS-defining event (e.g.TB) fever of unknown origin	trimethoprim 80 mg/ sulfamethoxazole 400 mg (TMP-SMX) 2 tablets daily
<i>Toxoplasma gondii</i>	CD4+ lymphocyte count < 100/mm ³	trimethoprim 80 mg/ sulfamethoxazole 400 mg (TMP-SMX) 2 tablets daily
<i>M. avium complex (MAC)</i>	CD4+ lymphocyte count < 50/mm ³	azithromycin 1200 mg once per week OR clarithromycin 500 mg twice per day

Sub-Saharan Africa

Most hospitals in sub-Saharan Africa do not currently have facilities for CD4+-lymphocyte counts. Infection with MAC is rare. UNAIDS has made provisional recommendations that adults and children living with HIV/AIDS in Africa should receive TMP-SMX as part of a minimum package of care. UNAIDS has based these recommendations on

evidence from industrialized countries and studies carried out in Côte d'Ivoire on both HIV-positive TB patients and symptomatic HIV-positive patients without TB. TMP-SMX may prevent several secondary bacterial (*S. pneumoniae*, *S. typhimurium*), parasitic (*Toxoplasma gondii*, *Isospora belli*, malaria) and fungal (*Pneumocystis carinii*) infections.

The following HIV-positive adults should receive TMP-SMX in a dose of two tablets daily:

- all persons with symptomatic HIV infection;
- asymptomatic persons with CD4+ lymphocyte count < 500/mm³;
- pregnant women after the first trimester.

12.11.4 Primary chemoprophylaxis in children

TMP-SMX should be offered to all HIV-exposed infants from six weeks of age, using the following criteria:

- any child born to an HIV-infected woman irrespective of whether the woman received ART in pregnancy;
- any child who is identified as HIV-infected within the first year of life by PCR (polymerase chain reaction), HIV serology or by a clinical diagnosis of HIV infection (according to WHO or national guidelines)
- children older than 15 months who have had a *Pneumocystis carinii* event, have symptomatic HIV infection, an AIDS-defining illness or a CD4+ lymphocyte percentage less than 15%.

The dose should be 150 mg TMP/750 mg SMX per m² three times per week. Cotrimoxazole syrup may not be available: for an infant of 6 weeks, give half of a cotrimoxazole tablet (trimethoprim 80 mg/sulfamethoxazole 400 mg) daily on Monday, Wednesday and Friday.

These are preliminary recommendations, that recognize the need for more research to determine cost-effectiveness in different settings, optimal timing of the start of therapy, duration of prophylaxis and affordable alternatives.

12.11.5 Secondary chemoprophylaxis in adults

Several severe or life-threatening opportunistic infections in HIV-positive patients have high recurrence rates after initial successful treatment. Lifelong secondary prophylaxis is generally recommended. The table below shows recommended drug regimens for secondary chemoprophylaxis in adults.

Pathogen	Drug regimen (first choice)
<i>Pneumocystis carinii</i>	trimethoprim 80 mg/sulfamethoxazole 400 mg (TMP-SMX) 2 tablets daily
<i>Toxoplasma gondii</i>	sulfadiazine 500 mg 4 times daily + pyrimethamine 25 mg daily OR trimethoprim 80 mg/sulfamethoxazole 400 mg (TMP-SMX) 2 tablets daily
<i>M avium complex</i>	Clarithromycin 500 mg twice daily + ethambutol 15mg/kg once daily OR azithromycin 500 mg once daily + ethambutol 15 mg/kg once daily
<i>Cryptococcus neoformans</i>	fluconazole 200 mg once daily
<i>Histoplasma capsulatum</i>	itraconazole 200 mg twice daily
Cytomegalovirus	ganciclovir
Salmonella species (not <i>S. typhi</i>) bacteraemia	ciprofloxacin 500 mg twice daily for 6–8 months

Bartlett JG , Gallant JE. *Medical management of HIV infection*. Baltimore, MD, Johns Hopkins University School of Medicine, 2000-2001.

French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1 infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*, 2000, 355: 2106–2111.

World Health Organization. *Improving child health. IMCI: the integrated approach*. Rev.2. Geneva (WHO/CHD/97.12) (www.who.int/child-adolescent-health) 1997.

Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. *New England journal of medicine* 2000, 342: 1416–1429.

World Health Organization. *Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries*. Geneva, 2000 (WHO/FCH/CAH/00.1).

Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Geneva, 2000, WHO/UNAIDS.

Wiktor SZ, Sassin-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet*, 1999, 353: 1469–1475.

World Health Organization. *Guidelines for the clinical management of HIV infection in adults*. Geneva, 1991.

World Health Organization. *Guidelines for the clinical management of HIV infection in children*. Geneva, 1993.

World Health Organization. *AIDS in Africa: a manual for physicians*. Geneva, 1992.

World Health Organization. *Guidelines for the management of sexually transmitted infections*. Geneva, 2003.

World Health Organization. *Improving child health. IMCI: the integrated approach*. Geneva, 1997 (WHO/CHD/97.12 Rev.2)

13.1 INTRODUCTION

TB/HIV patients may receive care in different settings. These settings include the patient's home, local health centre, district hospital, and tertiary referral hospital. Coordination of care in different settings promotes continuity of care for the patient. NTP staff and general health service staff need to be aware that many HIV-positive TB patients develop other HIV-related illnesses during anti-TB treatment. Delivering interventions to reduce the frequency of opportunistic infections (e.g. cotrimoxazole prophylaxis, ART) requires effective collaboration with HIV/AIDS programmes.

TB/HIV patients sometimes know that they are HIV-positive and later on develop TB. More often, they only find out that they are HIV-positive after developing TB. In either case, the TB control programme needs to collaborate closely with other services providing support and care for HIV-positive individuals. The clinician treating TB/HIV patients is in a key position to refer patients to appropriate services.

13.2 THE EXPANDED SCOPE OF A NEW APPROACH TO DECREASE THE BURDEN OF TB/HIV

Since HIV fuels the TB epidemic, HIV programmes and TB programmes share mutual concerns. Prevention of HIV should be a priority for TB control; TB care and prevention should be priority concerns of HIV/AIDS programmes. Until recently, the efforts to control TB in HIV-infected people have mainly focused on implementing the DOTS strategy for TB control. Through the identification and cure of infectious TB cases, the strategy aims at interrupting the transmission of *M. tuberculosis* infection.

The expanded scope of a new approach to TB control in populations with high HIV prevalence comprises interventions against TB and interventions against HIV (and therefore indirectly against TB). Interventions against TB include intensified case-finding, cure and TB preventive therapy. Interventions against HIV (and therefore indirectly against TB) include condom promotion, STI treatment or prophylaxis, and ART. Previously TB programmes and HIV/AIDS programmes largely pursued separate courses. However, they need to collaborate in areas of

mutual concern in their support to general health service providers. An integrated system of HIV/AIDS and TB care uses available health service providers to ensure continuity of care for TB/HIV patients.

13.3 REFERRAL TO LOCAL HIV/AIDS CARE SERVICES

One of the important features of a successful NTP is integration of TB control activities with the general health services (see Chapter 2). This means that at the district and primary health care levels, the general health service staff manage TB patients according to NTP guidelines. NTP staff provide support.

General health service staff and NTP staff need to know what local HIV/AIDS services are available for HIV-positive patients. The Ministry of Health may run a system for accreditation of the range of local providers of HIV/AIDS services. They include the government, nongovernmental organizations (NGOs), community organizations, private practitioners and employer health services. Often it is possible to refer patients directly to these providers of HIV/AIDS services.

Some TB/HIV patients choose not to accept referral to HIV/AIDS services. It is important to respect patients' wishes and confidentiality. In many districts there is a district coordinator for HIV/AIDS. District NTP staff liaison with the district coordinator for HIV/AIDS promotes the easy referral of TB/HIV patients to HIV/AIDS services.

In many towns and cities there are now HIV counselling and voluntary testing centres. Some of the people attending these centres may have TB. A study in Kampala, Uganda, showed that 6% of people attending the HIV counselling and voluntary testing centre had undiagnosed TB. NTP collaboration with these centres is important. Staff in the centres should ask clients about chronic cough and refer TB suspects to the NTP for sputum microscopy.

13.4 BENEFITS OF SUPPORT FROM LOCAL HIV/AIDS CARE SERVICES

The HIV/AIDS care services available vary from place to place. They include HIV/AIDS care groups within the general health services, HIV/AIDS community support groups and HIV/AIDS home care schemes. TB/HIV patients may gain the following benefits from the support of local HIV/AIDS services:

- access to voluntary counselling and HIV testing;
- knowledge about safer sexual behaviour and use of condoms;
- preventive therapy for HIV-related opportunistic infections;
- (e.g. trimethoprim-sulfamethoxazole, TMP-SMX);
- early identification and treatment of any new infections, including sexually transmitted infections;
- symptomatic treatment in end-stage disease;
- emotional support;
- support for the family;
- possible access to ART.

13.5 A FRAMEWORK FOR HIV/AIDS CARE THAT INCORPORATES INTERVENTIONS TO ADDRESS TB

Close collaboration is necessary between different health service providers at the different levels of the health care system. This will facilitate the referral of patients along the “continuum of care”.

13.5.1 Home and community care

Local responses involve people in their homes, neighbourhoods and community organizations. They take responsibility for addressing HIV/AIDS as a shared community concern. Community interventions to support PLWH should include supporting TB patients to complete treatment. Some PLWH regard TB as an ominous sign of AIDS. A more optimistic view of the development of TB is as an opportunity to seek help for a treatable condition. The prospect is of an increased healthy life expectancy. Targeted information, education and communication interventions can encourage the more optimistic view.

General health services staff can refer patients directly to HIV/AIDS care services. Community care means providing the patient with access to care as close to home as possible. Some HIV/AIDS care services provide home care for AIDS patients. The home care provider may be a health care worker or community volunteer. See WHO's *AIDS home care handbook* for more information.

Home care alone is not enough for a TB/HIV patient. TB patients need to continue to receive their anti-TB treatment, directly observed by a trained and supervised home care provider. This training and supervision requires collaboration between the HIV/AIDS home care scheme and the NTP. Also, the HIV/AIDS home care provider can recognize problems with anti-TB treatment and refer patients as necessary to the NTP.

13.5.2 Primary care

Primary care measures for detecting and treating common HIV-related diseases should include diagnosis and treatment of infectious (sputum smear-positive pulmonary) TB. Primary care staff need to detect TB cases among persons presenting with, or found through screening to have, symptoms of TB. The most important symptom is prolonged cough. Detection of infectious TB cases requires access to quality-assured TB sputum microscopy. Special attention to case detection is necessary in congregate settings (e.g. prisons, health care facilities) and among people attending VCT centres.

There are two preventive treatments that should be available at primary care level for the prevention of common HIV-related diseases. Isoniazid is effective as preventive treatment of TB. Cotrimoxazole may prevent common bacterial infections.

Health care workers and HIV-infected patients are often exposed to the risk of TB in health facilities. Health services have a responsibility to implement measures to decrease nosocomial risk of TB in health facilities. They also need to protect health care workers from occupational exposure to HIV.

Information for communicable disease surveillance passes from primary care level to those responsible at district level. This includes reporting of TB cases and recording of TB treatment outcomes. Systems of surveillance of HIV-related diseases other than TB are currently lacking or poorly developed at all levels of care. TB surveillance can be a starting-point for the development of these systems.

An effective NTP ensures integration of TB diagnosis and treatment activities with general health service provider activities (see Chapter 2). So primary health care staff are in a good position to identify and treat common HIV-related problems during or after anti-TB treatment. Good communication between general health service staff and HIV/AIDS care workers is important for continuity of care of TB/HIV patients.

The IMCI strategy, developed by WHO, provides management guidelines for sick children. In outpatient settings, the aim of the strategy is to improve diagnosis and treatment of childhood illnesses. In the home setting, IMCI has several aims. These include promoting appropriate care-seeking behaviour, improved nutrition and preventive care, and ensuring the child receives the care prescribed.

13.5.3 Secondary care

Measures applicable at secondary care level are additional to those applicable at the primary care level. Measures for detecting and treating common HIV-related diseases should include diagnosis and treatment of sputum smear-negative pulmonary TB and extrapulmonary TB. Diagnosis usually requires investigations often available only at secondary level, e.g. X-ray and biopsy.

Primary health care staff can manage many HIV-related problems in health centres and dispensaries. Sometimes TB/HIV patients develop problems requiring investigations and treatment unavailable at primary health care level. Then they need to be referred to the district hospital, either to the outpatient department or for admission. After treatment, often the district level staff can refer the patient back to the primary care or community level. Good channels of communication promote continuity of care.

The IMCI strategy includes management guidelines (see Suggestions for Further Reading) for district level care of children with HIV-related problems.

13.5.4 Tertiary care

Measures applicable at tertiary care level are additional to those applicable at the secondary care level. They include diagnosis and treatment of complications of common HIV-related diseases. Specialist management of complicated forms of TB (e.g. peritoneal and pericardial TB) is often available only at the tertiary level.

District level staff sometimes are faced with difficult problems of diagnosis or treatment. The patient may benefit from transfer to a tertiary referral hospital. It is usually wise to obtain advice on the telephone before transferring the patient. This is to ensure that the specialist agrees that the patient is likely to benefit from the referral.

The table below shows HIV/AIDS and TB care integrated at different levels of the health care system. Availability of interventions depends on whether a country is low-, middle- or high-income.

Level of care	Low-income	Middle-income	High-income
Home and community	Information and education Condoms Breastfeeding advice Palliative care Support groups	As per low-income level plus a) terminal care with health professional input b) formula feeds for infant nutritional supplementation	As per middle-income level plus a) terminal care with advanced technology b) domiciliary treatment of HIV-related diseases
Primary care (health centre)	VCT for HIV Prevention of HIV transmission Detection and treatment of common HIV-related diseases (e.g. TB) Prevention of common HIV-related diseases Pain relief Intensified TB case-finding Disease surveillance (e.g. TB) Decreased nosocomial transmission and protection of health workers	As per low-income level plus a) antiretroviral drugs for prevention of mother-to-child transmission b) prevention of fungal infections	As per middle-income level plus clinical and laboratory monitoring of HIV progression

Secondary care (district hospital)	As for primary care level plus a) safe blood b) terminal in-patient care c) possible access to ART	As per low- income level plus disease surveillance of less common HIV-related diseases	As per middle- income level plus a) diagnosis and treatment of uncomplicated HIV-related illness b) access to ART c) post-exposure prophylaxis
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13.6 THE PRIVATE SECTOR

The private sector includes private medical practitioners and traditional healers. Many patients choose to go to one or both.

13.6.1 Private medical practitioners

Ideally there should be close collaboration between private practitioners and the NTP. This can result in improved management of TB patients according to NTP guidelines. Private practitioners serve the community and can guarantee their TB patients good care by following NTP guidelines. Private practitioners can register TB patients with the NTP and share continued management. Private practitioners do not have to give up their patients entirely to the NTP. Some TB/HIV patients prefer to go to a private practitioner for reasons of confidentiality. In a country where the NTP is very good, many patients will prefer the NTP to a private practitioner. More countries are now introducing schemes for training and accreditation of private practitioners as TB and HIV/AIDS care providers.

13.6.2 Traditional practitioners

TB is a difficult disease for traditional practitioners. Many do not understand it, do not know how to cure it, and do not have the appropriate drugs. General health services can collaborate with traditional practitioners. For example, traditional practitioners can recognize TB suspects and refer them. Traditional healers often have an important role in supporting PLWH when they are ill.

13.7 OPERATIONAL RESEARCH AIMED AT IMPROVING INTEGRATED TB AND HIV/AIDS PREVENTION AND CARE

TB and HIV programmes need to collaborate in implementing the interventions set out in the above framework (see section 13.5). They comprise HIV interventions relevant to TB control and TB interventions relevant to HIV/AIDS care. TB and HIV programmes need to mainstream these interventions as part of their routine activities. Operational research is necessary to improve the delivery of integrated TB and HIV/AIDS prevention and care.

13.7.1 Promoting voluntary counselling and testing (VCT) for HIV as an entry point to better TB care

There are several benefits of promoting VCT for HIV (see Chapter 6). One potential benefit is improved access to various HIV prevention and care activities, including TB interventions. The ProTEST initiative, coordinated by WHO, is one of several operational research initiatives on integrated HIV/AIDS and TB care. This initiative aims to promote HIV voluntary testing as a key to a more coherent response to TB in settings with high HIV prevalence. The name “ProTEST” reflects the promotion of voluntary HIV testing, as an entry point for access to HIV and TB prevention and care. The initiative supports district-level experience in several field sites. These sites are combining efforts against HIV and TB to reduce the combined TB/HIV burden. Local experience will inform the development of a district-based model for the integrated delivery of health care services. Integrated delivery involves all service providers, e.g. government, NGOs, community and the private sector. The results from the field sites will inform the development of policy guidelines for scaling up the model, if shown to be effective and affordable.

13.7.2 The Practical Approach to Lung Health (PAL)

Strengthened general health services are also crucial to ensure that HIV-infected persons have access to care for common HIV-related diseases. These include the respiratory diseases that constitute a large part of the burden of HIV-related disease. The use of a syndromic approach may improve the care of patients with common respiratory problems by general health service providers. The Practical Approach to Lung Health (PAL) represents WHO’s contribution to promoting this approach by developing guidelines and algorithms.

Gilks C, Floyd K, Haran D, Kemp J, Squire B, Wilkinson D. *Care and support for people with HIV/AIDS in resource-poor settings*. London, UK Department for International Development, 1998 (Health and Population Occasional Paper).

Godfrey-Faussett P, Maher D, Mukadi YD, Nunn P, Perriens J, Raviglione M. How can HIV voluntary testing contribute to a more coherent response to tuberculosis in high HIV prevalence settings? *Bulletin of the World Health Organization*, 2002, 80: 939-945.

World Health Organization. *Provision of HIV/AIDS care in resource-constrained settings. Report of a meeting*. Geneva, 1994.

World Health Organization. *A strategic framework to decrease the burden of TB/HIV*. Geneva, 2002 (WHO/CDS/TB/2002.296).

World Health Organization. *Improving child health. IMCI: the integrated approach. Rev.2*. Geneva, 1997 (WHO/CHD/97.12) (www.who.int/child-adolescent-health).

World Health Organization. *Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries*. Geneva, 2000 (WHO/FCH/CAH/00.1).

World Health Organization. *Guidelines for collaborative TB and HIV programme activities*. Geneva, 2003 (WHO/CDS/TB/2003.319; WHO/HIV/2003.01).

World Health Organization. *AIDS home care handbook*. Geneva, 1993.

World Health Organization. *Report of the first international review meeting. Practical Approach to Lung Health Strategy, 4–6 September 2002, Rabat, Morocco*. Geneva, 2003 (WHO/CDS/TB/2003.324).

World Health Organization. *Community contribution to TB care: practice and policy*. Geneva, 2003 (WHO/CDS/TB/2003.312).

14.1 INTRODUCTION

From the public health point of view, the best way to prevent TB is to provide effective treatment to people with infectious TB. This interrupts the chain of transmission. Good treatment programmes are the best prevention programmes. HIV-infected individuals are particularly susceptible to infection with *M. tuberculosis* and the development of TB. What are the ways of protecting HIV-infected individuals from exposure to TB in health care settings? What is the role of BCG? HIV-infected individuals who are already infected with *M. tuberculosis* have a high risk of developing active TB. Can we do anything to decrease this risk? This chapter addresses these questions.

14.2 PROTECTION OF HIV-POSITIVE PERSONS AGAINST EXPOSURE TO TB

HIV-positive patients and staff in health units face daily exposure to TB. The risk of exposure is greatest in adult medical wards and TB wards where there are many PTB cases. Often the wards are crowded and badly ventilated. We do not yet know the size of this risk.

Training of health care workers about the importance of infection control measures should assist in the implementation of control activities. Prompt diagnosis and treatment of patients with sputum smear-positive PTB helps to reduce exposure to TB. Prompt outpatient diagnosis and treatment of PTB patients avoids hospital admission. This is an advantage in decreasing exposure to TB in hospital wards. In some NTPs there is a move away from an inpatient intensive phase towards outpatient management.

Known HIV-positive health workers should not work with PTB patients. They should therefore not work in TB wards or adult medical wards.

14.2.1 Environmental control

Good ventilation helps reduce TB transmission indoors. Sunlight is a source of ultraviolet light, which can kill TB bacilli. So, ideally, wards should have large windows. Laboratories that process sputum specimens for AFB should follow published guidelines to minimize TB transmission to laboratory workers.

PRACTICAL POINT

In wards, outpatient clinics, sputum collection rooms, microbiology laboratories, surgical and autopsy suites, keep the doors closed and the windows open.

14.2.2 Face-masks

A face-mask decreases the risk that the person wearing the mask can infect other people. So a TB suspect or a TB patient, if possible, should wear a mask when moving from one part of a hospital to another. Health workers often wear a mask for protection against TB, e.g. when working on the TB ward. In fact, a mask is generally not very good at protecting the person wearing the mask from inhaling other people's infectious droplets. The exception is when the health worker is supervising a cough-inducing procedure, e.g. bronchoscopy or sputum induction using nebulized hypertonic saline. HEPA (high efficiency particulate air) filter masks can prevent the inhalation of very small droplet nuclei. However, HEPA masks have certain drawbacks. They are very expensive, have to be fitted correctly to be effective, and need to be changed regularly.

14.2.3 Patient education

Health workers should teach TB suspects and TB patients simple measures to decrease the risk of transmitting TB. These include covering the mouth with the hand when coughing, and using sputum pots with lids. When examining TB patients or suspects, ask them to turn their head away, to avoid coughing directly at the health worker.

14.2.4 Pulmonary TB suspects

In the majority of cases, PTB suspects attend as outpatients for the diagnosis of TB. In some cases it is necessary to admit PTB suspects to hospital. If possible admit them to a separate ward from other patients. There are often no facilities to separate PTB suspects from other patients. At least try to keep PTB suspects in a part of the ward away from other patients. Staff should also encourage PTB suspects to spend daylight hours outside the ward if the weather is good. Sputum for smear examination should be collected as rapidly as possible. The laboratory should process and examine sputum smears rapidly and efficiently. Hospitals should ensure a minimum of delay in delivering smear examination results back to the wards. Adults accompanying small children with possible TB may also themselves have TB and be the source of the child's disease.

14.2.5 Patients with sputum smear-positive pulmonary TB

Ideally, sputum smear-positive PTB patients should start anti-TB treatment as soon as the smear results are known. In many NTPs, sputum smear-positive PTB patients spend at least part, and often all, of the intensive phase of anti-TB treatment in hospital. Isolation of these patients in TB wards helps reduce the risk of TB exposure to other patients. Do not admit a patient to the TB ward until you have made the diagnosis of TB. TB suspects with HIV infection and high susceptibility to TB should avoid exposure to TB. They may turn out not to have TB.

14.2.6 Patients with multidrug-resistant TB (MDR-TB)

In many cases it is impossible to predict or to detect MDR-TB, and in many countries this information never becomes available. However patients with known MDR-TB require special management at a referral centre. These patients may have prolonged periods of infectiousness. It is therefore necessary to minimize the possibility of contact with other patients who do not have TB or do not have MDR-TB. They should be in a **separate** area or facility, preferably in well-ventilated individual patient rooms. If this is not feasible, then it is necessary to establish a ward or an area of a ward for MDR-TB.

PRACTICAL POINT

Patients with MDR-TB must be separated from patients who have HIV infection. In many countries, outbreaks of MDR-TB have spread very rapidly on wards for AIDS patients.

14.3 ROLE OF BCG IN PREVENTING TB IN HIV-INFECTED INDIVIDUALS

14.3.1 Background

BCG (Bacille Calmette-Guerin) is a live attenuated vaccine derived originally from *M. bovis*. The route of injection is intradermal. The usual dose is 0.05 ml in neonates and infants under the age of 3 months, and 0.1 ml in older children. In countries with high TB prevalence, WHO recommends a policy of routine BCG immunization for all neonates.

The benefit of BCG is in protecting young children against disseminated and severe TB, e.g. TB meningitis and miliary TB. BCG has little or no effect in reducing the number of adult cases of PTB.

14.3.2 BCG protection against TB in HIV-infected children

It is not known if HIV infection reduces the protection conferred by BCG against TB in children. There is some evidence that conversion to a positive tuberculin test after BCG is less frequent in HIV-infected children. The significance of this finding for protection against TB is not clear.

14.3.3 BCG safety in HIV-infected children

There have been a few case reports of local complications and disseminated BCG infection after BCG immunization of HIV-infected children. However, prospective studies comparing BCG immunization in HIV-infected and uninfected infants showed no difference in risk of complications. So, in the vast majority of cases, BCG immunization is safe.

14.3.4 WHO recommended policy on BCG and HIV

WHO recommended policy depends on the TB prevalence in a country, as shown below. In a country with high TB prevalence, the possible benefits of BCG immunization outweigh the possible disadvantages.

Country TB prevalence	WHO recommended policy
high	BCG for all children (according to standard programme) except children with symptoms of HIV disease/AIDS
low	Do not give BCG immunization to HIV-infected children

Low prevalence of TB is defined as

- average annual notification rate of smear-positive PTB for the past 3 years equal to or less than 5/100000,
- average annual notification rate of TB meningitis in children under 5 years for the past five years less than one case per million, and
- average annual risk of tuberculous infection 0.1% or less.

BCG is not the only immunization in the EPI that may help to protect a child against TB. Measles and whooping cough lower a child's resistance to TB. So whenever you treat a child for TB, check his or her immunization record. If the child has not received scheduled immunisations, encourage the mother to bring him or her for immunizations, once symptoms of TB have resolved. WHO has collaborated with UNICEF in establishing guidelines for immunization. The recommendation is that individuals with known or suspected asymptomatic HIV infection **should** receive all EPI vaccines, according to national schedules.

14.5 PREVENTIVE TREATMENT

Preventive TB treatment refers to decreasing the risk of a first or recurrent episode of TB. A first episode of TB may occur in someone exposed to infection or with latent infection. A recurrent episode of TB occurs in someone who has previously had TB.

- a) Aimed at decreasing the risk of a first episode of TB

People at high risk of developing TB may benefit from preventive treatment, as an intervention currently for individual benefit rather than as a public health measure to control TB. For example, WHO has for many years recommended isoniazid preventive treatment (IPT) for children who are household contacts of infectious index cases of TB, and who, after screening, are found not to have TB.

WHO and UNAIDS recommend IPT for 6 months for tuberculin-positive HIV-infected individuals who do not have TB. However, even where tuberculin testing is not feasible, IPT may still be valuable in HIV-infected individuals at high risk of TB. Among PLWH, IPT is likely to provide protection against the risk of developing TB through two mechanisms. Firstly, by decreasing the risk of progression of recent infection, and secondly, by decreasing the risk of reactivation of latent *M. tuberculosis* infection. In populations with high TB prevalence, the duration of benefit following completion of a 6-month course of IPT is limited (up to 2.5 years). This is probably due to continued exposure to *M. tuberculosis* infection. The duration of protection depends on the duration of preventive treatment.

- b) Aimed at decreasing risk of a recurrent episode of TB

Among TB patients who complete SCC, the recurrence rate is higher in HIV-positive than in HIV-negative TB patients. Post-treatment prophylaxis (for example with isoniazid) can decrease the risk of TB recurrence in HIV-infected individuals, although it does not prolong survival. Further studies are needed to confirm the benefit, establish the optimum regimen (drugs and duration), and assess operational feasibility, before treatment aimed at decreasing risk of TB recurrence can be recommended.

14.5.1 Target groups for preventive treatment

A 6-month course of preventive treatment with daily isoniazid (5 mg/kg) is effective in preventing progression of *M. tuberculosis* infection to disease. However, preventive treatment for all individuals infected with *M. tuberculosis* is not a recommended TB control strategy. It is not feasible to try to identify all individuals infected with *M. tuberculosis*. TB disease develops in only 10% of these individuals. So it is not cost-effective to identify and treat all infected individuals in order to prevent disease in 10%. However, it is possible to identify certain groups at high risk of progressing from *M. tuberculosis* infection to TB disease. It may be cost-effective to target preventive treatment at these high-risk groups. Young children are at special risk, especially if they are HIV-infected. HIV infection, in children and in adults, is a potent cause of progression of *M. tuberculosis* infection to TB disease (see Chapter 1).

Infants of mothers with PTB

A breastfeeding infant has a high risk of infection from a mother with PTB, and a high risk of developing TB. The infant should receive 6 months' isoniazid treatment, followed by BCG immunisation. An alternative policy is to give 3 months' isoniazid, then perform a tuberculin skin test. If the skin test is negative, stop the isoniazid and give BCG. If the skin test is positive, continue another 3 months' isoniazid, then stop isoniazid and give BCG.

Children under 5 years of age

It is important to screen child household contacts of adults with sputum smear-positive PTB (see Chapter 4). Screening identifies those children under 5 years of age without symptoms. Give these children 6 months' isoniazid preventive treatment. Children under 5 years of age with symptoms need to be investigated for TB. If investigations show TB, the child should receive anti-TB treatment. If investigations do not show TB, the child should receive isoniazid preventive treatment.

HIV-infected individuals

Controlled clinical studies have shown that IPT reduces the risk of TB disease in HIV-positive individuals also infected with *M. tuberculosis*. The evidence of *M. tuberculosis* infection is a positive tuberculin skin test. In HIV-positive individuals, an extra benefit of a reduced risk of TB may be a reduced rate of progression of HIV infection.

14.5.2 Role of isoniazid preventive treatment in HIV-positive individuals

The theoretical benefits of IPT are attractive. The table shows the potential disadvantages and necessary precautions.

Potential disadvantage	Necessary precaution
risk of drug toxicity (especially liver damage)	do not give to people with chronic disease or who regularly drink excessive amounts of alcohol
emergence of drug resistance (if the patient has undetected TB disease and not just <i>M. tuberculosis</i> infection)	in all cases exclude TB disease by CXR, in patients with cough of 3 weeks' duration or more , do sputum microscopy
diversion of resources from NTP activities	funding must be from sources other than NTP (e.g. AIDS control programme, voluntary sector) or extra funding sources for the NTP must be found

14.5.3 WHO/UNAIDS recommendations on preventive therapy against TB in HIV-positive persons

Services needed before setting up a preventive therapy service

Before a preventive therapy service is considered, the following prerequisites should be in place:

- adequate capacity for HIV counselling, which should include IEC about TB;
- sufficient trained health care staff;
- linkage between HIV care and TB control services;
- good TB control programme with high cure rates and combined default/failure rates at the end of treatment of less than 10%.

Recommendations for a preventive therapy service

- Preventive therapy against TB should be part of a package of care for people living with HIV/AIDS.
- Preventive therapy should be used only in settings where it is possible

to exclude active TB and to ensure appropriate monitoring and follow-up.

- Information about TB and preventive therapy should be made available to HIV-positive people.
- Preventive therapy should be provided from within settings that include voluntary counselling and testing (VCT) services for HIV.
- The priority for TB control programmes continues to be the detection and cure of infectious TB cases.
- Procurement and supply of anti-TB drugs must be regulated by national authorities in order to prevent the development of drugresistance.

Steps in the delivery of preventive therapy

Those who have a positive HIV test should receive:

counselling on TB

screening for active TB

Ask whether persons have a cough: those with a cough should be screened for TB; those with no cough should have a CXR; if the CXR is normal proceed to next step

targeting those most likely to benefit

Preventive therapy is recommended for tuberculin-positive HIV-positive persons who do not have active TB. Sometimes it is not possible to perform tuberculin testing. In these circumstances, HIV-positive persons may still be considered for preventive therapy if they are

- a) living in high TB prevalence areas
- b) health care workers
- c) household contacts of TB patients
- d) prisoners
- e) miners

provision of preventive therapy to those without active TB

Isoniazid is the recommended drug - 5 mg/kg (max. 300mg) given as a daily, self-administered therapy for 6 months. Individuals are seen monthly and receive one month's supply of drugs at each visit

monitor for adherence and toxicity

Those who interrupt therapy should be followed up. The aim is to provide at least 6 months of therapy during a one-year period Stop isoniazid in those who develop symptoms and signs of active TB or hepatitis.

evaluation of outcome

Regularly assess the effectiveness of preventive therapy (attendance, adherence, toxicity, withdrawals, completion of therapy)

Conclusions

IPT is not an alternative to the DOTS strategy for controlling TB. However, there are many opportunities for providing IPT to people living with HIV which could prevent many cases of active TB. Systems need to be developed to greatly increase the accessibility of preventive therapy to people living with HIV in settings of high TB prevalence. At the same time it is crucial to avoid compromising NTP quality.

SUGGESTIONS FOR FURTHER READING

Harries AD, Maher D, Nunn P. Practical and affordable measures for the protection of health care workers from tuberculosis in low-income countries. *Bulletin of the World Health Organization*, 1997, 75: 477–489.

Reider HL. *Interventions for tuberculosis control and elimination*. Paris, International Union Against Tuberculosis and Lung Disease, 2002.

World Health Organization. *Childhood tuberculosis and BCG vaccination. BCG - gateway to EPI*. Geneva, 1989.

World Health Organization. *Global Programme for Vaccines and Immunization. Immunization Policy*. Geneva, 1995.

World Health Organization. *Guidelines for the management of drug-resistant tuberculosis*. Geneva, 1996 (WHO/TB/96.210, Rev.1).

World Health Organization. Preventive therapy against tuberculosis in people living with HIV. *Weekly epidemiological record*, 1999, 74: 385–400.

World Health Organization. *Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings*. Geneva, 1999 (WHO/TB/99.269).

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