

Chapter 1: The Development of the 2006 Updated Clinical Practice Guidelines for Tuberculosis

I. Background

Rationale

This document updates the previous Clinical Practice Guidelines for Tuberculosis released in the year 2000. It is written for all physicians and other healthcare professionals of various specialties and should be helpful in the various settings of clinical practice- whether private, public, mixed, hospital, institutional and so on. The scope of this Clinical Practice Guidelines (CPG) was broadened to include key issues in tuberculosis (TB) management and was not limited to pulmonary TB.

The 2000 Philippine Clinical Practice Guidelines (CPG) on the Diagnosis, Treatment and Prevention of Pulmonary Tuberculosis was a joint effort of 16 professional societies and agencies, with major participation of the Philippine Society for Microbiology and Infectious Disease (PSMID), Philippine College of Chest Physicians (PCCP), TB Control Service of the Department of Health, Philippine Academy of Family Physicians (PAFP) and the Philippine Coalition Against Tuberculosis (PhilCAT). A testament to the cooperative spirit of stakeholders involved in TB Control, it was awarded the 2003 Outstanding Monograph by the National Academy of Science and Technology. However, since its publication in 2000, numerous recent developments in the local TB scene have occurred, including the phenomenal expansion of the use of the DOTS strategy, reaching nearly 100% coverage in the public sector by 2003, the introduction of Public-Private Mixed DOTS (PPMD), the implementation of DOTS Plus for multi-drug resistant TB (MDR-TB), the formulation of the Comprehensive and Unified Policy for TB Control (CUP), introduction of fixed-dose combinations (FDC), conceptualization and implementation of the TB Diagnostic Committees, and many more. In addition, medical literature on TB has expanded at rapid rate since the last review. These developments make it imperative to update the 2000 CPG on TB.

Objectives

The objective of this Update is the same as the 2000 CPG: to develop a clinical practice guideline based on current medical evidence to help

physicians improve the management of tuberculosis among Filipino adults.

More specifically, the 2006 CPG Update aims to:

1. To determine new areas or issues on the diagnosis, treatment and control of pulmonary TB which need to be reviewed and discussed.
2. To update the TB CPG with recent clinical data and current developments.
3. To develop guidelines for the management of extrapulmonary TB.

Rationale Behind the 2006 TB Update:

- Updated recommendations and evidence will further strengthen the National Tuberculosis Program (NTP) of the Department of Health (DOH).
- Updated reports will showcase the positive results and benefits of managing all TB patients thru the globally-endorsed strategy of Directly-Observed Therapy, Short Course (DOTS) as experienced in the Philippines.
- Updated commitment of the professional societies will be an engine to merge efforts of the private practitioners into the government infrastructure of the NTP.
- Updated information will empower all health practitioners in the Philippines so that they can manage TB using best practices and allow them to contribute towards worldwide and national TB targets.
- Updated information will be in line with the International Standards for Tuberculosis Care (ISTC).

Box 1: Rationale Behind 2006 Update of Philippine Clinical Practice Guidelines for Tuberculosis

II. Methods

The 2006 Clinical Practice Guidelines Update on Tuberculosis was developed through the efforts of various committees as follows: Steering Committee, Technical Working Committees (TWCs), Advisory Committee, Technical Review Panel and the External Reviewers. The membership of the committees included individuals who have past or current interest or work in tuberculosis as well as representatives nominated from participating societies and agencies (Appendix A). Together, these committees formed

the 2006 Tuberculosis Clinical Update Taskforce. An overall Steering Committee coordinated the activities. The most important task of reviewing the 2000 CPG, evaluating available evidence and coming up with an evidence-based draft was done by three large technical working committees which divided the scope of the guideline to: the Diagnostic Committee, the Treatment Committee and the Control and Prevention Committee. The Advisory Committee provided comments, suggestions and ideas during the whole process. The Consensus Group approved recommendations of the Basic Issues and Questions to be tackled in the Update and later voted on and approved the Consensus Statements. The External Advisers made their comments after the Final draft is made. The Secretariat was manned by staff provided by the Philippine Tuberculosis Initiatives in the Private Sector (PhilTIPS) and the PSMID. Partial funding was obtained from the PhilTIPS. Numerous pharmaceutical companies also provided logistic support and hosted several meetings of the technical working committees and the plenary meetings of the Consensus Group.

An initial general assembly of all taskforce members was held on May 13, 2005 at the Lung Center of the Philippines. This First Plenary Meeting was dedicated to formulating the key questions which must be addressed in the TB Update.

In the next six months that followed, the bulk of the task of reviewing the evidence and appraising recent medical literature as well as formulating the initial statements of recommendations was primarily completed by the three TWCs on: Diagnosis of TB, Treatment of TB and Control of TB. Each technical committee was composed of representatives from key societies and included: the Philippine Society of Microbiology and Infectious Diseases (PSMID), the Philippine College of Chest Physicians (PCCP), the Philippine Academy of Family Physicians (PAFP), the Philippine College of Radiology (PCR) and the Philippine College of Occupational Medicine (PCOM) and the Department of Health (DOH). Several small consultative meetings were held with advisers during this period. By October 2005, after intensively working on critical appraisal and formulating evidence-based recommendations, the three committees together submitted their technical reports with their draft statements to the Advisory Committee. This was put together and comprised the First Draft of the TB Update and consisted of seventy Statements of Recommendations. Revisions were incorporated based on the reviews and comments of the members of the Advisory Committee. The Second Draft was put together by January 2006.

The Second Plenary Meeting was held on February 15, 2006. In this

session, Consensus on the CPG statements from representatives of the professional societies on all of the issues and questions were drawn by secret balloting. Recommendations were graded according to level of evidence as appraised by the technical working groups. To reach a consensus, at least 75% of those present must agree on the particular recommendation.

Statements with unresolved and difficult issues were consulted with the Advisory Committee on March 2006. A second round of secret balloting among the Consensus Panel was done during March to April 2006. After this second round, consensus was reached for all the statements of recommendations.

The First Public Forum to present the final recommendations of the updated CPG was held on May 6, 2006 at the Philippine College of Physicians Annual Convention. The audience in this forum was mostly internists.

The Third Draft of the TB Update was forwarded for external review by the External review committee and by the Board of each of the participating professional societies on August 6, 2006.

The Final Version of the TB Update was submitted for publication on September 30, 2006.

System of Grading Recommendations and Levels of Evidence

The grading of the recommendations and levels of evidence used for this 2005 guideline adopted a grading system similar to the one used in the 2000 CPGs and are as follows:

Grading of Recommendations:

- Grade A:** The recommendation is based on strong evidence and comes from at least one study at Level 1
- Grade B:** The recommendation is based on moderately strong evidence and comes from at least a study at Level 2
- Grade C:** The best evidence available may be a study at Level 3 or lower; or may be an expert opinion

Levels of Evidence for Rating Studies on DIAGNOSIS

- Level 1:** All 5 of the following criteria are satisfied
 - (a) There was an independent interpretation of the result of the diagnostic test without knowledge of the results of the gold standard.

- (b) There was an independent interpretation of the result of the gold standard without knowledge of the result of the diagnostic test.
- (c) The study participants consisted of patients suspected but not known to have the disorder of interest.
- (d) The diagnostic test and gold standard are both described in sufficient detail to allow reproducibility.
- (e) The study population consists of at least 50 patients with, and 50 patients without the disorder of interest.

Level 2:	4 of the 5 criteria are met
Level 3:	3 of the 5 criteria are met
Level 4:	2 of the 5 criteria are met
Level 5:	1 of the 5 criteria are met
Level 6:	None of the criteria are met

Levels of Evidence for Rating Studies on TREATMENT

Level 1:	A well-designed meta-analysis or well-designed randomized controlled trial that demonstrates a statistically significant difference in at least one major outcome OR if the study failed to show a statistically significant difference, the sample size is adequate to exclude a 25% difference in relative risk with 80% power
Level 2:	An RCT that does not meet the Level 1 criteria
Level 3:	A non-randomized trial with concurrent controls
Level 4:	Before-after study or case series with historical controls
Level 5:	Case series without controls

Chapter 2: Current State of Tuberculosis in the Philippines

I. Burden of Illness of Tuberculosis in the Philippines

Tuberculosis (TB) is still a major public health concern in the Philippines, ranking as the sixth (previously fifth) leading cause of morbidity and mortality based on recent local data.^{1,2}

Globally, the Philippines is ninth, previously ranked seventh, among 22 high burden countries and ranks third, previously second, in the Western Pacific region based on its national incidence of 133 new sputum smear-positive cases per 100,000 population in 2004 (from 145 new cases per 100,000 in 2002)³

The Philippine Health Statistics recorded a total of 27,000 deaths from tuberculosis, at the turn of the century.¹ The National Tuberculosis Program (NTP) reported 130,000 to 140,000 TB cases, mainly discovered and treated in government health units, of which 60% are highly infectious smear-positive cases.⁴ As of 2004, the case detection rate (CDR) improved from 53% in 2003 to 68% and the cure rate increased from 75% in 2003 to 80.6%. Both are however still below global targets of 70% and 85% respectively.

The involvement and participation of the private sector in the NTP implementation was started in 2003 and private-public mix DOTS (PPMD) facilities were established. An additional 3% was contributed by the private sector to the CDR, increasing it to 71%. Success rates, which include cured and completed treatment cases, have reached 88.5% for the past 3 years. The most important effect of PPMD is that it resulted in a marked improvement of the public sector performance in the PPMD site itself, from 53% to 68%.

A third national prevalence survey is due in 2007, to determine the impact of the revised NTP ten years since DOTS has been implemented nationwide.

Economic Impact of Tuberculosis

Tuberculosis in the country exacts serious economic consequences caused by loss of income due to disability and premature death. Based on the incidence⁵, mortality data⁶, and the 1997 Philippine population by age and gender, assuming a duration of illness at 2.2 years, Peabody and

colleagues estimated that 514,000 years of healthy life or disability adjusted life years (DALYs) are lost, due to illness and premature death from TB each year, affecting predominantly males and the most productive age group.⁷ The actual number of DALYs may be higher due to under reporting or misreporting.

Based on treatment effects regression analysis of TB impact on daily wage rates using 1998 APIS data at prevailing prices in 2002, men with TB earn Philippine Peso (PhP) 451 less than those without TB; and females with TB earn PhP 216 less than those without TB. This translates to almost PhP 8 billion loss of income per year for the country. Foregone income is approximately PhP 26.4 billion due to premature deaths from TB, which does not yet include direct and indirect cost of treatment, productivity losses and income loss due to disability from TB.⁷

The prevalence of tuberculosis is highest among the poor, elderly and urban dwellers.

Multi-Drug Resistant Tuberculosis (MDR-TB)

Based on the 1997 National Prevalence Survey (NPS)⁸, the incidence of MDR-TB, defined by the WHO as in vitro resistance to both isoniazid and rifampicin, is 4.3%. In the Sentinel Surveillance Study involving 4 sites in the Philippines (the National Capital Region, Zamboanga, Cebu, and La Union), the MDR-TB rate was 5.1%, while the Multicenter TB Study done in 1998 covering seven regions reported 9.7%. Looking at selected areas in the country involving 265 patients with positive AFB smears and TB cultures, the rate of MDR-TB was 6.4% in Metro Manila, 9.6% in La Union, 4.4% in Zamboanga, and 5.2% in Leyte.⁹

Tertiary hospitals in the Philippines also show alarming rates. Fifty-two percent of culture-positive previously treated patients progressed to become treatment failures and eventually became MDR-TB in a study by Quelapio and colleagues.¹⁰ Investigating the susceptibility of MDR-TB strains from 50 patients undergoing re-treatment to second line-agents, another hospital noted high resistance rates against ofloxacin (20%), ethionamide (34%), kanamycin (46%), and cycloserine (48%).¹¹

Global rates for MDR-TB vary in published literature. The first and second global report on MDR-TB released in 1997 involving 35 countries, and 2000 involving 58 countries respectively, showed a rate of 1.4%. In selected “hot-spot” areas, however, the rate was noted to be as high as 54%. Areas reporting higher MDR TB rates were noted to have a higher number of previously treated patients and a poor tuberculosis control program.¹²

Tuberculosis in Special Populations

There is a paucity of local data describing the incidence of tuberculosis in special groups of individuals.

HIV Patients. Resurgence of tuberculosis in the 1980's has been attributed to the discovery of the human immunodeficiency virus. Presently, estimates ranging from 2.4 to 7.5% of HIV-infected individuals in less developed countries are assumed to develop active TB each year.¹³ The rate of development of active TB was noted to be similar in tuberculin positive and tuberculin negative HIV patients – 7.1/100 person-years versus 6.7/100 person-years.¹⁴ Here in the Philippines, limited data on TB/HIV co-infection exists. HIV prevalence in the general population is reported as less than 1% (<0.1 to <0.2%)¹⁵. Montoya and colleagues documented 39 (48.75%) of 80 HIV infected patients having Mycobacterial infection, 34 of whom had a positive AFB smear. Of the 25 patients with positive cultures, 22 (88%) had *M. tuberculosis*.¹⁶ In a retrospective review involving 72 patients with HIV/AIDS, 10 (13%) were diagnosed to have tuberculosis.¹⁷ At present, the degree of infectiousness of an HIV patient with TB remains unknown.

Health Care Workers. Risk of developing tuberculosis is higher among health workers in the medical and tuberculosis wards (13%), compared to other areas in the hospital (3%). This is 40 times higher than the general population.¹⁸ In a cross-sectional study of medical and chemical engineering students in different levels of their training programs, tuberculosis infection was determined using the tuberculin skin test (TST). Medical students were noted to have an increasing prevalence of positive reactions to TST as they advance (4.6%, 7.8%, 16.2%, respectively, $p < 0.001$), while chemical engineering students do not (4.2%, 4.3%, 4.4%, respectively, $p = 0.913$). The risks were greatest during the years of clinical training, when medical students have increased contact with patients.¹⁹

Children. Tuberculosis in children has not been given much attention until 1993 when the World Health Organization recognized the burden of tuberculosis in children. Most cases in children are due to the spread of tuberculosis from sputum positive adults. In industrialized countries, the frequency of tuberculosis will be less than 10 per 100,000 population, though in slum dwellers, this may rise to 60/100,000. In South Africa, and India, the caseload from birth to 15 years is between 20 to 39%.²⁰ In the Philippines, a prevalence study in a rural community involving 240 children showed that 52.1% who got exposed to sputum positive adults and only 43.1% with exposure to adults with PTB based on positive chest x-ray findings, were positive purified protein derivative (PPD) reactors.²¹

Elderly. Tuberculosis in the geriatric population warrants investigation due to the increasing longevity and waning immunity in this group. In Hong Kong, cases of tuberculosis in individuals above 60 years old increased from 31.9% to 45.4% from 1989 to 1998. In this age group, tuberculosis is diagnosed in advanced state and is usually accompanied by other co-morbid illnesses.²² In a home for the aged, utilizing miniature chest radiographs, Llado and colleagues were able to determine the prevalence of pulmonary tuberculosis at 9.4%.²³

Other Immunocompromised Conditions. End-stage renal disease patients, diabetics, individuals with connective tissue disease, i.e., systemic lupus erythematosus and receiving chronic steroid therapy, and patients with hematologic or solid-organ tumors are another subgroup of patients commonly afflicted with tuberculosis. The incidence of tuberculosis in dialysis-requiring patients was 134 per 100,000 person years with more than half of the population presenting with extrapulmonary manifestations.²⁴ The condition is suspected in patients with prolonged fever, commonly of an unknown origin.²⁵ In a local review of cases, TB, as presumptively diagnosed by radiographic abnormalities, was found to be the most common infection, occurring in 309 (37.3%) diabetic patients.²⁶ In diabetic patients with confirmed tuberculosis, cavitory lesions (82%) are more predominant than non-cavitory lesions (59%).²⁷ In systemic lupus erythematosus patients, prevalence of tuberculosis from Philippines, Singapore and Mumbai ranged from 5 to 30%.²⁸

II. The National Tuberculosis Program: Historical Perspectives and Major Achievements

The major points in the history of tuberculosis control in the Philippines are summarized in the boxes below.

Box 2. Historical Points in the Tuberculosis Control in the Philippines 1910-1950.

History of Tuberculosis Control in the Philippines (1910-1950)

- **1910: Mortality rate due to Tuberculosis was 487 per 100,000**
- The *Philippine Islands Anti-Tuberculosis Society* (now known as the Philippine Tuberculosis Society Inc or PTSI) was founded on July 29, 1910 by Governor Cameron Forbes. Mrs Eleanor Franklin Egan was its first President and Honorable Sergio Osmeña was its first Vice-President
- 1911: San Jan del Monte Sanitarium was opened with 14 nipa hut cottages to admit TB cases
- 1918: Santol Sanitarium opened. Treatment consisted of fresh air, sunshine, nutritious food, bed rest and isolation
- Radiologic services began with fluoroscopy as initial test for case finding
- **1932: Mortality rate due to TB was 223.85 per 100,000**
- 1932: TB Commission was created (Act No. 3743)
- 1933: Powers and duties of TB Commission transferred to Bureau of Health
- 1934: Sweepstakes Law (RA 4130) established the Philippine Charity Sweepstakes Office (PCSO) to fund Society's operations
- 1938: Santol Sanatorium was renamed as Quezon Institute
- The name of society was changed to Philippine Tuberculosis Society Inc, PTSI.
- 1944: Streptomycin (SM) was first used as part of the treatment for TB
- 1947: Mainstays of TB treatment were pneumotherapy, thoracoplasty and prolonged hospitalization
- 1948: Quezon Institute was rehabilitated after WWII
- 1949: First case of pneumonectomy in a far-advanced case

Box 3. Historical Points of Tuberculosis Control in the Philippines 1950-1990s.

**History of Tuberculosis Control in the Philippines
(1950- 1990)**

- **1950 TB Commission became Division of Tuberculosis under the Office of the Secretary of Health**
- TB Center within the DOH with the TB Ward at San Lazaro Hospital
- Treatment offered: Streptomycin (SM) injection and Para-Amino Salicylate (PAS) tablets
- Extension services thru Chest Clinics, mobile radiographic (or xray) units and educational campaigns
- 1951: BCG vaccination started
- 1954: Tuberculosis Law (R.A. 1136) which created the Division of Tuberculosis and the National Tuberculosis Center of the Philippines at the DOH compound
- 1954: Triple drug therapy with Isoniazid (INH), PAS and SM
- 1958: E.O. 288 established the Bureau of Disease Control and the Division of TB was placed under it.
- 1964: Minglanilla Prevalence Survey in Cebu Province which showed the prevalence of smear positive was 4/1000.
- **1968: National TB Program expanded with the creation of Rural Health Units (RHU). Services offered: direct microscopy, domiciliary care, selective Xray, BCG vaccination, TB registry. Treatment offered: 12 months of INH-SM**
- **Mid 70s with huge expansion of TB Program and active partnership between the DOH and PTS: New thrust on 1) case finding through sputum microscopy with more microscopes and training for microscopy at the RHU level, 2) case holding with medicine available; 3) importance of BCG vaccination, later became compulsory and part of the Expanded Program for Immunization (EPI)**
- 1973: PTS home program launched; PCCP was formed
- 1974: Treatment offered: 18 months of INH-SM-Ethambutol
- 1976: Establishment of National Institute of Tuberculosis (NIT) in cooperation with the WHO and UNICEF intended for human resource development and operational researches

- 1981-1983: first National TB Prevalence Survey by the NIT
- 1980s: the Lung Center of the Philippines opened
- **1984: More NIT researches led to the introduction of a new treatment regimen called the Short-Course Chemotherapy (SCC):**
 - **2 months Intensive Phase of INH-Rifampicin-PZA or 2HRZ**
 - **4 months Continuation Phase of INH-Rifampicin or 4HR**
- 1986 after the People Power revolution, the Ministry of Health became the Department of Health (DOH). The TB Control Service was created.
- 1987: the strengthened National TB control Program was launched and the SCC was adopted nationwide. Medicine was available in blister packs. Manual of Procedure was revised. PTS and DOH partnership was further strengthened, with PTS Chest clinics adopting National TB Program.
- 1989, 1990, 1993: Philippine College of Chest Physicians-led Tri-Chest Organization with DOH and other agencies released consecutive parts of the First National Consensus on Tuberculosis.

Box 4. Historical Points in Tuberculosis Control in the Philippines 1990-2000s.

**History of Tuberculosis Control in the Philippines
(1990s to 2000s)**

- 1990: NTP received financial and technical support from Italian government and World Bank improving TB control at Regions 5,8,10, other cities and provinces.
- 1991: Local Government Coded devolved the DOH health services to the local government units (LGUs) which became the implementers of the NTP.
- 1990s: TB efforts in Cebu was boosted by support of the Japanese International Development Agency (JICA)

- 1992: the Quezon Institute was restored by the PCSO
- 1994: The Philippine Coalition Against TB (PhilCAT) was organized with key professional societies involved in the fight against TB along with the DOH as founding members⁵⁷
- 1995: TBCS issued Revised Policies and Guidelines on the Diagnosis and Management of TB with new thrust to improve case holding.
- 1995: University of Santo Tomas TB Clinic introduced use of directly observed treatment in managing outpatient TB
- **1996: DOH piloted the Directly Observed Treatment Short course (DOTS) strategy in three areas: Batangas, Antique and Iloilo City**
- **1996 onwards: expansion of DOTS with the strategy officially adopted by the NTP with active participation of the LGUs,** various partners in TB including WHO, World Bank, JICA, World Vision-Canadian International Development Agency, Italian Cooperation for Development, Australian Aid and Medicos del Mundo.
- 1996: August 19 was proclaimed as National TB Day Proclamation
- 1997: The Philippine Pediatric Society (PPS) presented the Second Consensus on Childhood Tuberculosis during PhilCAT convention
- 1997: the DOH subcontracted the conduct of the Second National TB Prevalence Survey with the Tropical Disease Foundation. The prevalence of sputum positive individuals was 3.1 per 1000 population and the annual risk of infection was computed at 2.3%
- 1998: PhilCAT led the first local commemoration World TB Day on March 24
- **1998: The National TB Control Program became one of the flagships of the DOH**
- **1999: The First Clinical Practice Guidelines on the Diagnosis, Treatment and Control of Tuberculosis was developed spearheaded by the Philippine Society of Microbiology and Infectious Diseases (PSMID) with the PCCP and the DOH.**
- **1999: The TB Control Program became the No. 1 priority health program of the LGUs.** Procurement of anti-TB drugs was transferred to the Regional Health Offices

Box 5. Historical Points in Tuberculosis Control in the Philippines 2000 to Present

**History of Tuberculosis Control in the Philippines
(2001 to Present)**

- 2001: the PTSI continued to flourish with 52 branches across the country. They strengthened the implementation of DOTS. The Quezon Institute was renovated.
- 2001: PTSI hosted the 21st Eastern Region IUATLD Conference jointly with the PCCP.
- 2001: The first DOTS-Plus Project was initiated by a private agency the Tropical Disease Foundation Inc. (TDFI). Being the first and only Green Light Committee approved facility, TDFI expanded its DOTS services to include management of MDR-TB cases through its DOTS-Plus initiatives.
- 2002: The ***Comprehensive and Unified Policy (CUP)*** on TB control was issued by President Gloria Macapagal-Arroyo on March 2003 as Executive No. 187. This was a joint product of many public and private organizations spearheaded mainly by the DOH and the PhilCAT. The CUP synchronized the different TB control efforts of the various agencies, with the NTP guidelines as the implementing framework.
- 2002-03: The DOTS strategy achieved nationwide coverage in the public health sector. All public health centers, RHUs and their substations were utilizing the NTP policies and the DOTS strategy for their local TB control efforts.
- 2003: The first National Drug Resistance Survey was initiated with the external support of the WHO and JICA. The results became the basis for the policy to address MDR-TB.
- The NTP maintained the quadruple therapy but shifted its policy from use of single drug formulations (SDF) to fixed dose combination (FDC). This is the present treatment formulation under the NTP for all DOTS facilities.
- 2003: The Philippines received an international grant through the Global Drug Facility (GDF) for additional drug support, vis-à-vis PPMD installation. The regular drug procurement of the NTP is also coursed through this agency.

- 2004: the Hospital-based NTP-DOTS policies were issued to involve hospitals in the provision of DOTS services and strengthen the inter-facility referral network.
- The Lung Center of the Philippines became the government's counterpart support to the DOTS-plus initiative.
- Since then the coverage of DOTS broadened to include all other key health sectors. The Public-Private Mix DOTS (PPMD) strategy enhanced private sector adherence to the NTP-DOTS. The ***Operational Guidelines on PPMD*** was developed by the NTP in cooperation with the PhilCAT, WHO and GFATM.
- What followed was the development of various models and approached to operationalize the PPMD with strong support from partners such as the PhilCAT-Centers for Disease Control (CDC)-USAID, PhilTIPS-USAID, and the GFATM.
- Among the major TB projects were 1) the PhilTIPS project assisted by the USAID which focused on improving TB services of the private sector; 2) the LEAD project also assisted by the USAID which looked into improvement of the quality of services of the public sector through strengthened local governance and capacity development; and 3) several rounds of the GFATM through the PhilCAT, World Vision and the TDFI which worked on additional PPMD units, creation of social demand and expansion of the DOTS-plus.
- In line with the ***Health Sector Reform Agenda (HSRA)***, the ***DOTS certification*** to ensure the quality of DOTS services as delivered by all DOTS facilities and the ***Philhealth TB OPD Benefit Package through the process of DOTS certification*** to allow sustainability of quality services were institutionalized.
- 2005: The ***Third Revision of the Manual of Procedures (MOP) of the NTP*** was released.

III. Assessment of Tuberculosis Control in the Philippines

Tuberculosis remains a major health problem despite laudable efforts of the National TB Program after the implementation of DOTS in 1996. Since the introduction and maintenance of DOTS in the public sector, and the subsequent expansion involving the private sector, several accomplishments have been reported.

In spite of the remarkable achievements, several issues and concerns related to TB control have been identified. Various problems linked to factors attributable to the patient, the health care provider, and the program contributes to the persistence of tuberculosis in the country.

Patient-related Factors

The health seeking behavior of patients with tuberculosis is highly variable as shown in the 1997 National Prevalence Survey. In this study by Tupasi²⁹, patients with symptoms suggestive of TB took no action (43%), self-medicated (31.6%) or consulted a health care provider (25.4%), which include private medical practitioners (11.8%), public health centers (7.5%), private hospitals (4.4%) and traditional healers (1.7%). Among those confirmed to have the disease, 32.9% did nothing.

Significant differences in the health seeking behavior were noted when symptomatic subjects were stratified into those with and those without bacillary disease ($p=0.003$), by symptoms reported ($p<0.001$), or by age group ($p<0.001$). Patients with chest or back pains (Odd's Ratio [OR] 1.33, 95% CI 1.08-1.62) were likely to take no action; conversely, those aged 40-59 (OR 0.74, 95% CI 0.62-0.89) and 60 and over (OR 0.59, 95% CI 0.47-0.74) were likely to consult. Self-medication was significantly less likely in those presenting with hemoptysis (OR 0.40, 95% CI 0.26-0.62) or chest/back pain (OR 0.57, 95% CI 0.46-0.72) and in those aged 60 years and over (OR 0.74, 95% CI 0.58-0.94).¹⁹

Determinants to utilize government health centers included bacillary disease (OR 2.21, 95% CI 1.17-4.17), presence of two or more symptoms (OR 2.23, 95% CI 1.50-3.30), hemoptysis (OR 3.0, 95% CI 1.81-4.96) and age groups 40-59 (OR 1.76, 95% CI 1.21-2.56) and 60 and above (OR 2.31, 95% CI 1.53-3.50). Determinants to consult private doctors were: age group 60 and over (OR 2.67, 95% CI 1.94-3.66), residence in urban (OR 1.39, 95% CI 1.03-1.88) and urban poor areas (OR 1.72, 95% CI 1.26-2.36). Chest/back pain was a determinant for consulting a traditional healer (OR 4.42, 95% CI 2.07-9.41), aged 40-59 years (OR 0.43, 95% CI 0.22-0.88) and 60 and above (OR 0.08, 95% CI 0.01-0.62) were less likely to consult traditional healer.¹⁹

A survey conducted by Portero et al³⁰ in Metro Manila, Philippines in 2002 showed that only the factor of no intention to seek health care among TB symptomatics correlated significantly with average family income; those with low income (< Php 2,000 monthly) were seven times more likely than

those with medium and high incomes not to intend to seek medical care (OR 7.10, 95% CI 8.25-6.11). Similarly, those with low income were almost twice more likely than the rest to self-treat for TB (OR 1.74, 95% CI 2.06-1.46).³⁰

Perception and belief have been reported to influence health-seeking behavior.³¹ The knowledge, attitude and perceptions towards tuberculosis among Filipinos are likewise variable. The National Demographic Health Survey (2003) among TB patients showed the following findings³²: (a) there is a high level of awareness for both men and women that TB is curable (89%, 92%, respectively); (b) majority identified smoking as the main cause of TB (57% in men, 47% in women) followed by alcohol drinking, fatigue and microbes or germs or bacteria; (c) sharing of eating utensils is still the most widely accepted mode of transmission; (d) 53% of persons delay consult despite symptom/s because TB is perceived as harmless; and (g) awareness of DOTS strategy is less than 20%. In the same survey, government facilities emerged as the most common source of anti-tuberculosis drugs among individuals who took anti-TB medicines, which is less than 25%; proximity is the main reason for the choice of health care provider, while the choice of private physicians or clinics is based on and perceived quality of service. A similar study conducted in Malabon reported TB to be acquired by allowing sweat to dry from body, vices and hard labor; and delay in health seeking is due to high cost of medical care.³³

Socio-economic conditions play an influential role in the perceived knowledge of TB patients concerning the disease's diagnosis and treatment. Knowledge of a disease is essential to its control. A study by Portero et al²⁰ found level of education as the only independent variable associated with TB knowledge. A college degree and a higher family income were associated with a higher level of understanding of tuberculosis as a disease, while a non-formal education was associated with the belief that tuberculosis is an inherited disease; a majority of respondents from this category linked TB with poor living conditions and air pollution. Although TB knowledge score was not influenced by the source, the radio (78.6%) was the most popular medium for TB information in any socio-economic group.²⁰

Healthcare Provider-related Factors

In 2003, strengthened government commitment and funding led to 100% DOTS coverage of public health units; however case detection rates did not meet global targets.³⁴ Of those who sought professional care, TB

symptomatics preferred private practitioners and hospitals because of perceived quality of service, guaranteed confidentiality and flexibility of treatment, compared to health centers where microscopy services and anti-TB drugs are free (16.2% versus 7.5%).^{35,36,37}

The Philippines has a large number of private providers (both for-profit and non-profit), representing a large available resource nationwide, utilized even by the lower income groups, as yet untapped by the national TB program.³⁸ It is estimated that 20,000 to 35,000 of sputum smear positive patients seek treatment from private physicians each year.⁵ Private doctors see an average of 16 TB patients a month, roughly one in ten patients, or 14% of their average patient load, mostly by pulmonologists (27%), infectious disease specialists (12%), internists (10%), general practitioners (9%), family medicine (9%), and non-pulmonary specialists (8%). TB suspects also comprise a large proportion of the patient loads of radiologists (50%), surgeons (29%) and pathologists (20%).⁹

However, recent surveys conducted since 1998 (Table I) still showed poor compliance by the private sector to the standards set by the WHO-NTP in the diagnosis and treatment of tuberculosis.⁶⁻⁹ Case finding and holding mechanisms, including reporting in the private health sector remain variable, individualized, and generally not linked to the NTP. General practitioners posted the lowest average vignette scores followed by those practicing in schools, work areas, hospital outpatient (OPD) and emergency room (ER) areas compared to specialists when asked about their knowledge on tuberculosis and DOTS.⁹

Table I. Summary Table of Studies on Private Physicians and their Adherence to the WHO-NTP Standards on the Diagnosis and Treatment of Tuberculosis.

	Manalo et al 1998 ³⁹	Medicos del Mundo 2001 ⁴⁰	PhilCAT/ CDC 2002 ⁴¹	UP Econ Study 2004 ⁴²
No. of doctors surveyed	214	1355	188	1535
Coverage	Family physicians, Nationwide	Nationwide	NCR-Cavite	Nationwide

(Continue next page)

(Table I continuation...)

Average number of new TB pts seen/mo	Not reported	5-10	5	16
Use of x-rays as primary diagnostic tool	Not quantified	87.9%	95%	45%
Use of sputum microscopy as primary tool	Not quantified	17.4%	59%	12%
Treatment adherence to NTP (%)	29%	10.7%	16%	25%
Number of treatment regimen variations	>100	64	>80	
Recording/Reporting	Variable	Variable	Variable	Variable

Private physicians referred their patients to health centers only if they cannot afford to pay microscopy examinations done at the private laboratory and/or unable to buy branded anti-TB medications.⁸ Only 20% of physicians surveyed nationwide referred to health centers; most referrals are confined within the private sector.⁹ There is fear of losing patients to health centers, mistrust in the quality of free government TB drugs, habitual drug shortage in the past, perceived attitude problem among government workers, perceived “slow” patient services, and lack of knowledge of the NTP and its free services.⁴³ This manifests the explicit lack of strategies and policies to inform the private sector about renewed government efforts and involve them in the revised National TB Program, one of the major findings of the WHO global assessment in 2001.⁴⁴

National TB Program-Related Factors

TB control programs must prioritize the prevention of new infections through the elimination of the source of transmission. At the moment the TB control program is focusing on achieving the benchmark of 90% successful completion of therapy for all patients with active disease.^{45,46} This will become possible with effective case finding and efficient case holding. Through the adoption of DOTS under the NTP in 1996, policies and mechanisms have been laid down to guide the country's approach to meeting the targets of 70% detection rate and 85% cure rate set by the WHO in order to significantly decrease TB prevalence rates.

IV. Current Activities on Tuberculosis Control

What is currently being done to address patient-related problems?

In 2002, the creation of social demand for DOTS services is one of the directions of the Global Fund through production of broadcast and print IEC materials, focused community organizing, and provision of innovative promotional approaches to improve the knowledge, attitude and practices of TB clients. The World Vision Philippines, Health Promotion Center, DOH, and the LGUs were involved to implement these projects. The impact of such activities still remains to be seen.

What is currently being done to address provider-related problems?

Recognizing the potential and pivotal role of the private sector as the missing link to achieve global targets in case detection and cure rates, the Philippines pioneered to adopt officially the public-private mix (PPM) strategy in its national TB program in 2003.^{47,48}

In 2003, PPM models supported by CDC, PhilCAT and DOH were pilot-tested in different private clinic settings, which led to replication and creation of more PPM sites nationwide, public- or private-initiated, as technical and financial support from the Global Fund and Philippine Tuberculosis Initiatives in the Private Sector (PhilTIPS) poured in. Also, PhilHealth has included adequate reimbursement for TB case management to public and private units accredited to provide DOTS services, including

DOTS referring doctors.^{49,50,51} Regional Centers for Health Development (CHDs) and NTP Coordinators became the government infrastructure that implemented, consolidated and scaled up initiatives to involve private hospitals, clinics, health maintenance organizations (HMOs) and individual private practitioners as DOTS partners at various levels.^{52,53,54} In preparing the government health sector for this public-private collaboration towards TB control, the Local Enhancement and Development (LEAD) Project conducted governance strengthening and technical/capacity building activities for government doctors.

Six professional medical societies have committed to engage its members to DOTS implementation through its integration in the residency and fellowship training programs. These societies were the Philippine College of Physicians (PCP), the Philippine College of Chest Physicians (PCCP), the Philippine Academy of Family Physicians (PAFP), the Philippine College of Occupational Medicine (PCOM), the Philippine Society for Microbiology and Infectious Diseases (PSMID) and the Philippine Pediatric Society (PPS). The Association of Private Medical Colleges (APMC) has likewise mandated the integration of TB and NTP education in the medical curriculum. At least two-thirds of medical schools have become involved in DOTS activities at various levels.

As of June 2006, there are 379 PhilCAT-certified PPMD facilities (332 public, 47 private), of which 222 are PhilHealth-accredited. There are 2,474 private practitioners who have been re-trained on the NTP to engage them as either DOTS referring physicians, members of the TB Diagnostic Committee, or as PPMD providers. However, DOTS training was limited to medical society conventions, training institutions, project and local coalition initiatives. A sustained, regular, massive DOTS information dissemination for all private physicians remains to be seen.

The UP Econ study⁹ shows that of the private doctors managing TB, 75% are aware of DOTS, however, only 35% reported adopting it in actual practice either as referring physician (52%), provider (26%), certifier (18%), or TBDC member (15%). About 28% still report exclusively using chest x-ray as primary diagnostic tool. Even among those who claimed to be DOTS-trained referring doctors and certified DOTS provider, vignette scores of knowledge on DOTS were variable and barely met acceptable cut-offs. There are relatively low levels of formal DOTS engagement and even lower levels of actual TB DOTS practice. One-time information dissemination alone or financial incentives itself is not sufficient to encourage formal adoption and actual practice of TB DOTS. Both are needed and must be sustained.

Regression analysis in the same survey shows the following findings that may have impact on future information dissemination efforts:

- Those who are likely to be DOTS-aware are those who are PhilHealth-accredited, with more recent TB training within one year, who are pulmonary specialists, members of specialty societies, and who are engaged in teaching and research.
- Those who are likely to adopt DOTS in private practice are those with multiple clinics, with awareness of the PhilHealth TB outpatient benefit package, who received DOTS training, who practice in clinics with access to sputum collecting equipment, who are pulmonary specialists, and who practice in work-based clinics.
- Those who are likely to seek certification as DOTS referring physician are those who already are PhilHealth-accredited health professionals, who have multiple clinics with larger patient load, who are aware of the PHIC TB out-patient benefit package, who have received TB DOTS training, who practice in clinics with sputum collecting equipment, who are pulmonary specialists, who are based in HMO clinics, hospital OPD or emergency rooms, and more recent TB training.
- Those who are likely to seek certification as DOTS providers are those who are PhilHealth-accredited, who report awareness of the Philhealth TB out-patient benefit package, who have received TB DOTS training, who are in clinics with sputum collecting equipment.
- Those who are likely to use sputum microscopy are those who are not accredited with private insurance firms (including HMO accreditation), who are members of specialty societies, who are aware of the Philhealth TB outpatient benefit package, who are younger, and who had more recent TB training.
- Those who are likely to use the NTP-recommended SCC regimen are those who are teaching, who have more recent TB training and who have lower TB patient load.
- Those who are likely to separate TB patient records are those who are not accredited with private insurance firms (including HMO accreditation), who are members of specialty societies, who do not own their clinics, who have greater TB patient densities, who have been trained, and who are aware of the PHIC TB outpatient benefit package.

- Those who are likely to utilize treatment partners to monitor drug intake are those who have multiple clinics, who are engaged in teaching and research, who have clinics in public health facilities and who are aware of the Philhealth TB outpatient benefit package.

These suggest the need for more intensified information campaigns both among physicians who actually manage TB patients and those who do not for possible referral to DOTS facilities. More information campaign activities should target (1) older physicians, (2) physicians with less recent TB training, (3) those in freestanding clinics, (4) non-members of specialty societies, and (5) general and family medicine practitioners, internists, and non-pulmonary specialists.

Among existing PPMD units, cost recovery mechanisms are not in place, not many are PhilHealth-accredited and reimbursements are operation-limited. Financial sustainability of PPMD units is yet to be assured.

Overall, the private sector has contributed an additional 3% increase in case detection rate through its 96 established PPMD's (Figure 1). The figure also shows the unexpected but pleasant marked improvement observed from the public sector in the various areas where the PPMD site is established, from 53% to 68%! These increases led to the breaching of the target detection rate of 70% in late 2004. A sustained monitoring scheme for the private sector is yet to be implemented

What is currently being done to address program-related problems?

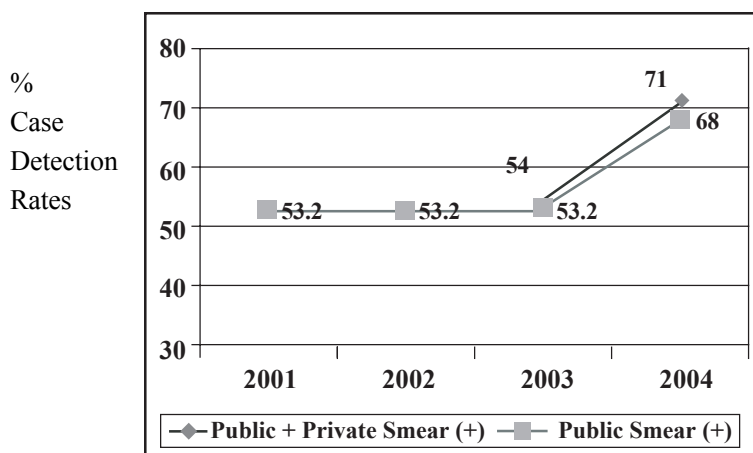
The NTP, through strengthened government and non-governmental support and funding, has created and implemented several policies and guidelines.

- The DOTS strategy achieved nationwide coverage in the public health sector between 2002-2003. All public health centers, RHUs and their substations were utilizing the NTP policies and the DOTS strategy for their local TB control efforts. To ensure quality assurance of the NTP's laboratory services, the National Tuberculosis Reference Laboratory (NTRL) was built at Research Institute for Tropical Medicine Compound in Alabang, through the support of the DOH-JICA partnership project.

- The first National Drug Resistance Survey was initiated in 2003 with external support from WHO and JICA. The primary implementer is the NTRL in coordination with various Regional TB Reference Laboratories and the local government's microscopy centers. Plan for dissemination of results is slated this year (2006). This is important for the NTP later, as its basis for policy formulation to address the threat of MDR-TB.
- The NTP maintained the quadruple therapy but shifted its policy from use of SDF to FDC anti TB drugs. This policy change was disseminated to all DOTS service providers nationwide and is the present treatment preparation under the NTP for all DOTS facilities, including the PPMD units.
- In 2003, the country got an international grant approval, through the Global Drug Facility (GDF), for additional drug support, vis-a-vis PPMD installation. Also, the NTP's regular drug procurement is now channeled through this international agency.
- The Comprehensive and Unified Policy (C.U.P.) on TB Control is a joint product of key government agencies spearheaded by the DOH and private organizations foreran by PhilCAT. This was issued by Her Excellency on March 2003 as Executive Order No. 187 to synchronize TB control efforts amongst these agencies, with the NTP guidelines serving as their implementing framework.
- In 2004, the Hospital-Based NTP-DOTS policies were revised to broaden the participation of hospitals on the DOTS strategy. This was initially intended for the government hospitals where strengthening of a facility referral network is being promoted. This Administrative Order also provides guidelines on provision of DOTS services for hospitals.
- The coverage of DOTS, to include other key health sectors, became inevitable to harmonize the TB control activities in the country. Private sector engagement to the NTP-DOTS was built on partnerships, through the PPMD strategy. The Operational Guidelines on PPMD was developed by the NTP, in cooperation with PhilCAT, the WHO and the Global Fund Against Tuberculosis and Malaria (GFATM).
- From 2003 up to present, various models and approaches to operationalize PPMD are currently being undertaken with supports coming from PhilCAT-CDC-USAID, PhilTIPS-USAID and the GFATM.

- Two USAID-assisted projects support the NTP. The PhilTIPS Project is focused on improving the TB services of the private sector through their engagement with the NTP while the LEAD Project enhances the quality of the public sector through strengthened local governance and capacity development.
- The GFATM Round 2, another approved international grant, embarked on the installation of additional PPMD units, creation of social demand and, expansion of DOTS-Plus. This is in partnership with PhilCAT, World Vision and the TDFI respectively. Its 4th component is the 3rd National Prevalence Survey, which will be conducted in 2007.
- The Lung Center of the Philippines (LCP) represents the Government's counterpart support to the DOTS-Plus initiative. The DOTS unit of LCP also functions as a satellite treatment center for MDRTB cases within its localized catchment area. Expansion of DOTS-Plus to the LCP is through GFATM assistance.
- At present, the External Quality Assurance (EQA) on direct sputum smear microscopy is being implemented on a phased basis. This system guards the quality of NTP laboratory services provided by the peripheral microscopy centers. The NTRL and the respective Regional TB Reference Laboratories oversee the system by strengthening its laboratory network.
- In view of the Health Sector Reform Agenda (HSRA) adopted by the country, the DOTS certification is developed to ensure the quality of DOTS services delivered by all DOTS facilities, both public and private. Likewise, the PhilHealth TB Outpatient Benefit Package, through the process of DOTS accreditation, serves as the NTP's health financing scheme to sustain such quality services.
- The 3rd revision of the MOP was undertaken by the DOH in partnership with local and international agencies. The 2004 edition includes the recent initiatives of the NTP with the perspective of a stronger private involvement in the Program.

Figure 1. Case Detection Rates of All Private-Public Mix DOTS Centers 2001-2004



V. Further Measures Necessary to Fully Achieve TB Control in the Philippines

The difficulties associated with different factors related to the patient, the healthcare provider and the national program require the following additional measures to achieve TB control:

Patient-related Factors

1. Efforts towards promotion of awareness among people regarding tuberculosis, through health education programs should be intensified. These activities should specifically address a) knowledge of the disease, b) health-seeking behavior c) attitudes towards self-medication and source of treatment, provided that:
 - a. Socio-economic factors should be considered in the design of TB information campaigns specifically the level of education.
 - b. It is community-based.
2. Mass media can play a key role in a program based on passive case-finding and free diagnosis and treatment to encourage people to seek medical care.

3. Policy makers should address socio-economic issues closely associated with tuberculosis as well and these are a) poverty b) low educational attainment c) poor living conditions.

Research Gaps on Patient-related Factors :

1. Health systems research to determine the obstacles among low-income patients to accessing free government TB health services
2. Evaluation of the effect of current education dissemination efforts on the knowledge, attitude and practices in the community

Healthcare Provider-related Factors

Current efforts, policies and program planning should further intensify involvement of the private health sector to engage them in various levels of DOTS implementation.

1. Focused, organized and regular DOTS education and re-training efforts should be prioritized among private practitioners actually managing TB patients, especially the general practitioners and those practicing in schools, work areas, hospital outpatient departments, and community areas to standardize case finding, and improve referral to DOTS facilities.
2. Referral to DOTS facilities, whether private or public initiated, must be encouraged to assure improved success rates because of access to free drugs, improved compliance rates through supervised treatment, standardized recording, and reporting to the national TB program. Private practitioners can retain management of the patients while avoiding the cost of monitoring and direct observation of drug intake. This will improve additionality by the private sector to the overall national case detection and cure rates.
3. Efficient, prompt and strengthened PhilHealth TB outpatient package reimbursement for referring physicians may provide add-on incentives for better referral mechanisms between the private physician and the DOTS unit.
4. Although the positive impact of PPM initiatives on case detection has been demonstrated in a few sites, there is a need to incorporate a careful and more comprehensive strategy to monitor and evaluate the current scale-up of PPMD expansion in the Philippines.

5. Financial sustainability of PPMD units should be evaluated. There may be a need to develop cost recovery mechanisms and greater commitment of LGU's for drug supply.

Research Gaps on Provider-related Factors:

1. Evaluate the impact of integrating TB education in medical schools on the medical practice of medical graduates in terms of case finding, holding and referral to DOTS facilities
2. Cost-effectiveness studies to assess the efficiency and feasibility of the PPMD programs
3. Operations studies to look into the obstacles in the PhilHealth OPD TB package reimbursement schemes to private and public DOTS facilities, including DOTS referring physicians
4. Evaluation of education dissemination efforts in the knowledge, attitude and practice (KAP) of doctors on TB especially among general practitioners

c. National TB Program-Related Factors

Based on the five essential components of DOTS, i.e. sustained political commitment, quality-assured TB sputum microscopy, standardized short-course chemotherapy, uninterrupted supply of quality-assured anti-TB drugs and standardized recording and reporting system, the following measures are necessary to further improve and sustain the NTP's achievements on TB control:

1. Sustained political commitment

Government must guarantee the continuous monitoring and improvement of the quality of DOTS implementation through a strengthened public sector that will (a) provide unhindered access to its services especially by the poor and marginalized, (b) ensure adequate and regular monitoring and supervision of its program at all levels, and (c) assure its sustainability through establishment of local, national and international coalitions of all stakeholders. A top-level commission with members from major stakeholders whose sole mandate is the control of TB in the country should oversee this whole process. The PhilCAT may fit this role.

Major policies were enacted to facilitate the provision of DOTS to all divisions and attached agencies of the DOH. The Health Sector Reform Agenda – a comprehensive strategy to reform the public health sector – made TB control a priority. NEDA lent its support to the NTCP by facilitating the inclusion of programs and projects supporting TB control in the Medium Term Public Investment Plan, by monitoring the progress of implementation of ODA-assisted TB control programs, and by assisting in the evaluation of tax deductions applicable to private donations for TB control programs and projects. The TB Prevention and Control Program of the Department of Education – School Health and Nutrition Center adopted DOTS in its management of TB cases among all primary and secondary school teachers and non-teaching personnel. The Department of Interior and Local Government Memorandum Circular No. 98-155 enjoined all local government units to pass a resolution declaring TB control as the primary public health program for 1998-2004, to adopt DOTS, and to create an anti-TB Task Force comprised of public health personnel, representatives from local medical schools and civic organizations, and private medical practitioners. It also encouraged the LGUs to make every public health center or facility a DOTS unit – replete with the requisite trained manpower, microscopy services, anti-TB drugs and reporting books to monitor the progress of patients.

These important programs developed were mainly for the public sector. The significant role played by the private sector was eventually recognized. The promotion of DOTS in both national government agencies as well as the private sector was instituted through Executive Order No. 187, series of 2003 as the Comprehensive and Unified Policy (CUP) for TB Control. This was a landmark policy that aimed to increase private sector participation in the NTP-DOTS program. The same order mandated the collaboration of public and private sectors in the management of an information and education campaign for the CUP. Private sector organizations included the Philippine Coalition against Tuberculosis (PhilCAT), the Philippine Medical Association, and the Association of Health Maintenance Organizations of the Philippines. The CUP deputized PhilCAT to carry out monitoring and accreditation functions.

Strategies to stimulate patient demand for TB services through government financial support were then put in place. The PhilHealth, in its effort to expand benefits to its members and dependents, initiated the development of the PhilHealth TB package to encourage doctors to refer patients to DOTS facilities. Thus, this will indirectly intensify the demand for TB services. PhilHealth accredited only those facilities providing DOTS as providers of the package.

Four factors can sustain political will: popular perception, scientific and medical consensus, and the media. (3) Thus, increasing the public's knowledge about the TB problem through media and other fora including those in the academe, and in industry activities may broaden popular perception and concern for the problem. In scientific societies, consensus has been worked for so as to standardize quality of care.

The PhilCAT represents an alliance of major stakeholders on TB control in the Philippines. Organized in 1994, PhilCAT was established with PCCP, DOH, PSMID, PTSI, Cure-TB and ACCP-Philippine Chapter as founding members. Thirty other organizations eventually joined and signed as members. Up to this time, PhilCAT has been actively coordinating several government and non-government agencies, including the academe and industrial groups, fostering understanding, cooperation and complimentary work, and strengthening the various advocacy strategies to control TB in our country.

2. Quality microscopy service

Since sputum exam remains to be the most cost effective means of detecting TB disease, there must be a sufficient number of laboratories across the country able to provide quality microscopy services. All regions of the country must have a reference laboratory. All laboratories both public and private must be certified before they are allowed to perform sputum exams. Quality assurance monitoring must be done prior to the renewal of licenses of laboratories to ascertain quality of services. Sputum microscopy of the highest standards must be assured in the training of future medical technologists. The call for mass education of the public regarding the value of sputum microscopy in TB control by a previous consensus group is reiterated.

The Research Institute for Tropical Medicine was named the reference laboratory, tasked with ensuring the highest standards in microscopy. The training and certifying of microscopists from across the country are its chief functions. In addition, an External Quality Assurance (EQA) on direct sputum smear microscopy to guard the quality of NTP laboratory services provided by the peripheral microscopy centers.

In a consensus arrived at by the Task Force on TB 2000, it was recommended that a mass media campaign was needed “since patients themselves may not like the sputum test and insist on certain actions not consistent with the program.”

3. Regular availability of drugs

TB drugs must be made available, accessible, and affordable. Studies on how TB drugs are allocated, distributed and utilized are vital towards this end. TB drugs should be included in the essential drugs list of the Philippines.

Through the concerted efforts of various agencies led by the Department of Health, grants from the GDF and the GFATM have allowed the Philippines to have globally procured, quality-assured TB drugs.

Free drugs from the GDF are in Fixed-Dose Combinations (FDC). These drug preparations combine two or more first-line anti-TB drugs in one capsule. They simplify treatment and – more importantly – prevent monotherapy, effectively reducing emergence of resistant strains. DOH Circular No 238 series 2003 called for the shifting from single drug formulations (SDFs) to FDCs in two phases until full nationwide coverage is achieved.

4. Standardized records and reports

Records and reports are the source of statistics on TB that are used to guide programs. These should be standardized and centralized in a TB center or by a TB commission. Networking and computerization will increase efficiency of this process.

The Manual of NTP details the standard forms and records that must be kept in DOTS facilities. The forms include the NTP Laboratory Request Form, the Laboratory Register, the NTP Treatment Card, the NTP Identification Card, and the TB Cash Register. Reports, on the other hand, comprise Quarterly Reports on Laboratory, Quarterly Reports on Case Finding, and Quarterly Reports on Treatment Outcome. Currently, DOTS program coordinators and workers manually tabulate these forms and reports.

While DOTS accredited programs meticulously work on these reports, a survey done by PhilTIPS on private practitioners showed that record keeping and monitoring is not as rigorous or standardized.

5. Supervised treatment DOT

Strengthen human resource capabilities through continuous training of CHWs, supervision and evaluation of their performance and more importantly provision of appropriate incentives and recognition for their contributions.

The utilization of thousands of community health volunteers who act as treatment partners (supervising the treatment of many TB patients) made significant strides in the Philippine DOTS strategy.⁵⁵ In addition to serving as observers of treatment, these volunteers have helped (1) raise community awareness of TB, its treatment and the importance of strict adherence to the regimen, (2) facilitate case detection and referral for diagnosis, (3) address stigma during patient encounters and indirectly through group discussions, (4) provide general support, (5) recognize drug adverse effects, (6) track those who interrupt treatment, and (7) document progress and outcome.⁵⁶

The Magna Carta for health workers in the Philippines has provisions for benefits that should rightfully be given to those who render health services. However, in many parts of the country, CHWs give their time and talent to serve their communities on a voluntary basis. Although commendable, the community, through its leaders, should also be able to do what is just for these health workers.

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Chapter 3: Diagnosis of Tuberculosis in Adult Filipinos

I. Definition of Terms

The case definitions for tuberculosis advocated by the World Health Organization (WHO)¹ and adopted by the National Tuberculosis Program (NTP) of the Philippine Department of Health (DOH)², are used throughout these guidelines. These definitions are enumerated here.

The *diagnosis of tuberculosis (TB)* refers to the recognition of an active TB case: the identification of a patient who is symptomatic due to lesions caused by *Mycobacterium tuberculosis*. A **TB case** is a patient confirmed (by microbiologic studies) to harbor the organism *Mycobacterium tuberculosis*. Infrequently, a case of TB may also be one where microbiologic work-up is negative but other data support or suggest the presence of the organism.

Cases are classified as *pulmonary tuberculosis (PTB)* or *extrapulmonary tuberculosis (EPTB)* according to the site affected by the *Mycobacterium tuberculosis*. Patients who have PTB and EPTB at the same time are classified as *Pulmonary* cases in most programmatic settings. Pulmonary cases are further subcategorized as either *smear positive* or *smear negative* based on the results of the microscopy of acid fast smears of sputum and other respiratory specimens.

Once the diagnosis of active TB is made, a case is also categorized according to previous treatment received. Thus, cases are either *New, Relapse, Return to treatment after default, Failures, Transferred-in, and Others*. Table II provides definitions of TB cases according to previous treatment received. This categorization helps guide the health provider on the recommended treatment regimens for that particular patient. This will be discussed more in the chapter on treatment.

Table II: Categories of TB cases according to Previous Treatment Received by the Patient

Subcategory according to Previous Treatment Received	DEFINITION
NEW	A patient who has never had treatment for TB or, if with previous anti-TB medications, this was taken for less than four weeks.

RELAPSE	A patient who has been declared cured of any form of TB in the past by a physician after one full course of anti-TB medications, and now has become sputum smear (+)
RETURN to TREATMENT after DEFAULT	A patient who stops taking his medications for two months or more and comes back to the clinic smear (+).
FAILURE	A patient who, while on treatment, remained or became smear (+) again at the fifth month of anti-TB treatment or later; or a patient who was smear (-) at the start of treatment and becomes smear (+) at the 2 nd month.
TRANSFER-IN	A patient whose management was started from another area and now transferred to a new clinic
CHRONIC CASE	A patient who became or remained smear (+) after completing fully a supervised re-treatment regimen

Since the release and implementation of the Comprehensive and Unified Policy (CUP)³ for Tuberculosis Control in the Philippines by the DOH and the Philippine Coalition against Tuberculosis (PhilCAT) in 2003, the diagnostic categories defined by the American Thoracic Society (ATS) of persons with TB according to exposure history, infection and disease (Class 0 – 5)⁴ has become less useful. In its place are the case definitions mentioned above which are more useful operationally for recording and standardized reporting. Table III shows the merging of the old and new terminology in TB.

Table III: Terminology of TB from the ATS (old) and WHO (new)

ATS Classification of Patients	WHO Case Definitions
0 – No TB exposure 1 – TB exposure, No evidence of infection. 2 – TB infection, No evidence of disease 3 – TB clinically active	Latent TB Active TB Case Pulmonary or Extrapulmonary Smear (+) or (-)
4 - TB not clinically active 5 – TB suspect (diagnosis pending)	

II. Outline of Issues in Diagnosis of Tuberculosis

Diagnosis of Pulmonary Tuberculosis

1. When should one suspect that a patient may have PTB?
2. What is the initial work-up for a patient exhibiting symptoms of PTB (TB symptomatic)?
3. Are there any other additional tests to do in a TB symptomatic found to be smear positive?
4. What is the approach to a TB Symptomatic who is smear negative?

Diagnosis of Extrapulmonary Tuberculosis

1. How does one reliably diagnose extra-pulmonary tuberculosis?

Diagnosis of TB in Individuals infected with Human Immunodeficiency Virus (HIV)?

1. How does one reliably diagnose pulmonary tuberculosis in HIV infected individuals?
2. What is the role of amplification techniques for TB in HIV-infected patients?
3. How does one reliably diagnose extra-pulmonary TB in HIV patients?

III. Recommendations on the Diagnosis of Tuberculosis

A. DIAGNOSIS OF PULMONARY TUBERCULOSIS

When should one suspect that a patient may have PTB?

- In the Philippines, **cough of two weeks or more** should make the physician and/or other healthcare workers suspect the possibility of pulmonary tuberculosis. **[Grade A Recommendation]**
- Cough with or without the following: night sweats, weight loss, anorexia, unexplained fever and chills, chest pain, fatigue and body malaise, is suggestive of TB.
- A patient exhibiting cough of two weeks or more with or without accompanying symptoms will be referred to as a ***TB Symptomatic***.

Summary of Evidence:

While it is true that there is no definite set of symptoms that could precisely identify patients with active pulmonary tuberculosis, several studies cited in the previous guideline⁵ have shown that over half of patients with bacteriologically confirmed TB would have any of the following: chronic cough, weight loss, sweats and chills, fatigue, body malaise and fever.

In these cited studies as much as three-fourths of patients would have chronic cough and weight loss. This becomes more important as a significant proportion of individuals seeking consultation at a primary health center is related to a complaint of cough.

More recent studies on the symptoms and signs of PTB affirm the significance of the symptom of cough of two weeks and the constellation of other constitutional symptoms. The descriptive multi-center study of Tattevin and colleagues done in France⁶ showed that among the various patient factors, the presence of symptoms suggestive of PTB was a significant predictor for culture-proven PTB ($p=0.0004$ on univariate analysis). Symptoms of TB were also found to be independently predictive of culture-proven PTB ($p=0.009$). For this study the patients with cough, fever or drenching night sweats for ≥ 3 weeks, hemoptysis were considered as having symptoms *typical* of TB; and patients with cough, unexplained fever, nonpurulent sputum production, anorexia and weight loss as having symptoms *compatible* with TB. The other independent predictors for culture positive TB on multivariate analysis were CXR pattern ($p<0.00001$) and HIV infection ($p=0.002$). Based on their data, the study proposed a Pulmonary Tuberculosis Prediction Model which had a sensitivity rate and negative predictive value (NPV) of 100%, a specificity of 48.4% and a positive predictive value (PPV) of 25%. (LEVEL I EVIDENCE)

A recently published study in India by Santha et al⁷ compared detection of smear-positive TB among out-patients with cough of ≥ 2 weeks versus cough ≥ 3 weeks. Results indicate that the prevalence of cough was 4% (2,210 had cough out of 55,561 out-patients screened). Of those with cough of two weeks or more, 267 were sputum smear positive. Among those 1,370 patients who had three weeks of cough, 182 were smear positive. Among those who did not voluntarily state that they have cough but said they did cough when prompted were less likely to be smear positive than those who volunteered information on cough (45/680 or 7% versus 222/1530 or 15%, $p<0.001$). The authors concluded that the detection of active PTB can be substantially improved by 1) actively asking for the symptom

of cough in all outpatients; and 2) using two weeks instead of three weeks as a the screening criterion for requesting sputum microscopy. (LEVEL I)

What is the initial work-up for a TB symptomatic?

- The initial work-up of choice for a TB symptomatic is the sputum microscopy. All patients who present with cough of two weeks or more **should preferably have three**, but at the least two sputum specimens sent for sputum microscopy for Acid Fast Bacilli (AFB). **[Grade A Recommendation]**
- Sputum microscopy is still the most efficient way of identifying cases of tuberculosis.
- Sputum smear for AFB is available, accessible, affordable, with results rapidly available, correlates well with infectiousness.
- While there is new evidence that the third sputum specimen usually contributes minimally to the diagnosis of active tuberculosis, three sputum specimens are still recommended until the same findings are validated in the local setting. **[Grade C Recommendation]**

Summary of Evidence:

As in the previous guideline⁵, sputum microscopy remains the test of choice as the initial work-up for TB symptomatic patients. The local study of Mendoza and Narciso⁸ was cited as having reported sensitivity and specificity rates of the sputum microscopy for AFB compared to the gold standard of TB culture as 51.8% and 97.5% respectively (LEVEL I). The PPV and NPV calculated from the data were 76.3% and 93.0% respectively, with a likelihood ratio of 21.58.

A more interesting development on sputum microscopy is the number of sputum samples: a debate between the traditional three specimens versus the more recent two specimens. Reduction of the number of required sputum smears to be submitted by patients from three samples to two samples has been gaining ground to increase the efficiency of laboratories that are burdened by too many samples to be evaluated. It is hypothesized that a thorough examination of two slides might provide a more sensitive and specific diagnostic routine than a rushed examination of three slides. This may also result in savings on sputum containers, slides and reagents, and time. This is especially useful in developing countries where there is a scarcity of resources.

The evidence for the proposed reduction in the required number of sputum from three specimens down to two is seen in several studies in different settings and from various countries⁹⁻¹⁷. These studies all consistently showed that the third smear did not add significantly to case finding efficiency. Six of the nine cited studies were performed in developing countries^{10,12,-16}, some were under program conditions^{11, 14-16}. (LEVEL I)

An incremental cost-effectiveness study evaluating sputum examination in the diagnosis of TB was done in 2000⁷. The results of the study showed that of the 166 AFB positive suspects who had three consecutive sputum smears examined sequentially, 128 (77.1%) were found on the first smear, a further 25 (15%) on the second smear and 13 (7.9%) additional cases were identified on the third smear. The economic analyses showed that the incremental cost of performing a third test, having already done two, increases rapidly with only a small gain in terms of additional cases of tuberculosis identified (US\$ 10.5 vs US\$ 44.8).

While awaiting for validation studies in the Philippines that will show the same trend shown in the above studies to support that two specimens are sufficient, the recommendation of three specimens of sputum remain.

Table IV: Summary Table of Studies on Sputum Microscopy 1998– 2004.

Authors/year/ country	Objectives	Methods	Outcome
Nelson 1998 County Hospital Minneapolis USA ⁹	To assess value of examining multiple sputum specimens for diagnosis of PTB	Smear and culture for TB of at least three specimens	-47% of patients had at least one smear (+) specimen, the third was the first smear (+) in only 13%.
Walker 2000 Rural district hospital Zambia ¹⁰	To compare incremental cost effectiveness of examining serial sputum smears for screening PTB suspects	Incremental cost-effectiveness analysis Health service provider perspective Measure of effectiveness is the number of TB cases diagnosed Rural district hospital	- Total of 166 AFB-positive with three sputum smears examined sequentially, 128 (77.1%) identified on the first smear, 25 (15%) on the second smear, 13 (7.9%) on the third smear- average cost of protocol three sequential test and incremental cost of performing a third test with two having already been done: US\$ 10.5 vs US\$44.8- difference

			between the average and incremental cost of performing a second test, with one test already been done : US\$7.6 vs US\$23.3
Wu 2009 c o u n t y laboratories, ShandongChina ¹¹	To analyse the yield of five repeated smear for the diagnosis of smear-positive TB	Nine smear microscopy centers serving a population of 8 million. Reviewed the diagnostic yield of three repeated examinations among all patients who submitted five sputum specimen.	smear microscopy of two spontaneous sputum examination is the most efficient and three sputum smear examinations provide a diagnosis in almost all cases
H a r r i e s 2000Nitchau district hospital Malawi ¹²	To assess the screening strategy for TB suspects using two sputum smears	Screening of all TB suspects with two sputum smear for 6 months	-: 186 (16%) of 1152 TB suspects were positive on two sputum smear, 173 (16%) of 1106 TB suspects were positive on three sputum smears- 29% reduction in the number so smears examined when two smear screening strategy was used- the cost of consumables using the three sputum smear was UD\$ 731 compared with US\$ 521 for the two sputum smear strategy.
C r a m p i n 2001Northern Malawi ¹³	To compare the sensitivity and specificity of two versus three smears for the diagnosis of pulmonary tuberculosis in a setting with high HIV prevalence	Tb suspects with sputum smear taken over a period 2-7 days , with at least one culture r e s u l t studiedFluorescence microscopy confirmed by Ziehl-Neilsen	- Of those detected as smear positive using three smears at least 97% would have been detected by two smears- the two smears only marginally reduce sensitivity and would slightly improve the specificity of diagnosis of TB

Van Deun 2002 TB Control Project in Bangladesh ¹⁴	To define the efficiency of numbers of microscopic fields screened and the sputum collection scheme used for diagnostic smear examination	In incremental diagnostic yield of different sputum sampling strategies	Using three specimens, 94.2% positive yield on the first specimen, and only 1% on the third specimen
Yassin 200342 diagnostic centres in southern Ethiopia ¹⁵	To determine value of submitting serial sputum samples for PTB diagnosis	Review of laboratory registers of 42 TB diagnostic centers	A total of 15,821 TB suspects submitted three smears each. 26% had at least one positive specimen. Of These the (+) smear was the first specimen in 91.6% of cases.
G o p i 2004General Hospital and 3 PHI in South India ¹⁶	To validate case detection strategy for PTB by smear microscopy of two sputum specimens versus three	Data from 1 general hospital and three peripheral health institutions Sputum collection – spot collection, early morning, spot collection Ziehl-Neilsen microscopy	- 9346 new patients, 7843 (84%) had three sputum smears : 895 were positive on at least two specimens (837 were positive on the first and second samples, 795 on the first and third, and 843 on the first and third.- of the 962 who were positive on one smear: first specimen detected 853, second specimen detected 938, and the third specimen detected 856.
L e o n a r d 2005Inner city hospital Atlanta USA ¹⁷	To assess the number of smears needed to establish PTB diagnosis	AFB and TB culture were done in 951 respiratory specimens of 425 patients	The sensitivity of smears from 239 non-HIV patients was 75%, 79%, 80% with 1,2,3 smears respectively and 57%, 61%, 62% in 142 HIV patients

How should sputum be collected when working up for TB?

- Patients must be encouraged to bring up sputum and not saliva.
- Sputum collected first thing in the morning for three consecutive days is recommended [**Grade C Recommendation**].
- Other modified schedules to allow collection in the shortest number of days and clinic visits is likewise acceptable [**Grade C Recommendation**]: Advise the patients to collect three sputum specimens within two days as follows:
 - First Specimen: Spot specimen collected at the time of first consultation
 - Second Specimen: Early morning specimen
 - Third Specimen: Second spot specimen collected when patient comes back the next day.

Summary of Evidence:

The manner of collecting sputum as recommended is the protocol of standardized instructions given by the National Tuberculosis Program (EXPERT OPINION)

There is no study to show that the above instructions and schedule of obtaining sputum for microscopy is superior to other procedures.

How should results of sputum microscopy be interpreted?

Results of sputum microscopy are interpreted and reported as follows:

- **SMEAR POSITIVE** if at least two sputum specimens are AFB (+).
- **SMEAR NEGATIVE** if none of the specimens are AFB (+).
- **DOUBTFUL** When only one of the 3 sputum specimens is (+).
 - When results are doubtful, a second set of three must be collected again.
 - If at least one of the second three is (+), the diagnosis is SMEAR POSITIVE.
 - If all of the second three are (-), the diagnosis is SMEAR NEGATIVE.

What can be done for TB Symptomatics who are unable to spontaneously expectorate sputum?

- Sputum induction with nebulization of a hypertonic (3%) saline solution is recommended for patients who are unable to spontaneously bring up sputum [**Grade B Recommendation**].
- Three specimens will increase diagnostic yield of the sputum microscopy test of induced specimens.
- The use of nebulization with hypertonic solution is an alternative that must be maximized in order to avoid further invasive procedures.
- Clinics and laboratories must be equipped and designed to perform sputum induction according to specifications of infection control.

Summary of Evidence:

Sputum induction with hypertonic (3%) saline is a non-invasive, safe and relatively well-tolerated procedure. This procedure is associated with a relatively high diagnostic yield when a single specimen was collected and high agreement was established even with results from fiberoptic bronchoscopy for the diagnosis of PTB. Several studies have shown no significant difference in the yields of AFB smears or cultures whether obtained via sputum induction or bronchoscopic lavage.¹⁸⁻²² This is recommended for individuals who are unable to self-expectorate or those with negative sputum smear results in three samples and a suspicion for PTB remains high.(LEVEL II)

Table V: Summary Table of Studies comparing the Diagnostic Sensitivity Rates using Induced Sputum (IS) with Bronchoscopic specimens (BS)

Author/Year	IS smear (%)	IS culture (%)	BS smear (%)	BS culture (%)
Andersen (1995)	19	87	12	73
Conde (2000)	34	67	38	75
McWilliams (2002)	96	—	52	—
Saglam (2005)	47	63	53	67

The different yield and sensitivity rates from various studies may have been influenced by the types of patients screened for the procedure, timing of the intervention, cooperation of the patient, experience of the physicians, and handling of the specimens.

The procedure is performed with the patient inhaling a mist of nebulized 3% hypertonic saline which subsequently irritates the airways causing the patient to cough.

This procedure must be done under supervision of a trained respiratory therapist or a physician. The saline and respiratory secretions are then spontaneously expectorated and subjected to microbiologic testing. Most common side effects reported are bronchospasm, nausea, and dizziness which are generally self-limiting.

Because of the risk for producing respiratory droplets which may contain the TB bacilli, the laboratories and clinics must be equipped with proper infection control measures to minimize such risks to its personnel and other patient clients.

Multiple induced sputum samples do increase the diagnostic yield.²³. Culture for *M. tuberculosis* is recommended only in selected cases since the cost is relatively high and facilities may not be available in all local areas.

APPROACH TO TB SYMPTOMATICS FOUND TO BE SMEAR POSITIVE

What additional tests should be done after a TB symptomatic has been found to be SMEAR POSITIVE?

- After a TB symptomatic is found to be smear positive, no further tests are required to confirm the diagnosis of PTB [**Grade C Recommendation**].
- Similarly, after a TB symptomatic is found to be smear positive, no further tests are necessary for the physician to initiate anti-TB therapy according to recommendations in the treatment section of this guideline under a DOTS program [**Grade C Recommendation**].

What is the value of chest radiographs (CXRs) in a smear positive TB Symptomatic patient?

- Chest radiographs are not routinely necessary in the management of a TB symptomatic patient who is smear positive [**Grade C Recommendation**].
- A chest radiograph in smear positive TB symptomatics may be helpful if other concomitant diseases or life-threatening conditions are being considered [**Grade B Recommendation**].

Summary of Evidence:

Many radiographic features of PTB are reported in literature with sputum smear and/or culture results as basis for determining disease activity.²⁴⁻²⁷ Recently, two large reviews were published which emphasized the variability of findings in CXR films. Even fibrosis and calcified lymph nodes or calcification were demonstrated in approximately 20-40% of individuals with active disease. Cavities may persist even after treatment in 12-22% of cases and in fact, can be viewed as a relevant complication of the disease. In a review of 232 cases of confirmed PTB, Ismail²⁸ showed that in 38% of cases, CXR findings may not show the typical changes due to tuberculosis. As such, radiographic determination of disease status based on the presence of architectural distortion, calcification, or parenchymal lesions is unreliable.

This can be anticipated since CXR findings in PTB is dependent on the host immune response, age, prior exposure to TB, and mycobacterium virulence.^{25,26,29} (EXPERT OPINION). Prior reports suggesting that patients with diabetes mellitus and the elderly are predisposed to atypical distributions of postprimary disease have not been confirmed with subsequent case-control studies. The traditional terms, “primary” and “postprimary” or “reactivation” disease have no distinguishing features based on well-established evidence and their use cannot be recommended.

Geng et al²⁹ analyzed the relationship between recently acquired and remotely acquired PTB, clinical variables, and radiographic features by utilizing molecular fingerprinting in a hospital-based series of 456 patients. This showed that time from acquisition of infection to development of clinical disease does not reliably predict the radiographic appearance of TB. HIV status is the only independent predictor of radiographic appearance, which may be due to the underlying altered immunity. (LEVEL III)

What is the value of PPD testing in a smear positive TB symptomatic patient?

- The tuberculin skin testing (TST), more popularly known as PPD (for purified protein derivative), will not add additional information in this clinical situation. Its performance is not necessary. **[Grade C Recommendation]**

An extensive discussion and set of guidelines on tuberculin skin testing for Filipino adults was recently released by the Philippine College of

Chest Physicians Council on Tuberculosis.³⁰ While it may strengthen a diagnosis of active TB disease, performing a PPD is not necessary anymore in a clinical situation wherein the sputum has already been shown to be positive for AFB. It may in fact cause confusion if a false negative result occurs such as when there is severe immunosuppression or disseminated TB³¹.

What is the value of various blood tests in a smear positive TB symptomatic patient?

- Certain blood or serum tests may be taken when specific risks for possible adverse events during treatment are present [**Grade B Recommendation**].

Smear positive patients do not require any further blood or serum tests to confirm the diagnosis of TB. The additional blood tests are recommended for certain individuals prior to instituting the anti-TB medications to reduce risk of adverse effects related to the drugs. Patients known to have liver problems or are elderly should have at least baseline determination of hepatic transaminases. Patients with known renal disease should have full evaluation of renal status.

These tests and monitoring their values are further discussed in the Chapter on Treatment (Chapter III, E: Treatment of TB in Special Situations).

What is the value of sputum TB culture and drug susceptibility testing (DST) in smear positive patients?

- Because of the increased sensitivity of TB culture to detect TB cases compared to sputum microscopy alone, international standards recommend that all adults suspected to have pulmonary tuberculosis should have TB culture in addition to sputum microscopy where resources permit.
- In the Philippines where resources are limited and laboratory capability for sputum culture is still being strengthened, sputum TB culture with DST is primarily recommended for patients who are at risk for drug resistance and should be done in the following smear positive patients:
 - o All cases of retreatment [**Grade A Recommendation**]

- o All cases of treatment failure [**Grade A Recommendation**]
- o All other cases of smear positive patients suspected to have one or multi-drug resistant TB (MDR-TB) [**Grade A Recommendation**]
- While TB culture will allow identification of mycobacteria species and early susceptibility testing, there is not enough basis to recommend routine TB culture for **new** smear positive immunocompetent patients with no identifiable risk factor for MDR-TB [**Grade C Recommendation**]

Summary of Evidence:

The rationale cited behind the recommendations in other countries³¹ on the routine performance of TB cultures in all specimens suspected to harbor the TB organism are as follows: 1) culture is more sensitive than microscopy; 2) growth of the organism is necessary for exact species identification; 3) drug susceptibility testing requires the growth of the organism; and 4) genotyping of cultured organisms may be useful to identify epidemiologic links or establish laboratory cross-contamination.

In the Philippines, use of TB culture with DST for patients already determined to be smear positive is reserved for those with risk factors to drug resistance and includes patients with previous history of treatment (Odds ratio [OR] 2.44, 95% CI 1.49, 4.01) and a previous treatment period longer than 3 months but less than 6 months (OR 4.6, $p=0.0001$)³².

The three traditional types of media for TB culture used here in the country include the egg-based (Lowenstein-Jensen), agar-based (Middlebrook 7H10 or 7H11 media) and the liquid based (Middlebrook 7H12). The mycobacterial growth in solid media takes about 3-8 weeks. This long wait has been markedly improved by recent advances in TB culture technology, shortening TB detection to as short as two weeks. Automated systems such as the BACTEC 460 (Becton Dickinson Microbiology Systems, Sparks MD), mycobacterial growth indicator tube (MGIT) system, and the BactT/ALERT MB Susceptibility Kit use the liquid based Middlebrook 7H12 broth media with additional material to allow mycobacterial detection by radiometric or colorimetric means. These new systems have been able to perform consistently well with faster and increased recovery of *Mycobacterium tuberculosis* from respiratory specimens of patients with PTB as early as 1-3 weeks. DST usually takes another two more weeks.

APPROACH TO TB SYMPTOMATICS FOUND TO BE SMEAR NEGATIVE

The approach to smear negative cases remains difficult in certain instances. Not infrequently these cases present as diagnostic dilemmas. In many instances, appropriate attention and focus are not routinely given to these cases. The management of smear negative cases remains subject to much individual variation partly because standards of care are lacking and not universally accepted among physicians.

The section that follows discusses tests and procedures frequently considered for use in the work-up for smear negative TB symptomatic patients.

What tests are recommended for TB Symptomatics who are smear negative?

For the TB Symptomatics whose sputum smears are negative, the following tests and procedures are recommended:

- TB culture with DST [**Grade A Recommendation**]
- Chest radiograph [**Grade A Recommendation**]
- Referral to the TB Diagnostic Committee (TBDC) [**Grade C Recommendation**]
- If there is doubt on the quality of sputum submitted, induction of sputum with hypertonic saline nebulization may be considered to improve sputum yield [**Grade B Recommendation**].

For smear negative patients, what is the role of TB Culture with DST?

- To increase TB case detection, patients who are smear negative by sputum microscopy should have TB culture performed whenever resources and laboratory facilities allow [**Grade A Recommendation**].
- TB culture with DST is strongly recommended in smear negative TB symptomatics who have risk factors for drug resistant TB [**Grade A Recommendation**]

Summary of Evidence:

The sensitivity and specificity of the sputum smear compared to sensitivity and specificity of the TB culture from studies published from 1998 to 2005 continue to affirm the superior sensitivity of the TB culture when compared to microscopy.^{31, 33-35} It is estimated that for sputum microscopy to be positive, at least 10,000 or 10^5 organisms per milliliter of sputum should be present. In contrast, TB culture can become positive with as few as 100 or 10^2 organisms per milliliter of sputum. In general the sensitivity of TB culture is reported to be between 80-85% with a specificity of 98% (LEVEL I). Therefore TB culture can detect more cases of active TB disease. This is the basis for its inclusion as part of the routine diagnostic work-up for most countries³¹ and in the International Standards for Tuberculosis³⁵.

The recommendation of other countries to routinely perform TB culture on all specimens suspected to harbor the TB organism cannot be routinely followed in the Philippines primarily because the test is expensive. Its cost in various laboratories range from Philippine peso P1,800 – 5,000 per specimen submitted. Additionally, the various laboratories performing the mycobacterial culture has yet to be standardized by the National Tuberculosis Reference Laboratory (NTRL).

TB culture has markedly higher test sensitivity rates compared to sputum microscopy alone. Its role becomes very important in detecting active disease in patients whose sputum smears are negative. Whenever resources permit, TB culture should be performed in smear negative patients to allow detection of TB and microbiologic confirmation of the case.

For smear negative patients, what is the role of the chest radiograph?

- Together with clinical history, the chest radiograph can be a powerful basis for decision making in the diagnostic approach to smear negative PTB patients.
- A TB symptomatic patient who is smear negative should have a chest radiograph [**Grade A Recommendation**].

Summary of Evidence:

In smear negative patients presenting with radiographic findings suggestive of PTB, a history with emphasis to possible prior TB treatment

and outcome as well as previous chest films are vital for one to arrive at an appropriate clinical decision. The radiographic findings that may suggest PTB in adults commonly include, but are not limited to the following:

- Upper lobe infiltrates
- Presence of cavities
- Lymphadenopathies
- Presence of calcification

A presumptive diagnosis of PTB is acceptable in symptomatic patients with suggestive findings on CXR. This may be sufficient to initiate treatment after due consideration of benefits and risks to the individual. Close monitoring and adherence to proper treatment standards through the Directly Observed Therapy, Short-course (DOTS) strategy are recommended on all patients started on treatment. The stability of CXR lesions can only be judged based on films taken 4-6 months apart.

Because of the importance of radiographic findings in the diagnosis of tuberculosis particularly in the subset of patients whose initial sputum smears are negative, interpretation and reporting of findings from a chest radiograph must likewise be standardized. The initial undertaking to standardize radiographic terms was spearheaded by the council on diagnostic procedures of the Philippine College of Chest Physicians (PCCP) and the Philippine College of Radiology (PCR) in 1997. Further efforts in this regard are currently being undertaken by the PCR as an offshoot of their statement issued last 2002 to concretize the contribution of their college in TB control with the acknowledgement of the role of radiographs in the context of the NTP and current available diagnostic modalities.

Radiographic terms will be used to describe structural or anatomic extent of the disease and not to imply activity status of the disease. The terms minimal and extensive will be utilized in consistency with the NTP and with global standards.

The traditional terms, “minimal”, “moderately advanced”, and “far advanced” as defined below will be replaced by “minimal” and “extensive” (encompassing the descriptions for moderate and far advanced). These terms are consistent with the recommendations from the NTP and the WHO.

Table VI. Traditional and New Radiologic Terms related to Tuberculosis

TRADITIONAL RADIOLOGIC TERMS	RADIOLOGIC TERMS NEW
MINIMAL <ul style="list-style-type: none"> affected area is less than the width of an interspace or rib no evidence of cavitation may occur anywhere in the lung but more common in the peripheral portion of the 1st or 2nd interspace 	MINIMAL (same definition as previous)
MODERATELY ADVANCED <ul style="list-style-type: none"> affected area comprise all or the greater portion of a lobe if a cavity is present measuring up to 4cm in diameter if multiple cavitations, the combined sum of the diameters is 4cm or less 	EXTENSIVE (to encompass both moderate and far advanced lesions)
FAR ADVANCED <ul style="list-style-type: none"> multilobar involvement cavities are larger than 4cm in diameter or if multiple cavitations, the combined sum of the diameters is greater than 4cm 	

The descriptive terms “inactive or old TB” should be discarded in favor of radiographically stable TB as viable bacilli may persist despite adequate therapy.

Some of the commonly used terms with their definitions are provided below:

1. *Cavity* – a focus of increased density whose central portion has been replaced by air, may or may not contain air-fluid level, surrounded by a wall usually of variable thickness
2. *Cicatricial changes/atelectasis* – refers to volume loss found in patients with local or general pulmonary fibrosis; secondary to fibrotic contraction, compliance is decreased

3. *Fibrosis* – scarring of lung parenchyma
4. *Infiltrates* – single or multiple irregular shadows; shadows of parenchymal abnormalities characterized histologically by cellular infiltration, whether interstitial or alveolar, excluding pulmonary edema changes
5. *Nodules* – well defined regions of dense confluent cellularity which is < 3 cm
6. *Masses* – well defined regions of dense confluent cellularity which is > 3 cm

The use of these radiographic descriptions hinges on a good quality CXR film with the following recommended attributes:

- The film must include the entire chest region bordered by the following anatomic structures on a postero-anterior view: superior- C7 level; lateral- soft tissues of both lateral chest walls must be visualized; inferior- both hemidiaphragms including costophrenic sulci.
- The film must be taken with the patient taking a good inspiratory effort and the film would show the hemidiaphragm reaching the level of the 9th posterior rib.
- The film size must be at least 11" x 14".
- The film must be of good penetration defined as visualization of only up to the first four thoracic vertebrae.

Films should be properly processed (fixed and washed) by a certified radiation technologist and approved by a licensed radiologist. This prevents unnecessary artifacts that may interfere with radiograph interpretation.

The use of mobile CXR facilities with miniature films should not be used for interpretation and commitment to a diagnosis of PTB. The WHO Expert Committee on Tuberculosis, in its ninth report, “noted that mass miniature radiography is a very expensive screening procedure for tuberculosis, even when the prevalence is high and therefore the policy of indiscriminate case finding by mobile radiography should be abandoned.”

For smear negative symptomatic patients, what is the role of the TB Diagnostic Committee?

- TB symptomatic smear negative patients with chest radiographs findings suspicious for TB should be referred to the TB Diagnostic Committee or an equivalent committee or specialist/s of the health

facility for further decision-making on management [**Grade C Recommendation**].

- The TB Diagnostic Committee (**TBDC**) is an innovation of the NTP. Its main function is to review symptomatic smear negative cases with CXR findings suggestive of PTB that may warrant anti-TB treatment.
- Health facilities who manage TB should ideally have its own TBDC [**Grade C Recommendation**]. By virtue of its function, the TBDC is multi-specialty in composition and usually involves the cooperation of physicians from various specialties such as the Infectious Diseases, Pulmonary Medicine, Internal Medicine, Family Medicine, Occupational Medicine, Radiology and nursing specialists.

Summary of Evidence:

The TB Diagnostic Committees (TBDC) were originally set up by the Department of Health National TB Program with the advise of WHO-Western Pacific Regional Office. It was set up in the provinces and cities where smear negative cases were predominant. This move was catalyzed by the observation of over reliance on chest radiographs as the sole modality in TB diagnosis in around 60% of total PTB cases in 1996. Supporting this new innovation was data from a study by Dr. Pierre Chaulet³⁶ in 1997 documented that a review of such practice in 101 cases revealed that 36.5% were in fact doubtful and 38.6% had no evidence of PTB on CXR. Such a practice of overdiagnosis of PTB using CXR cannot go unabated. It was noted that there was a large potential for waste of resources (manpower and drugs), undue psychological burden to certain individuals, and exposing them to potential harm from unnecessary anti-TB drugs.

The main function of TBDC is to review symptomatic smear negative cases with CXR findings suggestive of PTB or referred cases with such radiologic features that may warrant anti-TB treatment. This TBDC is mainly composed of an NTP coordinator, a radiologist, a clinician/internist often represented by a pulmonologist or an infectious disease specialist, and an NTP nurse who acts as the committee's secretary. Each symptomatic smear negative case with suspicious findings on the CXR is discussed and a consensus among the members is reached on the proper management. The decision of the TBDC is mainly recommendatory. This is forwarded to the referring physician or unit and must be adhered to if they will avail of the DOTS services provided by the health center. Although such committees

are present in various provinces, they are in different stages of development and current training to standardize their approaches are currently undergoing.

There are currently no published data on the impact of the TBDC in the diagnosis of TB (EXPERT OPINION).

What tests are not routinely recommended for a TB symptomatic who is smear negative?

The following tests have performed differently in varying settings. They **should not** be routinely performed except for selected patients and under experts' supervision:

- Amplification methods (like the Polymerase Chain Reaction or PCR) of respiratory specimens [**Grade B Recommendation**]
- Serologic tests for TB [**Grade A Recommendation**]
- Chest Computed Tomography Scan [**Grade B Recommendation**]

Summary of Evidence:

Amplification methods (ie Polymerase Chain Reaction)

Since its first application in 1989, nucleic acid amplification technology has been the Holy Grail in the search for a rapid diagnostic test for TB. The cost of this technology and the need for highly trained personnel has limited its application in the developing countries. A sizable number of level 1 evidence up to February 2002 has allowed for an assessment by meta-analysis of PCR in smear-negative PTB. Sarmiento et al³⁷ evaluated 45 original studies and 5 of which evaluated 2 different target genes thus considered to be 10 separate studies for a total of 50 studies included in the meta-analysis (LEVEL I). Their results showed that sensitivities for PCR were more variable than specificities with 76% of the studies having sensitivities of <90% compared to specificities in which only 15% had values <90%. Over-all, the factors which were found to increase the sensitivity of PCR were, the type of specimen in which bronchial specimens had significantly higher positivity rates to PCR compared to gastric specimens. Studies which did not report blinding tend to overestimate the accuracy of PCR. Specificity was increased if multiple specimens were tested for PCR implying that not all specimens may contain detectable amount of DNA. There was also a trend towards increased sensitivity if results were analyzed by patient (pooled sensitivity and specificity 72% and 88%, diagnostic Odds ratio [DOR] 26.1) compared to analysis by specimen (59%, 88% sensitivity

and specificity, DOR 18) but this was not statistically significant ($p=0.27$). This meta-analysis likewise evaluated the PCR procedure itself. They found out that purification increased the sensitivity of PCR but at the expense of specificity. The pooled sensitivity and specificity in this meta-analysis were 76% and 97% and positive predictive value 96% and a DOR of 51.11 (95% CI, 25.56-44.78). Hence, a positive PCR test provides enough certainty to initiate treatment and reduce the need for other diagnostic test. However, the negative predictive value of 80% will not sufficiently exclude the diagnosis of TB. The authors also highlighted the need for clinicians to be properly informed of the PCR technique used and the sensitivity and specificity of PCR in their respective laboratory.

The performance of PCR against the gold standard of microscopy and culture was recently studied in Kenya³⁸ which has high prevalence of TB and infections with human immunodeficiency virus (HIV). A total of 867 TB suspects were enrolled and nearly 60% (514) specimens had positive sputum PCR in at least 2 sputum specimens. Among the 352 PCR-negative TB suspects, 36 eventually were shown to be culture-positive for *M. tb*. The sensitivity and specificity of AFB smear of 3 specimens was 60% and 98% respectively, positive LR 33.42 and negative LR 0.41. In comparison, for PCR on 3 specimens gave higher values, 93% sensitivity, 84% specificity, positive LR 5.82 and negative LR 0.09 (LEVEL I). The effect of HIV on the performance of PCR was also ascertained and the results showed no significant difference in the sensitivities of HIV-positive and negative patients (89% versus 95% respectively, $p=0.43$) as compared to AFB smear, the sensitivity was higher among patients who were HIV-negative than in HIV-positive (69% versus 44%, $p=0.05$).

In contrast, usefulness of PCR in an area with low prevalence for TB such as Canada was studied in 2000 by Zahrani et al³⁹. Their results showed among 500 patients suspected of TB and who had sputum induction, only 60 patients were diagnosed with active TB, 44 were confirmed by culture and 16 were diagnosed based on therapeutic response after 3-4 months of anti-Koch's medications. The specificity of culture plus clinical diagnosis and PCR in the 60 patients were both 100% however, the sensitivity was lower with PCR at 42% as compared to the gold standard at 73% (LEVEL I). The results of the test for accuracy cannot confidently rule in nor rule out the diagnosis of TB although the authors attributed the low values to the low prevalence of TB in the setting where the study was conducted. However, the difference between the results from the study in Kenya might also be influenced by the perceived more experience on the use of PCR since 2000

and the improvement in the techniques of purification and the skills of the laboratory technicians.

The use of nested-PCR and real-time PCR to improve the sensitivity as compared to commercial NAA test kits were also investigated in separate studies both published in 2004 in the *Journal of Clinical Microbiology*⁴⁰⁻⁴¹. In both instances, only clinical specimens (respiratory and non-respiratory specimens) were analyzed. Comparing real-time PCR and the Gen-Probe Amplified M.tb Direct test (AMTDII) in 24 respiratory specimens, sensitivity and specificity were 90% and 100%, 80% and 100% respectively⁴⁰ (LEVEL I). On the other hand, performances of a nested-PCR assay (RAPID BAP-MTB) against BD Probe Tec ET System (DTB) on respiratory clinical specimens were compared to the gold standard TB culture⁴¹. The over-all sensitivity and specificity of the nested-PCR and DTB were 66.75% and 97.2%, 56.7% and 95.3% respectively. The positive and negative predictive values for nested PCR were 74.1% and 96% and DTB were 59.6% and 94.7% (LEVEL I). The authors attributed the superiority of nested-PCR to be due to low a bacterial load in the specimens. Likewise, the decreased false-positive results may be due to the lower possibility of amplifying the wrong gene locus when using nested-PCR.

The evidence so far has not clearly shown enough evidence to recommend the routine use of PCR for the diagnosis of active PTB but it may be a useful adjunct in cases where suspicion is high. In the study of T.K. Lim⁴² in Singapore which has an “intermediate” prevalence of TB. A total of 168 patients suspected with TB had respiratory specimens submitted for routine AFB smear and TB culture as well as PCR. 53 patients out of the 168 had active TB. The sensitivity and specificity of PCR were 77% and 100% compared to culture which had 81% and 100%. The positive and negative predictive values were 90% and 93%, 100% and 92% for PCR and culture. A significant and useful information that was shown in this study was that initiating anti-TB treatment by integrating clinical judgment with initial clinical evaluation and results of AFB smear, CXR and PCR even before the cultures for TB were known, increased the sensitivity of PCR from 77% to 96%, and the negative predictive value from 93% to 98%. The authors suggested that PCR should be used in appropriate group of patients with high likelihood of TB to optimize the cost-effectiveness of the test.

Serologic Tests for TB

The previous TB guideline⁵ has comprehensively discussed serologic tests for TB. In that previous guideline the statement on the role of serology

was stated as follows: “A positive ELISA test for TB is difficult to interpret in the Philippines because of the high local prevalence of TB infection. The test will be helpful in smear negative patients if the result is negative.”

Subsequent published data failed to provide evidence to change the previous recommendation and recommend any serologic test for routine use. On the contrary, the new recommendation is that serologic tests are neither useful to rule in or rule out the diagnosis of TB in difficult smear negative patients. Serological tests make use of immunologic methods to determine specific humoral and cellular responses of the host. These are then used to infer the presence of infection or disease. Most tests use modifications of either the enzyme-linked immunosorbent assay (ELISA) or the immunochromatographic methods to detect different antibody classes.

The study of Pottumarthy et al compared the performance of seven serological tests in three different TB groups with rigorous methodology (LEVEL I): active TB, pulmonary versus extrapulmonary; and smear positive versus smear negative. The seven tests included five ELISA tests: Tuberculosis IgA EIA, Pathozyme-TB complex, Pathozyme-Myco IgG, Pathozyme-Myco IgA and Pathozyme-Myco IgM; and two immunochromatographic tests: ICT Tuberculosis and Rapid Test TB. The sensitivity of the tests with sera from patients with active TB was only 16-57%. The sensitivity of the tests for patients who were smear positive pulmonary TB ranged only from 17-63%. Extracting data from this study and computing for Positive predictive value and negative predictive value in the local setting where our prevalence is reported 42 per 1000 population⁷⁰, the expected PPV and NPV would be seen in the following table.

Table VII. Performance of Serologic Tests for TB showing Extrapolated Positive and Negative Predictive Values (PPV and NPV) assuming a Local Prevalence of 42/1000 Population.

TEST	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ICT Tuberculosis	41	96	31.9	93.7
Rapid Test TB	25	87	7.7	96.3
Tuberculosis IgA EIA	57	93	26.3	98.0
Pathozyme –TB complex	16	97	19.05	96.3
Pathozyme – Myco IgG	55	89	18.0	97.8
Pathozyme – Myco IgA	41	85	10.7	97.0
Pathozyme – Myco IgM	18	80	28.1	95.7

The above table will show us that these serologic tests will not be useful in our local setting to strengthen the diagnosis of TB. The high NPV implies it might be useful if tests results are negative in excluding the possibility of TB.

Computed Tomography Scan of the Chest

The chest computed tomography (CT) scan has a role as an adjunctive tool in selected cases to establish the diagnosis of PTB and to evaluate differential disease entities that may mimic PTB or co-exist with a TB infection.

Earlier studies on chest CT and PTB were mainly descriptive focusing on imaging features of this disease. Recent studies evaluated the role of high-resolution chest CT (HRCT) scans in arriving at a diagnosis in smear negative cases.^{27,44}

Two case-control studies assessed the utility of chest CT in evaluating disease activity. In the study by Lee et al, the following CT features were observed in both active and inactive diseases: centrilobular branching linear opacities, lobular consolidation, acinar nodules, cavity, and ground glass attenuation. In another similar study, the following findings were present in active cases and were absent in patients with inactive disease: centrilobular nodules, tree-in-bud appearance, nodules 5-8 mm in diameter, and consolidation. This may suggest that although CT evaluation may be helpful in determining disease activity, definitive diagnosis still requires bacteriologic isolation of the TB bacilli^{26,46-47}.

The sensitivity and specificity rates of HRCT with cultures or tissue diagnosis as gold standard is both at 88% with a diagnostic accuracy in detecting disease activity of 88%, as reported in a prospective study by Tozkoparan et al²⁷. They noted that the findings of centrilobular nodules, other noncalcified nodules, consolidation and cavity were higher in the active cases. A similar result was demonstrated by Poey et al⁴⁴ with the additional findings of a ground-glass pattern and poorly-marginated nodules and infiltrates. The same study where the investigators monitored the evolutive patterns of treated cases, this showed that parenchymal abnormalities may still be present even on the 15th month from initiation of treatment. It should be noted that these studies were performed in less than fifty patients.

The routine use of chest CT to diagnose active PTB cannot be recommended at the moment. However, they may complement other diagnostic modalities because of their ability to provide greater detail than a

chest radiograph. They may have a role in situations where similar or co-existing disease entities are highly considered. They may also be utilized in the evaluation of possible complication or sequelae of PTB like bronchiectasis or cavity formation with fungus ball.

How should patients with radiographic findings suggestive of PTB be managed?

- Physicians and patients must be discouraged from initiating treatment for TB based on chest radiographs alone.
- An adult patient consulting with a chest radiograph suggestive of PTB should undergo sputum microscopy regardless of symptoms and follow a similar flow of diagnostic work-up as the TB symptomatic. **[Grade C recommendation]**

B. DIAGNOSIS OF EXTRAPULMONARY TUBERCULOSIS

How can one reliably diagnose extrapulmonary tuberculosis (EPTB)?

- The diagnosis of EPTB initially depends on the physician having a high degree of suspicion of TB in a patient at risk.
- For all patients suspected of having EPTB, appropriate specimens from the suspected sites of involvement should be obtained and processed for microbiologic, both microscopy and culture, as well as histopathologic examinations **[Grade A Recommendation]**.
- Sputum should likewise be sent for microbiologic studies **[Grade B Recommendation]**.

Summary of Evidence:

EPTB diagnosis depends on the physician considering the possibility of TB disease, especially having a strong suspicion at an early stage.⁴⁸⁻⁴⁹ Culture remains the gold standard for diagnosis. In selecting the appropriate clinical specimen, tissue biopsy yields a positive culture result more often than fluid aspirate.⁴⁸ Since there are generally fewer *M. tuberculosis* organisms in extra-pulmonary sites, identification of acid fast bacilli in specimens from these sites is less frequent & culture is more important.³⁵ Due to the low yield of microscopy, histopathologic examination is also an

important diagnostic test. However, even if pathologic examination revealing granulomatous lesions with Langhans giant cells are more suggestive of TB granulomas, the presence of acid fast bacilli may represent either typical or atypical mycobacterial infection.⁴⁸

Lymph Node Tuberculosis

For lymph node TB, one of the most common extrapulmonary sites, the best diagnostic procedure is excisional biopsy, which yields the diagnosis in 80% of cases.⁴⁸

Tuberculous Pleural Effusion

For the other most common extrapulmonary site which is pleural TB, microscopic examination of pleural fluid detects acid fast bacilli in only about 5-10% of cases.³⁹ In a study by Nerves et al on the probability of diagnosing pleural TB, variables such as prevalence of lymphocytes (>90%) & high protein levels (>4 g/dL) in pleural fluid as well as low age (<45 years) gave an LR+ of 8.6 and an LR- of 0.016, which increased the likelihood of and level of confidence in the diagnosis of a tuberculous pleural effusion.⁵⁰

Genito-urinary Tuberculosis

In the diagnosis of genito-urinary TB, definite diagnosis is established by urine mycobacterial culture. The most concentrated urine specimen is in the morning so that the first void urine is likely to give the highest yield.

Spinal Tuberculosis

The most common form of skeletal TB is involvement of the spine (Pott's disease). The diagnosis still depends on biopsy for culture and pathologic examination of the affected tissue because radiographs are not diagnostic.⁴⁸ Imaging modalities such as CT or MRI however help target the biopsy site. It is mentioned that MRI is the modality of choice because it can discriminate between abscess and granulation tissue and can delineate soft tissue masses and identify the amount of bone destruction.⁵¹⁻⁵²

Abdominal Tuberculosis

In the diagnosis of abdominal TB, while conventional barium studies

remain the mainstay in the diagnosis of intestinal disease and CT is excellent to assess extra-intestinal disease, imaging findings are not always specific. In a study by Suri et al⁵³, the role of ultrasound (US)-guided fine needle aspiration cytology (FNAC) in the diagnosis of abdominal TB was assessed among patients with non-palpable lesions on US/CT. The study concluded that splenic and lymph node FNAC had a high sensitivity rate of 87.5% and specificity rate of 78.6%. However, bowel and liver FNAC was not diagnostic.⁵⁴ In the retrospective review by Uzunkoy et al, the 7-year experience in a tertiary hospital in Turkey suggested that PCR of ascitic fluid obtained by ultrasound-guided FNA was a reliable method for the diagnosis of abdominal TB in patients with ascites and that such diagnostic procedure should at least be attempted before surgical intervention.⁵⁴

Tuberculous Meningitis

Diagnosis of tuberculous meningitis depends on a high index of suspicion. The cerebrospinal fluid (CSF) which initially shows leukocytosis, develops predominance of lymphocytes over a period of days; the protein level is elevated while glucose level is decreased. The CSF is seldom positive on direct smear and specimen should be sent for TB culture.

Tuberculous Pericarditis

TB pericarditis is rare and diagnosis is based mainly on the demonstration of AFB in pericardial material, or granulomatous inflammation with or without caseous necrosis in the pericardium. In a 14-year experience in a Taiwan hospital, 19 patients were treated with anti-TB medications based on a diagnosis of TB pericarditis. The diagnosis was confirmed with positive culture for *M. tuberculosis* in 35.3% (6 of 17 pericardial fluid specimens) and supported by histopathologic findings in 12 of 17 specimens.⁵⁵

C. DIAGNOSIS OF TB IN INDIVIDUALS WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV)

How does one accurately diagnose PTB in HIV infected person?

- Both sputum smear examination and TB culture are recommended as the initial tests to diagnosis tuberculosis in HIV infected individuals [**Grade A Recommendation**].
- As in non-HIV patients, examination of three sputum specimens is recommended. [**Grade A Recommendation**].

- A chest radiograph is additionally recommended as part of initial diagnostic work-up in HIV patients **[Grade A Recommendation]**.

Summary of Evidence:

As HIV infection progresses, CD4+ lymphocytes decline in number and function. The immune system is less able to prevent the growth and local spread of *M. tuberculosis*. The pathogenesis of TB can be altered by HIV either through reactivation of latent tuberculosis infection to active disease (more common) or by causing rapid progression from recent infection with *M. tuberculosis* to tuberculosis disease.

Pulmonary TB remains to be the most common form of TB in HIV-infected patients. Many studies reveal that pulmonary involvement occurs in 70-90% of all patients with TB. The presentation of pulmonary TB depends on the degree of immunosuppression.

The diagnosis of TB in HIV-positive patients is more difficult for three main reasons: 1) the sensitivity of the direct sputum smear examination is reduced in HIV-positive patients. Compared to HIV-negative patients with pulmonary TB, a lesser proportion of HIV-positive patients with pulmonary TB will have positive sputum smears; 2) X-ray abnormalities, which are not specific for TB in HIV-negative patients, are even more non-specific in HIV-infected with only minor abnormalities on chest X-ray or with abnormalities which do not look like classical TB; and 3) patients infected with HIV have frequent illnesses with pulmonary involvement caused by agents other than *M. tuberculosis*.

Table VIII. The Characteristics of TB Infection and Disease in Relation to the Stages of HIV Infection.

Features of Pulmonary TB	Stage of HIV Infection	
	Early	Late
Clinical picture	Often Resembles post-primary TB	Often Resembles primary TB
Sputum smear result	Often positive	Often negative
Chest X-ray	Often cavities are seen	Often infiltrates with no cavity

As in non-HIV patients, direct examination of patient specimens with the use of acid fast stains for mycobacteria remains the most useful rapid diagnostic method for TB.

Examination of three specimens significantly enhances the sensitivity for detection of PTB.

There has been a concern that the utility of acid fast smears may be reduced in HIV infected populations. The sensitivity of smear examination may be reduced in blunted inflammatory response (advanced stage HIV, or decreasing CD4T cell count) and relative absence of cavitory lesions. Because of the above concerns, many studies have been done comparing the yield of AFB smear in HIV and non-HIV patients and these are shown in Table 9 below.

Table IX. Summary Table of Studies on the Yield of AFB smear of Sputum in HIV versus non-HIV patients

Author	% AFB (+)
Finch ⁵⁶ n=164	
HIV +	14/20 (70%)
HIV -	103/144 (71%)
Smith ⁵⁷ n=176	
HIV +	
CD4 < 50	60%
CD4 50-200	58%
CD4 >200	60%
HIV -	56%
Elliot ⁵⁸ n=249	
HIV +	57%
HIV -	76%
Long ⁵⁹ n=289	
HIV +	67%
HIV -	79%
Klein ⁶⁰	
HIV +	45%
HIV -	81%
Theuer ⁶¹	No difference
Yajko ⁶²	No difference

Results of studies show substantial variability in trends. The retrospective study of Klein⁶⁰ found that significantly fewer HIV-seropositive patients with confirmed TB had positive smears of 45%, compared with control patients without HIV (81%). The number of sputum specimens examined in the two groups were similar. A larger study by Long et al⁵⁹ of 289 patients with pulmonary TB also found that the sensitivity of sputum smear examination was decreased in subjects who were HIV seropositive (79% vs. 66%).

However other studies have shown no difference in the sensitivity of AFB smears between HIV-seropositive and seronegative patients. The study by Finch et al⁵⁶ demonstrated that sputum smear is as sensitive for the diagnosis of TB in HIV-infected patients as it is in non-HIV infected patients. Seventy percent of all HIV-infected patients (14/20) and 71% of all non-HIV-infected patients (103/144) had at least one positive smear. The concordance of serial smears was high as demonstrated by the fact that a similar proportion of all specimens were positive: 68% (41/60) in HIV infected patients and 70% (304/435) in the non-HIV-infected patients.

Interestingly in the study by Finch the sensitivity for the diagnosis of TB dropped to 55% and 64% respectively when only the first smear was considered. The authors concluded that a single specimen was sufficient to establish the diagnosis in all HIV-infected patients with pulmonary TB. A single negative sputum smear made the diagnosis of TB significantly less likely. However, a minimum of two smears were necessary to achieve an acceptable early diagnostic yield.

No chest radiograph presentation was able to discriminate between HIV-infected patients with TB and pneumonia of other causes in most cases. The only radiographic findings that discriminated between HIV infected and non-infected were the presence of cavitation or a military pattern ($p=0.014$).

Johnson JL et al⁶³ evaluated the impact of HIV-1 co-infection on the bacteriologic and radiographic presentation of pulmonary TB. In this study, they demonstrated that HIV co-infection was associated with a higher frequency of negative and paucibacillary (very scanty or scanty) sputum AFB smears ($p=0.007$). The differences in the diagnostic yields of microscopy and culture between HIV and non-HIV infected were small and do not significantly affect the utility of these important diagnostic tests in developing countries. Examining more than one sputum specimen and monitoring cultured specimens for a full 8 weeks may assist in optimizing the diagnostic yield.

Smith RL et al⁶⁴ investigated the factors affecting the yield of acid-fast sputum smears in patients with HIV and tuberculosis, the likelihood of a positive acid fast sputum smear related to chest radiograph findings, CD4 cell counts, drug sensitivity and the presence of disseminated disease among 100 patients with HIV and 76 without HIV all with positive TB culture.

Overall, 60% of patients with HIV had positive acid fast smears, compared with 57% of non-HIV-infected patients. A relative absence of cavitory infiltrates did not substantially reduced the frequency of acid fast smears in patients with and without HIV. Patients with HIV and CD4 counts < 50, 50-200, and >200 had positive acid fast smear rates 58%, 60% and 56% respectively. HIV-infected patients with drug-resistant organisms had 65% positive smears. Smear positivity was 96% in patients with HIV infection and disseminated TB.

Aderaye G et al⁶⁵ evaluated the impact of HIV co-infection on the chest radiographic pattern and extent of disease and its relation to the load of *Mycobacterium tuberculosis* (Ethiopia). A total of 168 patients with culture verified PTB had their chest radiographs reviewed. HIV + patients were less likely to have cavitory disease ($p=0.001$) and more likely to have pleural effusion ($p=0.08$), miliary ($p<0.05$), interstitial patterns ($p<0.01$). HIV infected patients had a CXR classified as normal or with minimal involvement ($p=0.059$) and a reduced mycobacterial count. Middle and lower lung involvement were common in HIV positive patients.

According to the WHO Standard Operating Procedures for the Southeast Asian Region for the laboratory diagnosis of TB and *Mycobacterium avium* complex diseases in HIV infected patients, two approaches to the diagnosis of TB is recommended: 1) The direct approach which includes the detection of tubercle bacilli by smear and culture or the detection of its products such as detection of tuberculostearic acid, detection and identification of mycobacterial antigens by the use of polyclonal or monoclonal antibodies, analysis of mycolic acids by chromatography, and the detection of DNA or RNA of mycobacterial origin by hybridization with DNA probes with or without amplification of nucleic acids; and 2) The indirect approach relates to the measurement of host immune response against the mycobacteria- includes humoral immunity via the detection of antibodies against the bacteria and cellular response via skin tests. However, from a practical standpoint none of the above parameters except smear microscopy, culture on LJ medium, minimum set of identification to differentiate *M. tuberculosis* from NTM and drug susceptibility testing by the conventional method, are feasible in most of the Southeast Asian

countries. Also the contribution of PTB accounts for more than 90% of total tuberculosis manifestation in HIV patients.

What is the role of amplification techniques for TB in HIV-infected patients?

- Amplification techniques such as the PCR of respiratory specimens may be useful adjuncts to diagnose tuberculosis in smear negative HIV positive TB symptomatics [Grade B Recommendation].

Summary of Evidence:

Several gene amplification techniques can detect *M. tuberculosis* nucleic acid within hours directly from clinical specimens. Assays using the PCR or transcription-mediated application (TMA) have been evaluated extensively on clinical samples.

In reference laboratories, both tests are highly specific (>95%) and are more sensitive than staining for acid fast bacilli. Although both PCR and TMA are not FDA approved as tests to diagnose TB in patients with negative AFB smears, these assays may be useful in patients with diagnostically difficult cases, particularly if the two separate assays are positive.

The sensitivity and specificity of PCR were 93 and 84%, respectively. HIV status did not affect the sensitivity of PCR. In one series, TB was correctly identified in 99.7% of the true smear-positive and 82.1% of the true smear-negative by PCR. PCR detected *M. tuberculosis* in 11.7% of the culture-negative suspects, 60% of which had one or two PCR-positive sputum specimens. Of the 490 positive cultures, 486 were identified as *M. tuberculosis*. The high sensitivity of Amplicor PCR merits usage in a clinical setting with high TB and HIV burdens. Thus, PCR can be considered as an alternative to AFB. Effectiveness studies and operational studies are required to support an evidence-based decision of introducing PCR for TB control in high-burden environments⁶⁶⁻⁶⁸.

How does one reliably diagnose extrapulmonary tuberculosis in HIV infected patients ?

- As in non-HIV patients, the diagnosis of extrapulmonary TB in HIV patients relies heavily on the documentation of the *M. Tuberculosis* in the organs suspected to have the TB disease.

Summary of Evidence

Table 10 summarizes the yield of the mycobacterium from different clinical specimens in HIV patients based from the study of Shafer⁶⁹.

Table X: Diagnostic Yield of Clinical Specimens from HIV-Infected Patients With Tuberculosis Comparing microscopy with culture

SPECIMEN	% of TB Patients for whom specimen test is Positive	
	Microscopy	Culture
Sputum	40-67	74-95
Bronshoscopy		
Bronchoalveolar Lavage	7-20	52-89
Transbronchial biopsy	10-39	42-85
Urine	22	45-77
Blood	na	
Lymph nodes	37-90	40-95
Bone marrow	18-52	25-67
Liver biopsy	78	56-78
Cerebrospinal fluid	0-27	NA
Pleural fluid specimens		
Pleural Fluid	3-6	NA
Pleural biopsy	52-55	NA

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Chapter 4: Treatment of Tuberculosis in Adult Filipinos

I. The Public Health Responsibility of the Prescribing Physician for Successful Treatment of Tuberculosis

Effective treatment is not only an essential component of good patient care, but is also a key element of the public health response to tuberculosis. Besides restoring the health of the afflicted individual, effective treatment also renders the patient non-infectious, thereby removing the threat of transmission to the community. All healthcare providers who participate in the treatment of patients with tuberculosis must therefore recognize that they are not only treating an individual; they are also assuming an important public health function that entails a high degree of responsibility to the community.

These treatment guidelines define a level of care consistent with both the public health function and the individual patient care inherent in the management of tuberculosis. ***Curing the patient*** and ***protecting the community***, by minimizing the transmission of *Mycobacterium tuberculosis*, comprise the overall goals of tuberculosis treatment. It is important that both functions be carried out effectively as substandard care will likely result in poor patient outcomes, continued infectiousness, concomitant transmission of the infection to other community members, and the generation and propagation of drug resistance.

Successful treatment of tuberculosis entails benefits for both the individual patient and the community he resides in. The treatment of tuberculosis has been demonstrably more successful within the Directly Observed Treatment, Short Course (DOTS) framework. The responsibilities of physicians – whether in the public or private sector – are not only limited to the prescription of appropriate drugs; these responsibilities should also include assurance of the patient's successful treatment completion. This responsibility is a fundamental principle of tuberculosis control. The supervision of treatment should thus be shared between the National TB Program and the private physicians.

Five components of the DOTS Strategy

1. **Sustained political commitment** to increase human and financial resources and make TB control a nationwide priority integral to the health system

2. **Access to quality-assured TB sputum microscopy** for case detection among symptomatic patients
3. **Standardized short-course chemotherapy** for all cases of TB under proper case management conditions, including directly observed treatment (DOT)
4. **Uninterrupted supply of quality-assured anti-tuberculosis drugs** with reliable drug procurement and distribution systems
5. **A standardized recording and reporting system** enabling outcome assessment of all patients and assessment of the overall performance of the TB control program

II. Outline of Issues on the Treatment of Tuberculosis

Standard treatment regimens

1. Newly-diagnosed patients (no history of treatment)
 - a. What is the recommended treatment regimen for newly diagnosed smear-positive PTB patients?
 - b. What is the recommended treatment regimen for newly diagnosed smear-negative PTB patients?
2. Previously treated patients
 - a. How should relapse PTB patients be treated?
 - b. How should PTB patients who have interrupted treatment be managed?
 - c. How should treatment failures be managed?
 - d. How should suspected drug-resistant TB patients be managed?
3. TB in special situations
 - a. What treatment regimens should be used for pregnant and lactating women?
 - b. How should patients with hepatic dysfunction be managed?
 - c. How should patients with renal dysfunction be managed?
 - d. How should TB in elderly patients be managed?
 - e. How should TB in HIV patients be managed?
 - f. How should TB in patients with diabetes mellitus be managed?

4. Extrapulmonary TB
 - a. What are the effective treatment regimens for extrapulmonary TB?
 - b. How effective are the other modalities of treatment for extrapulmonary TB?

Organization and supervision of treatment

1. How effective is directly-observed therapy (DOT) compared to non-DOT in the administration of TB medications?
2. Who are the effective types of treatment partners?
3. Aside from DOT, what are the effective ways of monitoring adherence to treatment?

Modes of treatment administration

1. How effective are fixed-dose combination drugs compared to single-drug formulations?
2. How effective is daily vs. intermittent regimen for the treatment of TB?

Monitoring of outcomes and management of adverse reactions during treatment

1. What tests should be used to monitor treatment response and outcomes?
2. How often should we follow-up patients?
3. How should we classify treatment outcomes?
4. What tests should be done to monitor for adverse reactions?
5. How should adverse reactions due to anti-TB drugs be managed?

Adjunctive therapy for TB

1. What is the role of immunomodulators in the management of TB?
2. What is the role of micronutrient and vitamin supplementation in the management of TB?

III. Recommendations on the Treatment of Tuberculosis In Adult Filipinos

A. STANDARD TREATMENT REGIMENS

1. Newly Diagnosed Patients (No History of Treatment)

What is the recommended treatment regimen for newly diagnosed smear-positive PTB patients?

- The recommended treatment regimen for all adults newly diagnosed with smear-positive tuberculosis and no history of treatment is a short-course chemotherapy (SCC) regimen, consisting of two months of isoniazid, rifampicin, pyrazinamide and ethambutol (**2HRZE**) in the initial phase, and 4 months of isoniazid and rifampicin (**4HR**) in the continuation phase [**Grade A**].
- The initial phase of treatment (2HRZE) should be given daily, followed by daily or thrice-weekly administration of isoniazid and rifampicin during the continuation phase.
- The recommended dosages for daily and thrice-weekly administration in mg/kg body weight are as follows:

Drugs	Daily (range)	Thrice-weekly (range)
Isoniazid ⁵ (4-6)	10	
Rifampicin	10 (8-12)	10 (8-12)
Pyrazinamide	25 (20-30)	35 (30-40)
Ethambutol	15 (15-20)	30 (25-35)
Streptomycin	15 (12-18)	15 (12-18)

Summary of Evidence

4-drug vs. 3-drug regimen during the initial phase

Four drugs are recommended during the initial phase (2HRZE) because this regimen has similar efficacy rates in both fully sensitive and INH-resistant organisms [LEVEL 1]. Two drugs (4HR) suffice for the continuation phase because no additional benefit is derived from adding another drug – ethambutol – to this combination even among patients with initial INH resistance [LEVEL 2].

This modifies the 2000 Philippine clinical practice guidelines¹, which recommended a minimum of three drugs (2HRZ) in the initial phase of newly-diagnosed PTB and a 4-drug regimen if drug resistance is high based on surveys. Data from community surveys showed that initial INH resistance rates in the Philippines ranged from 11.5%² to 20.9%,³ necessitating the change in recommendations.

The World Health Organization (WHO) guidelines also recommend the SCC regimen (2HRZE/4HR) because it reduces the risk of selecting resistant bacilli in smear-positive patients with large bacillary loads. In these patients, the risk of selecting resistant bacilli is high because a large population of bacilli can develop spontaneous resistance to a single drug.⁴

The preferred regimen of the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA) is also 2HRZE/4HR or its variation, 2HRZE/4H2R2, where the maintenance phase of isoniazid, H, and rifampicin, R, is given twice weekly for four months.⁵ Based on a properly randomized controlled trial with clinical endpoints, these groups recommended four regimens for treating adults with organisms known to be susceptible to isoniazid, rifampicin, pyrazinamide, and ethambutol, [LEVEL 1]. Three of these regimens require an intensive phase of four drugs (2HRZE) while the 4th regimen recommended 2HRE only in situations when pyrazinamide cannot be given, or if the isolate is determined to be resistant to pyrazinamide (an unusual situation).

A retrospective analysis of data from the British Medical Research Council (BMRC) studies⁶ showed that there were **fewer treatment failures and relapses if a regimen containing four drugs during the initial phase (HRZE) was used for patients with isoniazid resistance.**

A randomized controlled trial compared two 4-drug regimens, 2HRZE7/6HE7 (an 8-month daily regimen) and 2HRZE2/4HRE2 (a 6-month twice-weekly regimen) with a 3-drug regimen (2HRZ2/4HR2, a 6-month twice-weekly regimen) in patients with drug-susceptible tuberculosis and those with isoniazid-resistant TB. The response rate with the twice-weekly 4-drug ethambutol-containing regimen was nearly 100%, but the documented relapse rates were high (11%). More importantly, the 3-drug twice-weekly non-ethambutol containing regimen was deemed unsatisfactory; especially in the isoniazid-resistant group because of **higher failure rates with the 3-drug regimen in populations with high isoniazid resistance rates** (see Table XI).⁷

Table XI. Summary of results of the clinical trial of short-course regimens⁷

Fully drug-susceptible group			Isoniazid-resistant group	
	Unfavorable response at end of treatment No. (%)	Relapse rate at 24 months No. (%)	Unfavorable response at end of treatment No. (%)	Relapse rate at 24 months
2HRZE7/6HE7*	305 (3.6%)	290 (5%)	94 (17%)	8%
2HRZE2/4HRE2**	263 (0.4%)	258 (11%)	59 (20%)	25%
2HRZ2/4HR2**	257 (9.3%)	229 (10%)	74 (62%)	15%

* completely unsupervised; ** partially or completely supervised

Two other retrospective studies confirm the similar efficacy rates of a 4-drug regimen in both fully susceptible and isoniazid-resistant bacilli. Bai et al demonstrated that the success rates of SCC regimens (2HRZE/4HRE) did not differ significantly at 94.4% and 97.4% for 108 isoniazid-resistant and 115 drug-susceptible patients. There were no relapses documented at 12 months after treatment in both groups, and there was no advantage using a regimen lasting longer than six months in isoniazid-resistant patients [LEVEL 2]⁸

A retrospective cohort study of patients from Hong Kong, the Dominican Republic, Italy, Russia, South Korea and Peru showed that 83% of 4,378 new culture-positive TB cases were treated successfully and only 3% experienced treatment failure using the standard SCC regimen (2HRZE/4HR). The success rate was 85% among TB cases with fully susceptible strains, while in cases with resistant strains (resistant to one or more drugs) it was 83%⁹.

Streptomycin vs. ethambutol as the fourth drug during the intensive phase

One RCT found no significant difference between an ethambutol-containing and a streptomycin-containing regimen in the intensive phase of treatment in terms of (1) treatment compliance, (2) the number of patients lost, (3) the number of patients who died, and (4) the bacteriologic response to the intensive phase of treatment. The regimen with ethambutol (HRZE) was better tolerated. The results of both regimens remained comparable during the continuation phase, although treatment failures occurred earlier in patients who had received streptomycin. The authors concluded that an

ethambutol-containing regimen was as effective as the regimen with streptomycin – with ethambutol being better tolerated [LEVEL 1].¹⁰

Li et al in a series of studies in China¹¹ supports these findings. In a comparison between an ethambutol-containing regimen (2E3H3R3Z3/4H3R3) and a streptomycin-containing regimen (2S3H3R3Z3/4H3R3), no significant differences in efficacy, relapse rate, and full course supervision were identified. The streptomycin regimen caused more side effects, and streptomycin skin testing yielded a 4.5% positive rate. Moreover, using streptomycin costs 84% more than using ethambutol. The authors concluded that an ethambutol-containing regimen is more appropriate for a tuberculosis control program. [Level 2]

Ethambutol as a third drug during the continuation phase

A retrospective analysis of trials conducted by the Tuberculosis Research Centre in India showed that the addition of ethambutol as a third drug to isoniazid and rifampicin during the continuation phase did not reduce the emergence of resistance (particularly to rifampicin) even among patients infected with organisms initially resistant to isoniazid.¹² Mitchison had earlier reported similar findings [LEVEL 2].⁶

What is the recommended treatment regimen for newly diagnosed smear-negative PTB patients?

- In the Philippines where INH resistance is high, a short-course chemotherapy regimen consisting of 2HRZE/4HR is recommended for smear-negative PTB patients who are either without HIV or with an unknown HIV status [Grade C].

Summary of Evidence

The 2000 Philippine Consensus on TB did not give treatment recommendations on smear-negative PTB patients.¹

Before the HIV/AIDS era, several clinical trials on smear-negative PTB patients have been conducted. The Hong Kong Chest Service treated smear-negative/culture-positive patients with four drugs (HRZS) and observed relapse rates of 32%, 13% and 5% for 2-month, 3-month and 6-months regimens, respectively. The clinical trial concluded that a four-drug regimen for smear-negative/culture-positive TB requires more than three months of treatment.¹³ A subsequent study by the BMRC showed relapse

rates of 2% and 8% for drug-susceptible and isoniazid or streptomycin-resistant organisms, respectively, treated with four months of an HRZS regimen. This clinical trial indicated that a minimum of four months' treatment with a four-drug regimen was adequate [LEVEL 2].¹⁴ Regimens of 6- or 9-months of isoniazid and rifampicin were also found to be effective in smear-negative/culture-positive TB.¹⁵

More recently, Teo et al. conducted a randomized controlled trial on the efficacy of a four-month regimen in patients with smear-negative TB. Three hundred fourteen patients were randomized to the following daily or intermittent regimens: (1) 2HRZ/2HR, (2) 2HRZ/2H2R2, or (3) 2HRZ/4H2R2. None of the 158 culture-positive and culture-negative cases who received the daily regimen had a relapse up to 60 months after treatment. In patients who received the intermittent regimen, only the culture-negative patients reported a relapse and one culture-positive patient reported treatment failure within the 60-month follow-up period. The trial concluded that a four-month daily or combined daily/intermittent regimen appears to be highly effective in the treatment of immunocompetent patients with smear- and culture-negative TB [LEVEL 1].¹⁶

The incidence of smear-negative PTB has been increasing since the advent of the HIV epidemic, particularly in African countries. Although it may be argued that such an increase may represent laboratory or clinical errors, several studies have shown that smear-negative disease is also the more common presentation in HIV-positive patients. A negative smear may thus signify an HIV-positive patient, rather than infection with a paucibacillary disease. Prudence then dictates that in determining the treatment regimen for smear-negative patients, the HIV status of the individual should be considered, particularly in HIV-endemic areas.¹⁷

HIV-negative patients with smear negative PTB or extra-pulmonary TB that is fully drug-susceptible have little risk of selecting resistant bacilli because their lesions generally harbor fewer bacilli. However, since initial resistance to isoniazid is very common in many areas, and the routine testing of HIV in TB patients is not usually practiced, the 2003 WHO guidelines recommended the inclusion of ethambutol as the fourth drug in the initial phase of treatment of smear-negative TB. [LEVEL 3]⁴

In areas where mycobacterial cultures and drug susceptibility testing (DST) are available, the 2002 ATS/CDC/IDSA guidelines recommend that smear-negative patients assessed to have PTB based on careful clinical and radiographic evaluation must be treated with isoniazid, rifampicin,

pyrazinamide, and ethambutol. If *M. tuberculosis* is subsequently isolated, treatment for active TB should be continued (2HRZE/4HR). Patients who have negative cultures but are presumed to have PTB should have follow-up clinical and radiographic evaluations after completing the initial two months of therapy to determine whether a response that can be attributed to anti-TB treatment occurred. If there is either clinical or radiographic improvement and no other etiology is identified, treatment should be continued for active TB with isoniazid and rifampicin for an additional two months. If, however, the patient demonstrates neither symptomatic nor radiographic improvement, then prior TB is unlikely; and treatment is then considered completed when at least two months of rifampicin and pyrazinamide have been administered. On the other hand, HIV-infected patients with culture-negative PTB should be treated for a minimum of six months [LEVEL 3].⁵

In HIV-affected areas, some studies suggested the use of rifampicin-based short-course chemotherapy under DOT for all new cases of tuberculosis, regardless of smear status. It is hypothesized that this universal regimen may provide survival benefits for HIV-positive cases, although no studies have been done so far. Moreover, a single short course chemotherapy regimen for all new cases will avoid confusion, simplify guidelines, increase completion and cure rates, and reduce non-adherence and side effects.^{17,18} However, the possibility of over treatment of non-tuberculosis cases and the disadvantage of significant additional costs should be weighed and addressed adequately.¹⁷

2. Previously Treated Patients

a. How should relapse patients be treated?

- A relapse patient is one who has been declared cured of any form of TB by a physician, after one full course of chemotherapy under DOT, and has become smear-positive again.
- For relapse patients who were treated under DOT, re-treatment using the Category II regimen (**2HRZES/1HRZE/5HRE**) is recommended. The re-treatment regimen consists of an initial phase of isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin given daily for two months, followed by one month of daily isoniazid, rifampicin, pyrazinamide, and ethambutol. The

continuation phase consists of five months of daily isoniazid, rifampicin, and ethambutol. Observational studies have shown that relapses after a previous SCC regimen given under DOT have the same drug susceptibilities as the initial treatment isolates. **[Grade B]**

Summary of Evidence

A relapse patient is one who has been declared cured of any form of TB by a physician after one full course of chemotherapy under DOT, and has become smear-positive again. Where TB cultures are routinely available, relapse refers to the circumstance wherein patients become and remain culture-negative while receiving anti-tuberculosis drugs but, at some point after completion of therapy, either become culture-positive again or experience clinical or radiologic deterioration consistent with active TB.¹⁹

A summary of 9 studies from the British Medical Research Council showed that 90.7% of patients developing relapse after treatment with a regimen of isoniazid, rifampicin, pyrazinamide and streptomycin remained fully susceptible to these drugs. Among the resistant strains, resistance to isoniazid was highest at 6.2% while resistance to both isoniazid and rifampicin (MDR TB) occurred in only 1.7% [LEVEL 2].¹⁹

In a review of several controlled clinical trials in India using standardized SCC under supervision, investigators showed that strains cultured during relapse had similar drug susceptibilities as the original isolates [LEVEL 2]. Of 1,356 patients with fully drug-susceptible organisms prior to treatment, 96.8% remained sensitive to the drugs during relapse. Of 31 patients with isoniazid-resistant strains prior to treatment, only 2 patients (6.5%) developed subsequent resistance to rifampicin.²⁰ The results support previous observations that relapses occurring after rifampicin-containing regimen given under DOT have the same drug susceptibilities as the initial treatment isolates [Level 3]. However, a subsequent review of relapse patients in India showed only 50.7% had fully susceptible isolates at the start of re-treatment, although the level of initial drug resistance was not reported.²¹

In a study of 832 patients receiving 4 different regimens containing rifampicin and INH, relapse occurred in 34 (4.1%) patients. The relapse strains were fully drug susceptible in 28 of 34 (**82%**) patients in whom relapse occurred.²² In another study patients previously treated for TB and who suffered a relapse or a recurrence of TB after previously abandoning their treatment, 22 of 31 (71%) had fully susceptible organisms and 24 (77%) achieved cure after re-treatment. Their rates of susceptibility and cure rates

where higher as compared with patients who failed to respond after their first- or second-line treatment.²³

In low-income countries where culture and DST are not routinely available, the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommend a standardized regimen for patients who have relapsed, had interrupted treatment, or have failed treatment. The re-treatment regimen consists of an initial phase of isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin given daily for two months, followed by one month of daily isoniazid, rifampicin, pyrazinamide, and ethambutol. The continuation phase consists of five months of daily isoniazid, rifampicin, and ethambutol.⁴ There are no randomized, controlled trials comparing this regimen with other possible regimens. The recommended re-treatment regimen had a 65% success rate and 30% failure rate among 37 relapse patients in Turkey²⁴ while an 80% success rate and a 3% failure rate were documented in 113 patients in Benin.²⁵ The difference in outcomes was attributed to the differences in MDRTB rates among relapse cases, i.e., 17.5% in Turkey and 11% in Benin.

In settings where mycobacterial cultures, DST, and second-line drugs are available, the ATS and the CDC recommend re-treatment using the standard 4-drug initial phase regimen until the results of susceptibility tests are known for relapse patients documented to have drug-susceptible organisms and were treated through DOT [EXPERT OPINION].⁵

In hyperendemic areas, exogenous re-infection with a new strain of *M. tuberculosis* may be responsible for the apparent relapse. DNA studies using restriction fragment length polymorphism analysis suggest exogenous re-infection in 75% (12 of 16) of relapse patients in Cape Town,²⁶ South Africa, 44% (8 of 18)²⁷ in Gran Canaria Island, Spain, and 16% (5 of 32) in Italy.²⁸ In these cases, and in situations where a strong suspicion of exogenous re-infection exists, the resumption of a standard four drug initial phase is indicated if the presumed source case is known to drug-susceptible TB. If the likely organisms are drug resistant, an empirically expanded regimen based on the resistance profile of the source may be suitable [EXPERT OPINION].⁵

b. How should persistently symptomatic patients treated outside of DOTS be managed?

- For persistently symptomatic patients who received non-supervised self-administered therapy or used regimens that did not contain rifampicin, the risk of acquired drug resistance is high. TB culture

and DST are recommended. The Category II retreatment regimen (**2HRZES/1HRZE/5HRE**) can be given pending DST results. **[Grade B]**

c. How should PTB patients who have interrupted treatment be managed?

For patients who interrupt treatment and return after default, the Category II re-treatment regimen (**2HRZES/1HRZE/5HRE**) is recommended **[Grade C]**.

Summary of Evidence

There are no studies supporting the treatment regimens for patients who have interrupted treatment. Current recommendations are based on expert opinion.

The WHO recommends a standard retreatment regimen (2HRZES/1HRZE/5HRE) for defaulters – patients who have completed at least one month of treatment and returned after at least two months interruption of treatment.⁴ In Turkey, the observed success rate for defaulters (N=20) with this re-treatment regimen was 85%, which was better than the success rate seen in relapse cases (65%).²⁴ A study by Abate et al, reported similar results in a comparison between relapse cases and defaulters.²⁹ On the other hand, only a 59% success rate for defaulters was observed in a study done in Benin (N=39) compared to 67% for relapse patients.²⁵

The local NTP guidelines recommend that new or re-treatment cases who interrupt treatment for < 2 weeks in duration should continue their current regimen. If the interruption is 2 to 8 weeks in duration but the smear is negative, the current regimen is also continued. However, if interruption is 2 to 8 weeks in duration and the smear remains positive, the current regimen is restarted from the beginning. For interruptions > 8 weeks in duration the patient is reclassified as “Return after Default” or “Others”, depending on the sputum status. The category II retreatment regimen is then started [EXPERT OPINION].³⁰

The ATS/CDC/IDSA guidelines state that there is no evidence on which to base the recommendations for managing interruptions in treatment, and no recommendations will cover for all of the situations that may arise. If treatment is interrupted for > 2 weeks during the intensive phase, treatment must be restarted from the beginning. However, if the lapse is < 2 weeks,

the treatment regimen should be continued. In either case, the total number of doses targeted for the initial phase should be given. If treatment is interrupted during the continuation phase after the patient has received > 80% of the planned total continuation phase doses given by DOT, further treatment may not be necessary if the patient's sputum was AFB smear negative on initial presentation. Patients who were smear-positive initially need continued treatment to complete the planned total number of doses. If the patient has received < 80% of the planned total doses, however, and the lapse is >3 months in duration, treatment should be restarted from the beginning. If the lapse is < 3 months in duration, treatment should be continued to complete a full course [EXPERT OPINION].⁵

d. How should treatment failure be managed?

- **Treatment failure** – a patient who remains smear positive towards the end of treatment, or after completion of a SCC under DOT.
- Sputum culture and DST should be done because treatment failure after SCC given under DOT is a strong indication of MDR-TB. The re-treatment regimen (2HRZES/1HRZE/5HRE) may be given after specimens for culture and DST are obtained, although failure rates with this regimen are quite high. [Grade C]
- Considering the complexity of the treatment of these patients and the significant amount of resources required, it is recommended that treatment failures be managed under a Programmatic MDR-TB Management (PMTM) program.* Pending the full integration of the PMTM program into the NTP, such patients should be referred to the TB regional coordinator for appropriate action.

* Makati Medical Center PMTM, Lung Center of the Philippines

Summary of Evidence

Failure is a strong indication for the presence of MDR-TB. In most settings, treatment failure with the standard SCC regimen had a higher probability of being multi-drug resistant, particularly if the whole treatment was directly observed and included rifampicin in the continuation phase. MDR-TB was present in 33% to 93.8% in patients who failed the first course of SCC, and rates tended to be higher if previous treatment was done under DOT [LEVEL 2].^{21,23,31}

The WHO recommends a standardized re-treatment regimen consisting of 5 drugs in the initial phase & 3 drugs in the continuation phase (2HRZES/1HRZE/5HRE). This standardized re-treatment regimen can cure patients excreting bacilli still fully sensitive to the drugs and those excreting bacilli resistant to isoniazid and/or streptomycin.⁴

However, because of the higher probability of MDR-TB among failures of the standard SCC, the re-treatment regimen is expected to have poor results (< 50% cure rates). Using this regimen in multi-drug resistant cases leads to an inadvertently ineffective therapy and causes further resistance in patients with MDRTB, also known as the **amplifier effect**. Data on patients from China, Russia, Korea, Hong Kong, Italy and Peru who were given the WHO-IUATLD recommended re-treatment regimen showed that only **57%** were treated successfully, 6% died, and 14% failed short-course chemotherapy. Failure rates among re-treatment cases were higher in those with MDR-TB and with isoniazid resistance alone or with other drugs. The authors concluded that SCC based on first-line drugs is inadequate for some patients with drug-resistant TB, even under DOT [LEVEL 3].⁹

Kritski et al.²³ in a prospective cohort showed that 53% of patients who had previously failed treatment with first-line drugs, had unfavorable outcomes (failure, death or abandonment) during re-treatment. In those who failed after treatment with second-line drugs, unfavorable outcomes occurred in 57%, while cure was seen in 36% only. On logistic regression analysis, **unfavorable response (failure to sterilize sputum culture, death, and abandonment) was associated with resistance to two or more drugs (p = 0.0002), cavitory disease (p = 0.0029), and irregular use of medications (p < 0.0001).** [LEVEL 2]

In a consecutive sample of 173 patients identified as treatment failures on DOT-SCC, 160 had culture positive TB and of these, 150 (93.8%) had active, pulmonary MDR-TB. 44 of the 150 (29.3%) had isolates resistant to INH, RIF, EMB, PZA and streptomycin, the first re-treatment regimen.³¹

A review of culture results of 1,472 patients who have received anti-TB drugs and who remained symptomatic or smear-positive despite receiving anti-TB drugs *under DOTS* for a minimum of 5 months showed resistance to one drug in 10.5%, to two drugs in 18.1%, to three drugs in 14.8%, and to all 4 drugs in 7.5%. *Resistance to INH and rifampicin was found in 56.2%.* Only 30% of the treatment failures had fully susceptible organisms compared to 50.7% in the relapse cases.²¹

In an observational study in Vietnam, only 33% (14 of 42) of patients who had documented MDRTB and had completed a standard WHO re-treatment regimen, became sputum smear-negative at the end of treatment [LEVEL 3].³²

For this reason, countries with a high proportion of MDR-TB among failures of the standard SCC should consider treating such failures with specially designed, individualized regimens. It should be emphasized, however, that the introduction of these regimens for such failures requires either individualized susceptibility testing (DST) or representative drug-resistance surveillance (DRS) data in the patient category concerned. Culture and DST should be quality-assured and all programmatic conditions for the introduction of a PMTM component within the regular DOTS program should be met. Standardized or individualized regimens should only be introduced in well-performing DOTS programs and should be specifically tailored to the local situation, i.e., in terms of drug-resistance, history of drug-use in the country, human and financial resources.⁴

In settings where relevant programmatic and DRS data are lacking, or in programs where most of the failures to the standard SCC are due to poor program performance, the re-treatment regimen should be applied until sufficient resources are available, the program is strengthened, and the conditions previously mentioned are met. Whenever program conditions permit the use of alternative regimens, the standard re-treatment regimen should not be used for failure cases at high risk for MDR-TB.⁴

Table XII. Summary Table of Studies on Sensitivity Patterns of Re-treatment Cases after Failure of Initial Treatment, 1997 - 2005

Reference	Site	No. of cases	Fully-sensitive Number (%)	MDRTB Number (%)
Kritski, 1997 ²³	Brazil	89	45 (50.1%)	29 (32.6%)
Becerra, 2000 ³¹	Peru	160	-	150 (93.8%)
Espinal, 2000 ⁹	Russia, China, Korea, Peru, Dominican Republic, Hong Kong	874		169 (19.3%)
Noeske, 2002	Cameroon	124	59 (47.6%)	17 (13.7%)
Shah, 2002 ²¹	India	373	112 (30%)	56%
Chiang, 2004	Taipei	33	10 (30.3%)	22 (66.7%)

Table XIII. Summary Table of Studies on Clinical Results of Re-treatment

Reference	Site	Number	Success	Failed	Died
Espinal, 2000 ⁹	Russia, China, Korea, Peru, Dominican Republic, Hong Kong	874 re-treatment cases	497 (57%)	124 (14%)	51 (6%)
Lan, 2001 ³²	Vietnam	42 (documented MDRTB)	14 (33%)		1 (2.4%)
Sureyyapasa, 2002	Turkey	57 (relapse & defaulters)	41 (71.9%)	13 (22.8%)	
Gninafon, 2004 ²⁵	Benin	236 (113 relapses, 84 failures, 39 RAD)	184 (78%)	7 (3%)	

3. Drug-resistant tuberculosis

When is drug-resistant TB suspected in a patient?

Drug-resistant tuberculosis is suspected in the following situations:

1. when a smear-positive patient does not respond to the standard WHO re-treatment regimen especially if the treatment was given under DOT
2. when a patient continues to have positive sputum smears after 2 months of SCC under DOT
3. when a patient has had a history of close or long-term exposure to a person with documented resistance to anti-TB drugs, or to a person with prior history of treatment whose susceptibility test results are not known

Drug-resistant tuberculosis is defined as resistance of the TB bacilli to one or more anti-TB drugs based on DST results.

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance of the TB bacilli to both isoniazid and rifampicin based on DST results

How should suspected drug resistant TB cases be managed?

- Immediate referral to highly specialized centers with a PMTM program is advocated for patients with drug resistant TB [Grade C]. This is because:
Approximately 50% or more of treatment failures are MDR-TB
Amplification of resistance can occur in at least 30% of patients given the re-treatment regimen
Second-line reserve drugs are more expensive, less effective, and have more side effects than the standard anti-TB drugs.
- Treating MDRTB empirically, especially with fluoroquinolones is not recommended [Grade C].
- Treatment under a PMTM program operating within an existing and well-functioning DOTS program is the recommended strategy for managing MDR-TB to ensure the following:
availability of quality-assured laboratory services, DST in particular
administration of individualized treatment regimens based on DST results
uninterrupted supply of high-quality second-line drugs
institution of measures to promote adherence to treatment
proper monitoring and evaluation of the treatment regimen.
- All patients should be advised on standard precautions including cough etiquette* to prevent transmission to other patients, household members or to the community.

*Cover your nose/mouth with a handkerchief/tissue when you cough or sneeze. Dispose used tissues containing respiratory secretions in the nearest waste receptacles. Wash your hands with soap and water or an alcohol-based handrub after coughing or sneezing. Avoid spitting. The patient may be advised to wear a surgical mask.

Summary of Evidence and Rationale

The management of MDR-TB is particularly difficult. It involves the use of second line, reserve drugs: drugs that are more expensive, less effective, and possess more side effects than the standard drugs. The second-line regimens often represent the patient's last best hope for cure; inappropriate management can therefore have life-threatening consequences.⁵ The WHO recommends **immediate referral** of patients with MDR-TB to highly specialized centers.^{4,5, 33,34} The likelihood of failure in a patient with probable MDR-TB is high (achieving less than 50% cure rates) when the

standard WHO re-treatment regimen is used. Furthermore, amplification of resistance to the other first line drugs is likely to develop (30%) if a single drug is added to a failing regimen.

Definitive randomized or controlled studies have not been performed among patients with various patterns of drug resistance. In the absence of ideal evidence, treatment practices are based on a mixture of general principles, extrapolations, and expert opinion.

Observational studies done on MDR-TB patients in both developed and developing countries utilized individualized treatment regimens composed of 3-9 drugs given for 12-24 months under hospital-based or domiciliary DOT. The success rates ranged from 63 to 83%. (See Table XIV)

In the Philippines, the Makati Medical Center, then called the DOTS-Plus pilot project reported the preliminary outcome of the first 149 MDRTB patients enrolled in the program from April 1999 to May 2000. Using individualized treatment regimens of five drugs, the rate of cure and likely cure rates in 79 patients who completed 12-18 months of treatment was 73.4%. Failure and likely failure rates were reported at 3.8% and 6.3% respectively, death at 3.8%, and default at 11.4%.³⁵

The Programmatic MDR-TB Management (PMTM), previously DOTS-Plus

The Programmatic MDR-TB Management, previously called the DOTS-Plus is a strategy for the management of MDR tuberculosis designed to operate within an existing and well functioning DOTS program. This strategy offers two general approaches to treatment anchored on existing program capabilities:⁴

1. Standardized treatment in which all patients with MDRTB receive the same treatment regimen derived from the predominant patterns of resistance in the community; or
2. Individualized treatment in which patients with MDRTB receive comprehensive drug susceptibility testing, and treatment regimens are tailored accordingly.

A PMTM program requires the following:³⁴

1. Linkage with a country's NTP

2. Specialized clinical expertise
3. A surveillance component
4. High-quality laboratory support
5. An uninterrupted supply of all second- and third-line drugs
6. Adequate personnel/resources to deliver care to the home or other institutions/facilities

The following comprise the components of a PMTM Program:

- Political commitment to treat TB including MDR-TB
- Coordination of efforts between & within the community, local government and international agencies
- A specialized unit for MDR-TB patients
- Availability of specific laboratory services including reliable DST
- An appropriate treatment strategy that utilizes second-line drugs
- A reliable supply of high-quality second-line anti-TB drugs
- Institution of parameters to promote patient adherence to treatment
- An information system for proper data management, monitoring of performance and evaluation of the intervention

A decision analysis modeled at different levels of program effectiveness of DOTS and DOTS Plus showed that under optimal implementation, fewer TB deaths would occur under DOTS-Plus than under DOTS using a hypothetical cohort. However, if implementation of DOTS-Plus is associated even with minimal decreases in the effectiveness of DOTS, more patients would die with TB under DOTS Plus than under DOTS alone. Specifically, the model predicted that under DOTS, 276 people would die from TB (24 MDR, 252 not MDR) over 10 years under optimal implementation in an area with 3% primary MDRTB. Optimal implementation of DOTS Plus would result in 1.5% fewer deaths. If implementation of DOTS Plus were to divert resources from DOTS resulting in a decrease of just 5% in the effectiveness of DOTS, 16% more people would die with TB than under DOTS alone. If the effectiveness of DOTS is decreased by 10%, a 40% increase in deaths would occur. In an area with 10% primary multi-drug resistant TB, optimal DOTS plus would result in 10% fewer deaths than under optimal DOTS, but 16% more deaths would occur if the effectiveness of DOTS is decreased by 5% as a result of implementation of DOTS Plus.³⁶ Thus, it is important that a scaled up

implementation of DOTS Plus will not divert resources from the first line of treatment. Further modeling using our updated MDR resistance rates and local costs is recommended to determine the cost-effectiveness of DOTS-Plus in the country.

The Makati Medical Center PMTM Clinic

In August 2000, the Green Light Committee of the WHO working group on DOTS-Plus for the management of MDRTB approved the Makati Medical Center DOTS Clinic as the first pilot project on DOTS-Plus in the Philippines. In 2006, the program was renamed Programmatic MDR-TB Management or PMTM. To date, this is the only accredited referral center for MDRTB patients.

Clinic Schedule:

Monday to Friday – 4:00 pm to 8:00 pm

Saturday – 12:00 noon to 4:00 pm

Contact Numbers:

(02) 8102874

(02) 8159911 loc. 7256 / 7288

Satellite Centers: (Monday-Saturday 8:00 am to 5:00 pm)

Quezon Institute

Lung Center of the Philippines

Requirements for Referral:

NTP Treatment Card

Clinical Abstract

What is drug-resistant tuberculosis?

Drug-resistant tuberculosis is a case of tuberculosis, usually pulmonary, excreting bacilli resistant to one or more antituberculosis drugs.³⁵

Primary vs. acquired resistance

Primary resistance refers to the bacterial resistance in present in patients who have not received prior treatment with antituberculosis drugs. **Acquired resistance** refers to the bacterial resistance in patients with some record of previous treatment. Primary resistance occurs as a consequence of the level of acquired resistance in the community. The greater the number

of patients who excrete resistant bacilli during or after treatment, the higher is the risk of transmission of resistant bacilli to healthy individuals and the greater the emergence of new cases with primary resistance.³⁵

What is multi-drug resistant tuberculosis (MDR-TB)?

A patient with MDR-TB is one who has active tuberculosis with bacilli resistant to rifampicin and isoniazid, the main antituberculosis drugs.

How does MDR tuberculosis develop?

The phenomenon of MDR tuberculosis is entirely man-made. The human errors which led to the development of MDR-TB are summarized as follows:^{35,37}

Health provider-related:

1. the prescription of inadequate chemotherapy to the multibacillary pulmonary cases, e.g. only 2 or 3 drugs during the initial phase of treatment in a new smear-positive patient with bacilli initially resistant to isoniazid;
2. the addition of one extra drug in the case of failure, and repeating the addition of another drug when the patient relapses after a regimen that is effectively equal to monotherapy;

Patient-related:

1. the patient's lack of knowledge (lack of information or inadequate explanation before starting treatment);
2. the difficulty experienced by poor patients in obtaining all the needed drugs because of the lack of financial resources or social insurance;

Management-related:

1. frequent or prolonged shortages of antituberculosis drugs due to poor management and/or financial constraints in developing countries;
2. poor case-management, e.g. treatment not directly observed especially during the initial phase.

What is the role of surgery in the management of MDRTB?

- **Indication for surgery**

Adjuvant resectional surgery may be considered for a patient with pulmonary MDRTB having reasonable lung function. (Grade C)

- **Timing of surgery**

To avoid serious and potentially fatal complications, an experienced surgeon must do the procedure when the bacillary population is likely to be at its lowest. Experience shows that the most favorable time is after two months of intensive chemotherapy. (Grade C)

- **Anti-tuberculosis chemotherapy after surgery**

After surgery, chemotherapy should be continued for 12-24 months to prevent relapse. (Grade C)

Summary of Evidence

The role of resectional surgery in the management of patients with extensive pulmonary MDRTB has not been established in randomized studies. Case series reports on cure rates with surgery have shown mixed results. A recent review of the results of adjuvant resectional surgery in MDRTB patients in Turkey showed favorable cure rates at 94.5% (70/74 patients) with relapse and treatment failure rates of 1.3%. Operative mortality was 2.5% and bronchopleural fistula developed in 4 patients. All the patients had at least 2 months of medical therapy before resection.³⁸

Table XIV. Summary Table of Observational Studies on MDR-TB

Authors/Year study was conducted	Country	# of patients in the study	Study Population	Regimen: Standardized vs. Individualized	Hospital vs Community-based	Treatment Duration	Follow-up Duration	Outcome
Tahaoğlu, et al ¹⁹ Mar 1992- Oct 1999	Turkey	138	Adult patients HIV (-), 34 new & 124 old infections; extensive disease in 63, limited in 95 patients	Individualized, with 3-9 drugs (mean 5.5) Regimen chosen from list of previously unused drugs and resistance pattern; surgical resection in 36 patients	Hospital	At least 18 months after "1" negative culture and at least 24 months in the absence of "1" line drugs	6-85 months after completion of treatment (mean 27 months)	Overall success rate: 77% (Cure in 78 patients 49%) Probable cure in 43 (27%) Treatment failure in 13 (8%) Incomplete treatment in 17 patients (11%) Death in 7 (4%) *Outcomes as defined by WHO
Perez-Guzman, et al ⁶ Apr 1994- Dec 1995	Mexico	50	Adults MDR =18 Non-MDR=13	Individualized, with 4-6 drugs Selection based primarily on drug sensitivity and secondarily on history of previous treatment	Community, self-administered	12 months	5 yrs	31 completed treatment —28 (90.3%) cured, Treatment failure in 3 (9.7%) 13 (26%) abandoned treatment Treatment irregular* in 6 (12%) After 6 months: relapse 4.8% (1/21) After 5 yrs. 77.8% (14/18) of cured patients remained asymptomatic
Yew, et al ⁴¹ Feb 1990- June 1997	Hong Kong	63	12-77 yrs old (mean 45.2+/-16) HIV (-)	Individualized, with 3-6 drugs (mean 4.7) Regimen chosen based	Hospital a DOT	Mean 14.0 +/- 3.7 months	Mean 24.5 +/- 16.5 months (3-75 months)	Cure in 51 (81%) (Treatment failure in 9 patients (14.3%) Death in 3 (4.7%) Relapse in 1/47 (2.1%)
Chan E, et al ⁴² Jan 1994- Dec 1998	Colorado, USA	205	2-85 yrs old (mean 39.9), 103 foreign- born with 50 origina-	Individualized, selection based on susceptibility tests and history of previous treatment* 130 patients	Hospital — DOT	15- 18 months after last sputum positive culture		

Mitnick C, et al ⁴³ Aug 1996- Feb 1999	Lima, Peru	75	ing from East Asia or Pacific island	Individualized, with 5-9 drugs (median 6) (Selection based on drug susceptibility tests	Community	At least 18 months (median 23 months)	7-66 months (median 40 months)	66 completed treatment —55 (83%) probable cure*, 5 (6%) withdrew, 1 failed**, 5 (6%) died* 12 months consecutive (-) cultures during treatment** (+) culture after 6 months treatment
Leimane V, et al ⁴⁴ Jan 1- Dec 31, 2000	Lavija	204	Adults, HIV +	Individualized: Initial regimen - 4 to 8 drugs chosen based on treatment history/Modified based on DST results — at least 5 susceptible drugs	Hospital —DOT	12-18 months after sputum culture conversion		135 (66%) Cure 14 (7%) Died 29 (14%) Failure 26 (13%) Default *WHO definition
Narita M, et al ⁴⁵ Jan 1994- July 1997	Florida, USA	81	Adults, HIV + (15/31-Community 16/39- Specialized TB Care)	Community: Median of 3 (0-5) Specialized TB Care: Median of 5 (3-10)	2 groups compared: Community (31) vs Specialized TB Care/ Hospital —DOT (39)	Community: Specialized TB Care: at least 12 months after sputum culture conversion to negative		Community: 15 (48%) completed treatment, 8 (26%) Death, 8 (26%) Incomplete treatment Spec TB care: 31 (79%) completed treatment, 7 (18%) Death, 1 (3%) Incomplete treatment
Tupasi T, et al ⁴⁶ Apr 1999- May 2002	Philippines	149	Adults	Individualized, 5 drugs/Basis: drug susceptibility and history of previous treatment	Community, DOTs: Plus Clinic	12-18 months of treatment	On-going	Preliminary results: (N=79) Cure and likely cure — 73.4% Failure — 3.8% Likely failure — 6.3% Death — 3.8% Default — 11.4%

WHO Outcome Definitions:

- Cured — patients who completed treatment and M. Tb culture negative for the last 12 months of treatment
- Treatment completers — clinically cured but not meeting the bacteriological requirement for cure
- Defaulter — patients with 2 or more consecutive months of treatment interruption
- Failure — more than 1 positive M. Tb culture during the past 12 months of treatment
 - those with 1 of their last M. Tb cultures positive
 - those remaining persistently M. Tb culture positive with treatment being stopped by physician
- Died — those who died from any cause at any point during treatment
- Probable cure — negative smears and cultures throughout treatment for at least 6 months
- Relapse — recurrence of positive smear or culture after achievement of a cure

B. ORGANIZATION AND SUPERVISION OF TREATMENT

1. How effective is DOT compared to non-DOT in the management of TB?

- All diagnosed TB patients should be offered patient centered, directly-observed treatment (DOT) in health care facilities with accredited DOTS programs (PPMD units, hospitals, clinics, local health centers etc), whenever possible, to monitor adherence to treatment and to ensure completion of treatment [Grade B]. Treatment of patients with TB is most successful within a comprehensive framework that addresses both clinical and social circumstances relevant to the patient.
- Self-administered (unsupervised) therapy without any plans to monitor or facilitate adherence to treatment is not recommended. The responsibilities of the physician – whether in the private or public sector – are not only limited to the prescription of an appropriate regimen but should include ensuring the successful completion of therapy.

Summary of Evidence

Data from studies of DOT done under program conditions indicate that it can be an effective and cost-effective strategy if properly implemented and with the proper resources. The data from randomized controlled trials, however, have so far failed to show the clear superiority of DOT over unsupervised treatment [LEVEL 2].

An updated systematic review of 4 RCTs (n=1,603) showed no statistically significant difference between DOT and self-administration of treatment in terms of the cure rates (RR 1.02; 95% CI 0.86, 1.21) and cure plus treatment completion rates (RR 1.06; 95% CI 1.00, 1.13). Stratifying the location of the DOT by home or at a clinic suggested a possible small effect with home-based DOT in terms of cure rates (RR 1.10; 95% CI 1.02, 1.18; 3 trials, n=1,365) and cure plus completion rates (RR 1.09; 95% CI 1.02, 1.16).⁴⁶

Though some of the apparent benefits of DOT may in fact represent the other components of the DOTS strategy of which it is considered an integral component, it is difficult to isolate the independent contributions of

these components under program conditions because they are often administered together as an integrated package. A qualitative study which explored the concept of DOT from different professional and geographical perspectives showed that the implementation of DOT is shifting from a rigid model involving observation of drug swallowing to one which includes incentives and enablers tailored to the local context and to the needs of specific groups of patients.⁴⁷

A review of the published treatment outcomes of contemporary (HIV-era) DOT cohorts (1990-2000)⁴⁸ examined the reasons and the frequency of TB management failures despite DOT. The review focused on treatment failures and post-treatment relapses. From 34 eligible studies comprising 6,822 patients diagnosed by culture and 71,431 diagnosed by smears, treatment failure under DOT in patients who remained on treatment occurred in <5% of patients in 26 of 30 reports. The average failure rate was $2.4\% \pm 2.2\%$ for 21 culture-based studies and $2.5\% \pm 1.7\%$ for 9 smear-based studies. However, on intention-to-treat analysis (including non-adherent or lost to follow-up patients) the combined rate of failure plus default was 11.1% for culture- and 10% for smear-based studies. The crude relapse rate was 3.6% in 21 culture-based studies (it was 3.2% and 3.3 % in 2 smear-based studies). The net effectiveness of DOT under program conditions ranged from substandard to excellent with the differences largely attributed to non-adherence. Most programs, however, obtained better results than the pre-DOT era, although 16 of the 34 studies failed to reach the WHO's target cure rate of 85%.

The cost-effectiveness of DOT was examined in four economic analyses based on urban experience in the US. In 3 of the 4 studies, universal DOT was determined to be both more effective and less costly per case cured than unsupervised treatment. The fourth study (based on outcomes in selected patients at low risk of default) questioned the cost-effectiveness of universal DOTS and suggested that enhancing the quality of suboptimal TB programs may be more useful than expanding DOTS coverage nonselectively.⁴⁶

Published experience with DOT administered under program conditions indicates that it has improved TB treatment outcomes in a wide variety of settings, although most of the data are observational, and the evidence for DOT's superiority over unsupervised pill taking is largely inferential. Universal DOT has the potential to improve long-term cure rates and to offer cost-effective options in most treatment settings, although its incremental utility would vary in magnitude. Studies where DOT failed

to outperform unsupervised therapy were conducted in settings with limited resources and suboptimal implementation, indicating that program quality must be strong for DOT to yield its potential benefits.⁴⁶

In China, a high-burden country, the cost of treating TB patients per disability adjusted life years (DALY) saved under DOT was lower than the cost under non-DOTS.⁴⁹ However, in another high-burden country, Pakistan, both cost per patient treated and cost per case cured were lower under unsupervised treatment than DOT in the health center, with a community health worker or with a family member.⁵⁰

In an earlier systematic review of studies from 1966 to 1996 by Chaulk et al., the relative effectiveness of DOT was compared with other interventions, in achieving treatment completion for pulmonary tuberculosis. Twenty-seven studies composed of 5 randomized or semi-randomized trials, 12 prospective trials without controls, 7 retrospective studies, 2 case-control studies and one cross-sectional report were included in the review. Twelve studies based on comprehensive DOT using multiple incentives and enablers reported the highest treatment completion rates, ranging from **86 to 96.5%** (median 91%). Relapse rates ranged from 0 to 11.5%. The 4 studies of DOT without incentives and enablers reported treatment completion rates ranging from **85 to 87.6%** (median 86.3%), with relapse rates from 0.8 to 4.9%. Partially supervised (modified) DOT treatment completion rates ranged from **78.6 to 82.6%** (median 78.6%). In 9 studies with non-supervised strategies, the treatment completion rates ranged from **41.9% to 82%** (median 61.4%), and relapse rates ranged from 2.1 to 4.5%.⁵¹

2. *Who are the effective types of treatment partners?*

- DOT can be done in the community under the supervision of lay health workers [Grade A], community volunteers [Grade A] and trained family members [Grade A]. Community-based DOT is as effective as, and less costly than, DOT administered at health facilities by clinic workers. Treatment success rates did not differ significantly between health facility-based DOT, community-based DOT and family member-based DOT.
- The mode of treatment supervision must take into consideration the patient's clinical, social and cultural circumstances.

Summary of Evidence

Three randomized, controlled trials have compared treatment outcomes between clinic-based DOT and community-based DOT. Two of the trials show that DOT administered in the community under the supervision of community volunteers had similar treatment outcomes as DOT in a health facility. Treatment success rates among patients under community and health-facility based DOT were 85% and 83%, respectively (OR 1.17, 95% CI 0.75, 1.83) in an urban district in Tanzania.⁵² An earlier study in a rural district in Tanzania showed no significant difference in conversion rate and cure rates between community-based DOT and institution-based DOT (OR 0.62, 95% CI 0.23, 1.71, and OR 1.58, 95% CI 0.32, 7.88, respectively).⁵³ A third clinical trial, however showed that supervision by local health workers (LHW) approached statistically significant superiority over clinic nurse DOT in terms of successful outcome (74% for LHW and 57% for clinic nurse), and risk difference (17.2%; 95% CI 0.1%, 34.5%).⁵⁴

Three cost-effectiveness studies showed that DOT using community health workers (CHW) entailed fewer maintenance expenses than DOT in health facilities. In Bangladesh, the cost per patient cured was US\$ 64 in CHW-based community centers, and US\$96 in government health facilities.⁵⁵ In Pakistan, the cost per patient treated was US\$180 in health center-based DOT and US\$115 in CHW-supervised DOT, while cost per case cured amounted to US\$310 and US\$ 172, respectively.⁵⁶ In an urban setting in Tanzania, community-based DOT was more cost-effective at \$128 per patient successfully treated compared to \$203 for a patient successfully treated with health facility-based DOT. Community based DOT reduced cost by 35%. The main reason for reduced cost was less number of visits to the clinic.⁵⁷

The use of family members as DOT supervisors also demonstrated similar results. A recent cluster-randomized controlled trial conducted in the hill and mountain districts of Nepal showed that community DOTS and family-member DOTS achieved success rates of 85% and 89% respectively (OR 0.67, 95% CI 0.41 to 1.10).⁵⁸

In a retrospective study in Thailand, the over-all cure rate was 80.4% when trained and supervised family members were used, compared to 76.2% for health service staff.⁵⁹ In Pakistan, cure and completed treatment rates were 67% for health-worker DOT and 62% for family-member DOT. In terms of cost-effectiveness, the implementation of family DOT was less expensive costing US\$102 per patient treated while health center DOT cost US\$180.⁵⁴

3. *Aside from DOT, what are the effective ways of monitoring adherence to tuberculosis treatment?*

- Monitoring adherence to treatment can be enhanced through repeated home visits, reminder letters, cash incentives, health education by nurses, and the use of community health advisers. These measures should be done utilizing the DOT strategy preferably under a DOTS program [Grade C]. Monitoring adherence to treatment should take into consideration the patient's clinical, cultural and social circumstances.

Summary of Evidence

The use of defaulter actions

One systematic review found that intensive measures through repeated home visits and reminder letters, improved treatment completion when compared with routine action (single reminder letter and home visit) for defaulters.⁶⁰ This Cochrane review included two RCTs conducted in India.⁶¹ The first RCT (170 people randomized; 150 followed up) showed that up to four visits to defaulters significantly improved completion of treatment compared with the routine policy of a reminder letter followed by one home visit (RR 1.32; 95% CI 1.02, 1.71). The second RCT (200 people) found that up to two reminder letters significantly improved completion of treatment (RR 1.21; 95% CI 1.05, 1.39), even in people who were illiterate.

The use of cash incentives

The above Cochrane systematic review found two RCTs conducted in the USA. The first RCT showed that cash incentives (US\$ 5, 1992 value) significantly improved attendance at first appointment compared with the usual care (RR 1.6, 95% CI 1.3 to 2.0). The second RCT⁶² found that cash incentives (US\$10, 1985 value) combined with health education significantly improved attendance in people on tuberculosis preventive therapy compared with the usual care (RR 2.4, 95% 1.5 to 3.7) but did not improve attendance in individuals with clinical disease (RR 1.07, 95% CI 0.97 to 1.19). [Level 2]

A randomized controlled trial⁶³ on drug users compared three groups: direct observation at a participant chosen site plus cash incentive per visit; direct observation at a designated site plus \$5 per visit; and direct observation at a participant chosen site without cash incentive. Both groups given cash

incentives were significantly more likely to complete treatment compared with the group given no cash incentives (OR 29.7, 95%CI 6.5 to 134.5 when DOT was done on a chosen site, and OR 39.7, 95%CI 8.7 to 134.5, when DOT done on designated site).

One RCT which compared immediate cash incentives versus deferred cash incentives in drug users with latent tuberculosis found no significant difference in treatment completion rates (83% vs. 75%, $p = 0.09$).⁵⁹

The use of health education

One RCT showed that health education by a nurse improved treatment completion compared with an educational leaflet alone (RR 1.30, 95%CI 1.18 to 1.37, when given by telephone, and RR 1.33, 95%CI 1.20 to 1.38, when given during a visit). However, the trial found no difference in treatment completion rates between consultation with a clinic doctor and the educational leaflet alone (RR 1.09, 95% CI 0.89 to 1.23).⁵⁸ Another RCT on drug users found that 5-10 minutes of health education to keep scheduled appointments had no significant effects on attendance rates for scheduled follow-ups compared with no targeted health education (RR 1.04, 95%CI 0.70 to 1.54).⁵⁸ [Level 2]

The use of community health advisers

One RCT showed that among 200 homeless people, consultation with health advisors recruited from the community significantly increased the rate of attendance for treatment compared with no consultation (RR 1.4, 95% CI 1.1 to 1.8).⁵⁸ [Level 2]

A cluster randomized trial among farm workers in South Africa found that motivation and support from a lay health worker was effective in ensuring treatment completion than a conventional DOT-based service. The treatment completion rate was 18.7% higher on farms in the intervention group compared to those in the control group.⁶⁴

C. MODES OF TREATMENT ADMINISTRATION

1. How effective are fixed-dose combination regimens compared to single drug formulations?

- Fixed-dose combination drugs with known bioavailability, given daily, are recommended for newly diagnosed TB patients because

they: minimize the risk of monotherapy and subsequent development of drug resistance [Grade C]; may improve adherence with lesser number of pills to swallow [Grade C]; and reduce prescription errors. [Grade C]

- Adherence and treatment success rates are the same for fixed drug combinations (3-drugs) and single drug formulations (SDF) when given under DOT.
- Single-drug formulations may still be used for: [Grade C]
 1. Patients who experience adverse reactions
 2. Patients with co-morbid conditions that require dose adjustments, e.g. those with hepatic and renal dysfunctions
 3. Patients with disease conditions where the treatment is expected to have significant drug interactions with anti-TB drugs, e.g. those with HIV, diabetes mellitus
 4. Patients at risk for adverse reactions, e.g. elderly patients, those with history of hepatitis

Summary of Evidence

Both the WHO and the IUATLD advocate the use of fixed dose combinations because of the theoretical advantages they pose: these drugs simplify administration and management, reduce the risk of medication errors, and decrease the risk of inadvertent monotherapy and subsequent emergence of drug resistance.⁶⁵ FDCs may be more acceptable to patients because of the lesser number of pills to swallow and the reduced incidence of adverse drug reactions [LEVEL 2]. However, the use of FDC may be associated with a slightly higher but within acceptable relapse rates than SDF [LEVEL 2]. (See Tables 5-7)

Four clinical trials reported that FDC and SDF are equally effective (Table 5). Success rates at the end of treatment were similar at > 95%, although the conversion rate was slightly higher with the FDC regimen (91.2 to 96.1% vs. 86.4 to 95%). However, relapse rates after 5 years were higher in the FDC group (9.3% vs. 2.2%).⁶⁶ These trials used 3-drug FDCs. There are no studies to date on the use of the 4-drug FDCs.

The beneficial effects of FDCs on drug resistance patterns in high prevalence countries are supported by indirect evidence. Relatively low prevalence of MDRTB have been recorded in Brazil and South Africa, where high quality FDCs have been used for decades. In Brazil, 0.9% of culture-positive TB cases in 1995-96 showed initial multi-drug resistance and 5.4%

showed acquired multi-drug resistance. In South Africa, the respective rates were 1.1% and 4.0%.⁶⁷ Additionally, Moulding et al. observed that self-administered treatment with combined isoniazid-rifampicin resulted in minimal acquired drug-resistance in HIV-negative TB cases despite modest rates of incomplete treatment.⁶⁸

The number of tablets taken may be reduced to as few as three or four a day for the whole course of treatment using FDCs. Fewer pills to swallow make treatment easier. In a Hong Kong study, only 1% of 312 patients who received FDCs complained about the quantity of drugs ingested, compared to 5% of 308 patients receiving single drug preparations.⁶⁹

Results from three clinical trials showed that treatment with FDC resulted in either lower or similar adverse drug reaction rates as treatment with single dose formulations.^{70,71,72} A study in Taipei showed that a 3-drug FDC plus separate ethambutol formulation had less cutaneous symptoms, liver function derangements, gastrointestinal complaints, visual disturbances and peripheral neuropathies compared to giving four separate drug formulations.⁶⁵ A study in Indonesia showed patients given a regimen using an FDC of four drugs had less gastrointestinal side effects and muscle joint complaints than those given the four drugs individually.⁶⁶ (Table XVII)

Table XV. Summary of outcomes of FDC vs. SDF studies

Reference	Acceptability	Compliance	Adverse drug reaction	Success at end of	Relapse treatment rate
Hong Kong, 1989 ⁶⁹	FDC > SDF	FDC = SDF	FDC < SDF		
Singapore, 1991 ⁷²			FDC = SDF	FDC = SDF	FDC > SDF
Beijing, 1998 ⁷³		FDC < SDF	FDC = FDC	FDC = SDF	
Taiwan, 2002 ⁷⁰		FDC = SDF	FDC < SDF	FDC = SDF	FDC > SDF
Indonesia, 2003 ⁷¹		FDC = SDF	FDC < SDF	FDC = SDF	

Table XVI. Summary of outcomes of FDC vs. SDF studies

		Sputum/ culture conversion		Treatment success		Relapse rate	
	Regimen(s)	FDC	SDF	FDC	SDF	FDC	SDF
Indonesia, 2003	2HRZE/4HR	186/198 (94%)	143/160 (89%)	188/198 (95%)	152/160 (95%)		
Beijing, 1998	2HRZ/4HR	207/227 (91.2%)	70/81 (86.4%)	224/227 (98.7%)	79/81 (97.5%)		
Singapore, 1991	2SHRZ/4H3R3;	46/46* (100%)	45/47 (96%)	46/46 (100%)	47/47 (100%)	3/46 (7%)	0/47 (0%)
	1SHRZ/5H3R3;	39/42 (93%)	42/46 (91%)	42/42 (100%)	46/46 (100%)	2/42 (5%)	1/46 (2%)
	2HRZ/4H3R3	39/41 (95%)	46/47 (98%)	41/41 (100%)	47/47 (100%)	3/40 (8%)	1/44 (2%)
	Total	124/129 (96.1%)	133/140 (95%)			8/128 (6%)	2/137 (1%)
Singapore, 1999	2SHRZ/4H3R3;					3/42 (6.4%)	0/42 (0%)
	1SHRZ/5H3R3;					4/41 (9.8%)	2/43 (4.5%)
	2HRZ/4H3R3					5/38 (12.2)	1/42 (2.2%)
	Total					12/121 (9.9%)	3/130 (2.3%)
Taiwan, 2002	2HRZE/4HR	25/26 (95%)	22/25 (88.9%)	26/26 (100%)	25/25 (100%)	1/26 (3.8%)	0/25 (0%)

* culture conversion

Table XVII. Summary of FDC vs. SDF studies (Other Drug Reactions)

		GI symptoms		Skin reaction		Muscle-joint	
	Regimen(s)	FDC	SDF	FDC	SDF	FDC	SDF
Indonesia, 2003	2HRZE/4HR	81/198 (41%)	89/160 (56%)	83/198 (42%)	67/160 (42%)	32 (16%)	38 (24%)
Beijing, 1998	2HRZ/4HR					8.9% (total ADR)	8.9% (total ADR)
Singapore, 1991	2SHRZ/4H3R3; 1SHRZ/5H3R3; 2HRZ/4H3R3 Total					Total ADR 52/128 (40.6%)	Total ADR 49/137 (35.8%)
Taiwan, 2002	2HRZE/4HR	0/26 (0%)	5/25 (20%)	4/26 (15.4%)	7/25 (28%)		

2. How effective is daily versus intermittent regimens for the treatment of TB?

A daily regimen is recommended during the initial and continuation phase of treatment, particularly if FDC is used. A thrice-weekly intermittent regimen with single drug formulations may be used during the intensive and maintenance phase. No significant differences in success rates were found between daily and intermittent regimens [Grade B]. Although twice-weekly intermittent regimens are also effective, they are not preferred because of the greater potential impact of missed doses on treatment success [Grade C].

Summary of Evidence

A systematic review by Mwandumba and Squire⁷⁴ yielded one RCT (399 subjects) that compared three times weekly versus daily chemotherapy for six months in people with newly diagnosed pulmonary tuberculosis.⁷⁵ No significant differences in bacteriological cure rates or relapse rates between the two regimens were found one month after treatment was completed. Bacteriological cure rate was 99.9% with 3 times weekly vs.

100% with daily; relapse rate was 5/186 (2.7%) with 3 times weekly vs. 1/192 (0.5%) with daily (RR 4.0; 95% CI 0.7, 24.1). However, the authors concluded that there is not enough evidence to assess the equivalence between fully intermittent, rifampicin-containing short course chemotherapy and a similar daily therapy in patients with PTB.

An RCT done in children⁷⁶ comparing twice weekly versus daily chemotherapy found no significant difference in cure rates between the two regimens (85/89 [95%] for twice weekly versus 114/117 [97%] for daily regimen; RR 0.98, 95% CI 0.84 to 1.02).

The two trials strengthen the hypothesis that no difference between cure rates exists between daily and intermittent (twice or thrice weekly) chemotherapy regimens, however, these studies may have lacked sufficient power to exclude a clinically important difference.

A randomized controlled trial in Singapore⁷⁷ compared four-month daily treatment (2HRZ/2HR) with combined daily treatment during the intensive phase and thrice weekly during the continuation phase (2HRZ/2H₃R₃) in smear-negative TB cases. There was no difference in the relapse rates after five years in the two groups.

A local study by Auer, et al.⁷⁸ compared daily versus thrice-weekly anti-TB treatment in twenty public health centers in Taguig, Metro Manila. Sputum conversion at two or three months for new cases was 79% for thrice weekly therapy (TWT) and 89% for the daily therapy (DT) (p=0.001). Treatment outcomes of 535 patients showed successful treatment in 69% (208/303) of those receiving TWT and 73% (169/232) of those receiving DT (p=0.3). Side effects were reported by 44% of patients on TWT and 38% on DT (p=0.02). The outcome of treatment was similar for daily and intermittent therapy. The authors noted that while TWT was popular among patients and health providers, it was also associated with more gastrointestinal side effects and a lower sputum conversion rate. Two earlier local studies comparing daily and twice weekly treatment also had similar success rates. Completion rates with twice weekly and daily treatment was 63% and 61%, respectively, in the study of Romulo et al⁷⁹, while Balanag et al.⁸⁰ showed success rates of 72% in the twice weekly regimen and 69% in the daily regimen. Treatment failure occurred in 2.2% in both groups.

3. *What is the recommended timing of administration of anti-TB drugs?*

- The first-line anti-TB drugs should be administered together; split dosing should be avoided.

- Although ingestion with food delays or moderately decreases the absorption of anti-TB drugs, the effects of food are of little clinical significance. Thus, if patients have epigastric discomfort or nausea with the first-line drugs, administration with meals or changing the hour of dosing is recommended. Administration with food is preferable to splitting the dose or changing to a second-line drug.

D. MONITORING OF RESPONSE AND OUTCOMES DURING TREATMENT

1. What tests should be used to monitor treatment response and outcomes? How often should we follow-up patients?

- Repeat sputum AFB smears using at least 2 specimens are recommended to monitor response and outcomes of treatment in smear positive patients. The absence of acid-fast bacilli on subsequent smears is a measure of treatment response in patients with tuberculosis.
- For newly diagnosed smear-positive patients with no history of treatment, repeat smears should be done at the end of the 2nd month of treatment [Grade A] and before completion of treatment at the 5th or 6th month [Grade C]. Patients who remain positive at the time of completion of the initial phase of treatment should have monthly follow-up smears until AFB bacilli are no longer detected.
- For previously treated smear-positive patients, repeat smears should be done at the end of three months, and if still positive, these are repeated at the end of the 4th or 5th month of treatment. If the smears remain positive at the end of the 4th or 5th month, culture and DST is recommended [Grade C].
- For smear-negative patients, monitor clinical signs and symptoms on each visit and do smears at the end of the 2nd month. Serial chest x-rays (6 months apart) are needed to assess stability/activity of the lesion. A chest x-ray may be repeated on the third month of treatment if there are signs that the patient is not improving. [Grade C]

Summary of Evidence

Treatment response may be assessed through clinical, radiographic and bacteriologic evaluation.

Mycobacterial culture

The most widely accepted measure of treatment response in patients with pulmonary tuberculosis is the disappearance of acid-fast bacilli (AFB) from sputum, determined by microscopic examination and culture.⁸¹ Cultures provide a more precise definition of “cure” in both sputum smear positive and negative tuberculosis cases. In 333 new culture-confirmed cases, 136(40.8%) were defined “cured” using cultures and 108 (32.4%) using smears ($p<0.05$).⁸²

After the initiation of chemotherapy, cultures show a rapid reduction of colony-forming units during the first two days. This coincides with the death (or the growth limitation) of rapidly growing bacilli in cavitary lesions. After two days, the remaining bacteria are killed in a process of slow sterilization.⁸³

Culture conversion occurs in approximately 50% after one month, in more than 85% within three months and in 95% after four months.^{77,84,85} In 198 cases of sputum-positive cases treated at the DOTS clinic of Makati Medical Center, mean conversion time was 71 ± 95.8 days, with a median of 56 days. New cases of PTB converted in 52 ± 20 days, while re-treatment cases took 90 ± 128 days – a statistically significant difference.⁸⁶ The median time to sputum sterilization was 59 days in a study on TB patients in Baltimore, Maryland, while the time to sterilization was prolonged in patients with cavitary lung disease (75 days vs. 52.5 days).⁸⁷

While sputum culture is more sensitive and specific than smear examination, the procedure is time-consuming.⁸⁸ Under program conditions in high TB incidence countries, routine monitoring by sputum culture is considered impractical; hence it is not recommended by the WHO.⁴

In previously treated sputum smear-positive patients, if the sputum smears remain positive by the fourth month of treatment, specimens should be sent to the laboratory for culture and sensitivity whenever possible.⁴

Sputum smears

During the course of therapy, 48% of smear-positive cases remain positive beyond four weeks, and 28.7% beyond eight weeks. After twelve

weeks and sixteen weeks of treatment, this further decreases to 17.8% and 10.3%.⁸⁰

The WHO and the IUATLD recommend that patients with sputum smear-positive pulmonary TB be monitored by sputum smear examination. For new cases, sputum smears are examined at the end of the second month of treatment, and patients who are still positive have their treatment extended for another month. At the end of the third month, a smear examination can be performed but is not obligatory as the continuation phase of the treatment regimen is implemented without considering these results. At the end of the fifth month, another smear is performed. If the patient is found to be positive, the result is recorded as a failure and the patient is put on a re-treatment regimen.^{4,89}

Sputum smears at the second month agree with the corresponding culture results in only 66.7% of specimens.⁹⁰ Among patients with positive smears at two months, only 49.3% to 54.5% are positive on TB cultures.^{80,86}

Sputum smears at the end of the second month of treatment have been used to predict outcomes at the end of treatment. A negative smear at two months is predictive of cure at the end of treatment, with subsequent cure rates ranging from 90 to 100% [LEVEL 1-3].^{86,91,92,93} Persistently positive smears at the end of two months is one of the strongest predictors of treatment failure, although it is not a very reliable indicator because of the low positive predictive values, ranging from 5 to 22% [LEVEL 1-3].^{86,87,88,89} Zhao and coworkers showed that among 626 new smear-positive TB cases who had negative smears at the end of two months, 97% remained smear-negative (“cured”) at five months and 98.2% at six months. On the other hand, among 100 TB cases that were smear-positive at two months, only 25% and 17% were considered treatment failures at five and six months. Nevertheless, patients who were still sputum positive at two and three months were 1.59 times ($1.2 < RR < 2.09$) more likely to be treatment failures than patients who converted during the third month. The presence of positive smears at three months was more predictive (40%) of subsequent failure than the smear status at two months.⁸⁸ Noeske and Ngueko also found that positive smears at two to three months were less likely (OR 0.37, 95%CI 0.20 to 0.69) to obtain cure at the end of treatment.⁸⁹

Persistently positive smears at the end of two months of treatment may also predict subsequent relapse. Patients who had positive smears at TWO months but achieved cure at end of treatment had a relapse rate of 8.3% versus no relapse in those who had negative smears at TWO months and achieved cure [LEVEL 2].⁸⁷

The presence of positive smears at the end of the fifth month has been used to indicate failure of the treatment regimen. However, comparison with culture results has shown that positive smears do not necessarily mean treatment failure. In a study by Vidal et al,⁹⁴ 10 (2.2%) out of 453 patients had positive smears at the end of treatment. Of the 10, eight had negative sputum cultures (indicating non-viable bacilli) and 2 had mycobacterium other than tuberculosis (MOTT). A cohort study by Al-Moamary, et al⁸⁰, showed that of the patients with persistently positive smear at 5 months, 77% had negative TB cultures and only 23% were truly treatment failures. These two studies [LEVEL 3] were done in developed countries (Spain and Canada); no data is available for developing countries.

Chest x-rays

The WHO considers monitoring the patient by chest radiography as unnecessary and uneconomical. In patients with smear-negative pulmonary or extra-pulmonary TB, WHO recommends clinical monitoring as the method of assessing response to treatment [LEVEL 3].⁴ According to Albert et al., the chest x-ray may not show significant improvements until the patient has received several months of treatment. Because it is inferior to clinical and microbiologic assessment, chest x rays have little role in determining response to therapy except when the diagnosis and treatment of tuberculosis are presumptive [LEVEL 3].⁹⁵

However Vidal et al recommend assessment of chest x-ray findings in patients with positive AFB smears after five months. Data from this study showed that 80% of patients with positive smears have either non-viable bacilli, or MOTT; hence, there is no need to prolong or re-initiate treatment if these patients are asymptomatic or demonstrate no changes on chest x-ray.⁹⁰ Al-Moamary⁸⁰ et al, in a cohort study also stated that radiographic improvement on treatment in the setting of persistently positive smears suggest that the positive smears are due to the presence of nonviable bacilli [LEVEL 3].

The 2000 Philippine TB consensus recommended that patients with a presumptive diagnosis of tuberculosis based on clinical and radiographic findings in the absence of microbiologic evidence should be monitored for changes in radiographic lesions over the succeeding three months.¹ However, the absence of pathognomonic features of active disease necessitates the use of serial chest x-rays (6 months apart) before deciding that the lesion is inactive [LEVEL 3].

According to ATS/CDC guidelines, patients diagnosed as PTB based on positive cultures may have a repeat chest x-rays after completing two months of treatment, but this procedure is not essential. Although unnecessary, a chest radiograph at completion of therapy may provide a baseline against which subsequent examinations can be compared. When initial sputum cultures are negative, a presumptive diagnosis can be made if radiographic improvement is noted, after the completion of two months of treatment. Here, a radiograph at completion of treatment is desirable but not essential [LEVEL 3].⁵

Clinical signs and symptoms

The 2000 Philippine TB Consensus found no studies correlating the resolution of clinical signs and symptoms with bacterial response to treatment. A local study³, which performed a Kaplan-Meier analysis on symptom relief with treatment, reported that fever and hemoptysis disappeared in four weeks, while cough disappeared in twelve to fourteen weeks on the average.

Before the HIV era, treatment with isoniazid and ethambutol, with or without rifampicin and streptomycin resulted in defervescence in 64% of patients after two weeks. In the HIV-era, treatment with isoniazid, rifampicin and pyrazinamide resulted in 93% of patients becoming afebrile within two weeks. Defervescence occurred within two weeks in 78% of patients with drug-susceptible organisms while only 9% of patients with multi-drug resistance became afebrile.⁷⁷

For patients with sputum smear-negative pulmonary TB and extra-pulmonary TB, the WHO recommends clinical monitoring as the method of assessing response to treatment [LEVEL 3].⁴

2. *How should we classify treatment outcomes?*

In order to facilitate monitoring, reporting, and cohort analyses, the recommended NTP treatment outcome classification and their definitions are as follows:

Cure refers to a sputum positive smear positive patient who has completed treatment and is sputum smear negative in the last month of treatment and on at least one previous occasion.

Treatment completed is the term used for a patient who has completed treatment but does not meet the criteria to be classified as cure

or failure. This group includes: (1) a sputum smear-positive patient initially who has completed treatment without follow-up sputum examinations during the treatment, or with only one negative smear during the treatment, or without sputum in the last month of treatment; and (2) a sputum smear-negative patient who has completed treatment

Died - A patient who *dies* for any reason during the course of treatment

Failure refers to a patient who is smear-positive at five months or later during treatment or a sputum smear-negative patient initially before starting treatment and becomes smear-positive during the treatment.

A **defaulter** is one whose treatment was interrupted for 2 consecutive months or more

A patient who has been transferred to another facility with proper referral/transfer slips for continuation of treatment is labeled **transferred out**.

Treatment outcomes for **MDRTB** are classified as follows:

1. Cured – patients who completed treatment and are culture negative for the last 12 months of treatment
2. Treatment completers – clinically cured but not meeting the bacteriological requirement for cure
3. Defaulter – patients with 2 or more consecutive months of treatment interruption
4. Failure – those with more than 1 positive culture during the past 12 months of treatment, those with 1 of their last cultures positive, or those remaining persistently culture positive with treatment being stopped by the physician
5. Died – those who died from any cause at any point during treatment

Summary of Evidence

To facilitate monitoring, reporting and cohort analysis, treatment outcomes as defined by the WHO, IUATLD and NTP may be used. The WHO and IUATLD recommend a formal system for monitoring outcomes of treatment that classifies all cases into one of six categories (cure, treatment completed, treatment failure, died, default, or transfer out). The assessment is based on clinical response and sputum AFB smears at completion of treatment.⁴

E. TREATMENT OF TB IN SPECIAL SITUATIONS

1. *How should TB in HIV patients be managed?*

- For patients with TB and HIV, regardless of AFB smear status, **2 months of HRZE in the initial phase followed by 4 months of HR in the continuation phase** is recommended [Grade A]. Treatment regimens should be given daily or at least thrice weekly [Grade A].
- The continuation phase may be prolonged to 7 months in patients who remain sputum culture positive after two months [Grade A].
- As much as possible, rifampicin is included in the entire course of treatment, as its absence will most likely delay sputum conversion [Grade A].
- Considering the significant drug interactions that often occur with concomitant administration of anti-retroviral agents and anti-TB therapy, patients with TB and HIV should be referred to centers* with expertise in the management of these two co-existing disease conditions.

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Summary of Evidence

A randomized, open-label trial in Zaire showed that a six-month anti-TB treatment regimen (2HRZE/4HR) resulted in similar failure rates between HIV-seropositive and HIV-seronegative patients with PTB. The study also showed that while prolonging the continuation phase to 10 months in HIV-infected patients with PTB resulted in lower relapse rates, survival was unaffected.⁹⁶ A trial in Haiti using a similar 6-month treatment course showed similar cure rates between HIV-seropositive and HIV-seronegative patients with PTB.⁹⁷

The 2003 ATS/CDC/IDSA guidelines on the treatment of tuberculosis and the International Standards for Tuberculosis Care recommend a six-month regimen for HIV patients similar to the regimen used for those uninfected with HIV.^{5,98}

For patients with a slow response to treatment and who still have a positive sputum culture after the first 2 months of treatment, the continuation phase may be extended to 7 months.

A randomized, placebo-controlled trial in Zaire has shown that prolonging the continuation phase to 10 months in HIV-seropositive patients with pulmonary TB resulted in lower relapse rates.⁹²

Use of rifampicin

A randomized clinical trial comparing rifampicin and non-rifampicin containing regimens in Uganda showed that sputum conversion is hastened when a rifampicin-containing regimen is used for HIV-infected patients with pulmonary TB.⁹⁹

Frequency of drug administration

HIV-infected patients with TB should receive daily or three times weekly administration of anti-TB drugs. There is no role for once or twice a week therapy in the treatment of TB in patients with HIV. A randomized trial involving HIV-infected patients showed that a once-weekly regimen using isoniazid and rifampicin resulted in unacceptably high rates of relapse due to acquired rifamycin resistance.¹⁰⁰ The CDC guidelines on the treatment of TB recommend that thrice-weekly or daily treatment with a rifampicin or rifabutin-based regimen be administered to HIV-infected patients with TB to prevent acquired rifamycin resistance.¹⁰¹

Anti-retroviral therapy and anti-TB medications

Whenever possible, anti-retroviral drugs (ARV) should not be started at the same time as anti-TB drugs in order to prevent paradoxical reactions brought about by immune reconstitution resulting from ARV therapy (e.g. worsening of signs and radiographic findings of TB). Furthermore, the possibility of numerous, possibly overlapping, adverse drug events may be avoided by not starting ARVs and anti-TB therapy at the same time. An observational cohort study showed paradoxical worsening in HIV-infected patients with TB who were treated either with a non-nucleoside transcriptase inhibitor alone (NNRTI) or with highly active antiretroviral therapy.¹⁰²

Significant drug interactions often occur with the concomitant administration of ARVs and anti-TB therapy. Referral to centers with the appropriate expertise in the management of these patients is recommended. Patients may be referred to the following institutions:

Research Institute for Tropical Medicine
Department of Health Compound, FILINVEST Corporate City,
Alabang, Muntinlupa City, 1781
Tel. Nos. (632) 809 7599, (632) 807 2628 to 32
Fax: (632) 842 2245

San Lazaro Hospital
Quiricada St., Sta. Cruz, Manila
Tel. Nos. (632) 732 3776 to 78
Fax: (632) 711 6979

Screening

Tuberculosis may be an AIDS-defining disease. Risk factors for HIV should be elicited in patients with TB. However, given the low prevalence of HIV in the Philippines (0.04%), the routine testing for HIV is not recommended for patients with TB at this time. HIV-infected patients, on the other hand, are at great risk for TB and should be screened for the disease.

2. What treatment regimens should be used for pregnant and lactating women?

- Isoniazid, rifampicin, pyrazinamide, and ethambutol have no known teratogenic effects and are considered safe for pregnant patients with TB. The standard short-course chemotherapy consisting of an initial phase using HRZE for two months followed by HR for four months is recommended if the probability of TB is moderate to high. [Grade B] Untreated TB is a greater hazard to a pregnant woman and her fetus than treatment of the disease. Infants born to women with untreated TB have higher risk of having fetal-growth retardation, being small for gestational age, having low APGAR scores and a low birthweight. [Grade B]
- Streptomycin may cause ototoxicity in fetuses and should not be used in the treatment of pregnant patients with TB. [Grade B]
- Pregnant women taking isoniazid should be given pyridoxine (Vitamin B6) at 25 mg/day because isoniazid may cause demyelination in the patient and in the fetus.
- Lactating women being treated for TB with the first-line anti-TB drugs may continue to breastfeed. The small concentrations of anti-TB drugs in breast milk do not produce toxicity in nursing newborns. [Grade B]

Summary of Evidence

There are no clinical trials on the use of the short-course chemotherapy regimen in pregnant and lactating women with TB. Untreated TB is a greater hazard to a pregnant woman and her fetus than treatment of the disease. Infants born to women with untreated TB have a higher risk of having fetal-growth retardation, being small for gestational age, having low APGAR scores and a low birth weight.^{103 104} Thus, treatment of a pregnant woman with suspected TB should be started if the probability of TB is moderate to high.

The previously recommended nine-month course of HRE in the 2000 Philippine TB Consensus is now replaced with the short-course chemotherapy regimen (HRZE). A population-based case-control study has shown that there was no increase in congenital anomalies in infants born to mothers who had been exposed to isoniazid, rifampicin, pyrazinamide, ethambutol, ethionamide, prothionamide and cycloserine.¹⁰⁵ In a case-control study on obstetrical outcomes among 29 women with extrapulmonary TB, none of the infants had any congenital anomalies¹⁰⁰. These women received isoniazid, rifampicin, ethambutol and pyrazinamide.

Streptomycin is the only anti-TB drug documented to have harmful effects on the human fetus. It interferes with the development of the ear and may cause congenital deafness. In 40 pregnancies among women being treated with streptomycin, 17% of the babies had 8th nerve damage with deficits ranging from mild hearing loss to bilateral deafness.

The fluoroquinolones have been associated with arthropathies in young animals; hence, they should be avoided if possible in pregnant women.¹⁰⁶

Pyridoxine must be given to pregnant women receiving isoniazid to prevent unwanted effects of demyelination, like peripheral neuropathy.⁵

The first line anti-TB drugs cross into breast milk in variable amounts. Breastfeeding, however, should not be discouraged for women being treated with these first-line agents, because the small concentrations of these drugs in breast milk do not produce toxic effects in the infant.^{107 108} Rifampicin is excreted into breast milk with milk to plasma ratio of 0.2. The amount transferred to the infant (0.05% of maternal dose) does not cause adverse effects. Pyrazinamide excretion into breast milk is minimal with a maximum of 0.3% of the ingested dose reaching the infant. Streptomycin is excreted into breast milk with milk to plasma ratio of 0.5-1.0. Since the drug is very poorly absorbed orally, no significant absorption by the infant is to be

expected from this. Ethambutol is secreted into breast milk with approximate milk to serum ratio of 1. All these anti-TB drugs are considered compatible with breast feeding by pediatric groups such as the American Academy of Pediatrics¹⁰⁹. The administration of fluoroquinolones, however during breastfeeding is not recommended.

Conversely, drugs in breast milk should not be considered as an effective treatment for active TB or latent TB infection in a nursing infant. Supplemental pyridoxine is recommended for both the nursing mother and her infant even if the infant is not receiving isoniazid.

3. *How should patients with hepatic dysfunction be managed?*

- Liver function tests (LFTs) should be done prior to instituting treatment for patients with chronic liver disease. Consultation with experts is strongly advised.
- Depending on the extent and severity of the liver disease, alternative regimens that can be used are the following: [Grade B]
 - o Isoniazid, rifampicin and one or two non-hepatotoxic drugs such as streptomycin and ethambutol for a total treatment duration of eight months (2HRES/6HR or 2HRE/6HE)
 - o Patients who may have more extensive liver damage, may receive an alternative regimen comprised of streptomycin, isoniazid and ethambutol in the initial phase, followed by isoniazid and ethambutol in the continuation phase, for a total treatment duration of 12 months (2HES/10HE)

Summary of Evidence

Patients with pre-existing liver disease have a greater likelihood of developing drug-induced hepatitis secondary to anti-TB treatment. The consequences of drug-induced hepatitis in these patients may range from severe to life-threatening. Baseline liver function tests (LFTs) should be taken prior to starting anti-TB drugs to aid in the choice of medications.¹¹⁰ Pyrazinamide may cause severe & prolonged liver damage, and should not be given to patients with established chronic liver disease.^{5,94} Regimens with the fewest potentially hepatotoxic agents should be used especially for patients with advanced and unstable liver disease. Variations seen in liver biochemistry profiles from pre-existing liver disease may also confound

efforts at monitoring for drug-induced hepatic toxicity.⁵ Thus, consultation with experts is advised in the management of these patients.

The incidence of pyrazinamide-induced hepatotoxicity and rash during treatment for active TB is substantially higher than with other first-line anti-TB drugs as reported in cohort studies. For instance, Yee et al in a cohort study of 430 patients, reported the incidence of adverse effects for pyrazinamide was 1.48 per 100 person months of exposure (95% CI 1.3, 1.6) compared to 0.49 (95% CI 0.42, 0.55) for isoniazid, 0.43 (95% CI 0.37, 0.49) for rifampicin and 0.07 (95% CI 0.04, 0.10) for ethambutol.¹¹¹ These results are in agreement with previous cohorts of patients treated in specialized centers in Britain,¹¹² Denmark,¹¹³ Germany¹¹⁴ and Argentina.¹¹⁵ In these studies, pyrazinamide was the most common causative agent for all side effects, hepatitis¹⁰⁹ and rash.¹⁰⁵

4. *How should patients with renal dysfunction be managed?*

- The renal function of patients with chronic renal disease should be measured prior to starting anti-TB therapy. The safest regimen for these patients is 2HRZ/6HR. [Grade C]
- Streptomycin and ethambutol should be used with caution. If these drugs need to be employed in the treatment regimen, their dosing intervals should be increased rather than decreasing the dose. [Grade C]
- Generally, anti-TB drugs should be given after hemodialysis to avoid drug filtration during the procedure. [Grade C]

Summary of Evidence

Patients who have chronic renal disease and are being treated for TB require alterations in dosage levels of anti-TB drugs because some medications are cleared by the kidney or are removed by hemodialysis.⁵ Renal function should be measured before treatment to assist the clinicians in choosing the appropriate anti-TB drugs.¹⁰⁶ Isoniazid, rifampicin and pyrazinamide are either metabolized by the liver or metabolized into non-toxic compounds, and may be given at normal dosages in patients with pre-existing renal disease.^{94,106} Ethambutol, streptomycin and the other aminoglycosides are excreted by the kidney; hence dosing should be modified by increasing dosing intervals.^{5,94,106} Reducing the dose is not preferred because the resulting peak serum concentrations may be too low.⁵ Isoniazid, rifampicin and ethambutol are not dialyzed to a significant degree;

supplemental doses of these drugs after hemodialysis are not needed. Pyrazinamide requires supplemental dosing if given before hemodialysis. It is recommended that medications be given after hemodialysis to avoid loss of drugs and to facilitate DOT.⁵

A review of 24 TB patients with chronic renal failure over a 13-year period at the Manchester Royal Infirmary in England from 1986-99 found a high incidence of side-effects associated with anti-TB drugs, occurring in 11 of 24 patients (46%) overall and nine of 16 (56%) dialysis patients.¹¹⁶ This is in contrast to patients with normal renal function wherein the reported incidence of drug reactions necessitating modification of treatment is lower at 5.1%.¹⁰⁸ Most common adverse effects identified in patients with chronic renal failure were neuropsychiatric, hepatic and gastrointestinal.

TABLE XVIII. Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for adult patients receiving hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg 3x/week
Rifampin	No change	600 mg once daily, or 600 mg 3x/week
Pyrazinamide	Yes	25–35 mg/kg per 3x/week
Ethambutol	Yes	15–25 mg/kg per dose 3x/week
Levofloxacin	Yes	750–1,000 mg per dose 3 x/week
Cycloserine	Yes	250 mg once daily, or 500 mg/dose 3x/week*
Ethionamide	No change	250-500 mg/dose daily
Aminosalicylic acid	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week
Amikacin	Yes	12–15 mg/kg per dose two or three times per week

Standard doses are given unless there is intolerance.

The medications should be given after hemodialysis on the day of hemodialysis

Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive

Accumulation, and to assist in avoiding toxicity

Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses

Recommended for patients receiving hemodialysis and verify adequacy of dosing, using serum concentration monitoring.

* The appropriateness of 250-mg daily doses has not been established. Do careful monitoring for evidence of neurotoxicity.

Adapted from the 2003 Joint statement of ATS/CDC/IDSA on the treatment of tuberculosis

5. *How should TB in elderly patients be managed?*

- Elderly patients with TB should receive the standard short-course chemotherapy (2HRZE/4HR). However, closer monitoring is recommended, and, when needed, dosage adjustments are done because elderly patients often have impairments in hepatic and renal function making them prone to drug-related adverse events and toxicity. [Grade B]

Summary of Evidence

Elderly patients frequently have decreased hepatic & renal clearance making them more susceptible to adverse events. Drug half-life and organ responses may also be altered in elderly patients. These individuals may have concomitant illnesses, which require intake of several drugs. Rifampicin induces liver enzymes, which can accelerate the clearance several other medications used in the elderly (warfarin, steroids, oral hypoglycemic agents, digoxin, theophylline and beta-blockers). Close monitoring of these patients is necessary, with adjustment of dosages, as required.¹⁰⁶

In a local review of 421 PTB patients treated at the Philippine General Hospital Out-patient Department, significant risk factors associated with adverse effects on bivariate analysis were age > 60 years old (OR 1.8; 95% CI 1.1, 2.9), history of hepatitis (OR 21.6; 95% CI 1.2, 398.3) and use of fixed-dose combination preparations (OR 3.0; 95% CI 1.7, 5.4). However, adjustment for confounders was not done in this study.¹¹⁷

A retrospective cohort of 430 patients with active TB treated in Canada between 1990-99 identified age over 60 years as one of the factors significantly associated with the occurrence of any major side effect (adjusted hazard ratio 2.9; 95% CI 1.3, 6.3). Other factors identified were female sex (adjusted HR 2.5; 95% CI 1.3, 4.7), birthplace in Asia (adjusted HR 2.5, 95% CI 1.3, 5.0) and HIV-positive status (adjusted HR 3.8; 95% CI 1.05, 13.4). Specifically, pyrazinamide-associated adverse events were associated with age over 60 years (adjusted HR 2.6; 95% CI 1.01, 6.6) and birthplace in Asia (adjusted HR 3.4; 95% CI 1.4, 8.3). Rifampicin-associated adverse events were associated with age over 60 years (adjusted HR 3.9; 95% CI 1.02, 14.9) and HIV-positive status (adjusted HR 8.0; 95% CI 1.5, 43). In terms of the adverse effects, hepatitis (adjusted HR 7.7; 95% CI 1.5, 40) and gastrointestinal intolerance (adjusted HR 6.4; 95% CI 1.2, 36) were significantly associated with age > 60 years. Time to a serious side effect was also significantly more rapid in female and older patients.¹⁰⁷

6. *How should TB patients with diabetes mellitus be managed?*

- Diabetic patients with TB should receive the standard SCC regimen (2HRZE/4HR). Close monitoring of these patients should be done because of the potential drug interactions between anti-TB drugs (particularly rifampicin) and the medications for diabetes. [Grade C]

Summary of Evidence

Rifampicin reduces the serum levels of some oral hypoglycemic drugs such as the sulphonylureas. Patients should be closely monitored, and drug dosages modified as needed.¹⁰⁶

Diabetes mellitus is a chronic disease that can alter the immune response of these patients, making them more predisposed to infections such as tuberculosis. There are no specific studies, thus far, on the effective regimens for TB in DM patients.

F. EXTRAPULMONARY TB

1. *What is the effective treatment regimen for extrapulmonary tuberculosis?*

- The basic principles of treatment for pulmonary tuberculosis also apply to extrapulmonary disease. A 6-9 month regimen consisting of 2 months isoniazid, rifampicin, pyrazinamide and ethambutol in the initial phase followed by 4-7 months of isoniazid and rifampicin in the continuation phase is recommended, unless the organisms are known or strongly suspected of being resistant to the first line drugs [Grade B]. The exception to the statement is *tuberculous meningitis* for which experts recommend a treatment duration of 9-12 months [Grade C].

Table XIX. Treatment duration for extrapulmonary TB

Site	Duration of therapy (months)	Level of evidence
Lymph node	6	Level 1
Bone and Joint	6-9	Level 1
Pleural disease	6	Level 2
Pericarditis	6	Level 2
CNS TB including meningitis	9-12	Level 3
Disseminated disease	6	Level 2
Genitourinary	6	Level 2
Abdominal TB	6	Level 1

*Duration of therapy for extrapulmonary tuberculosis caused by drug-resistant organisms is not known. Adapted from the 2003 Joint Statement of ATS, IDSA, and CDC on the treatment of tuberculosis

Summary of Evidence

Lymph Node Tuberculosis

In a randomized controlled trial comparing a thrice weekly 6-month regimen (4HRZS/2HR) with a thrice weekly 9-month regimen (4HRZS/5HR) in the treatment of cervical tuberculous lymphadenopathy, there were no significant differences in both primary failure (RR 2.23, 95%CI 0.21-23.76) and five-year actuarial remission rates ($p=0.44$).¹¹⁸

A systematic review by van Loenhout deemed six months of therapy (including isoniazid, rifampicin and pyrazinamide) appropriate for tuberculous lymphadenitis. Conclusions were based on eight randomized trials and comparative studies of thrice weekly to daily regimens (644 patients, 534 completed treatment and follow-up). Treatment for 6 months resulted in a relapse rate of 3.3%, (95% CI 1.7-5.5) while treatment for 9 months resulted in a relapse rate of 2.7% (95% CI 0.6-7.8).¹¹⁹

Large cervical TB adenitis has the propensity to swell further in the first month of treatment creating the specter of a wrong diagnosis. In these cases, the anti-TB treatment is maintained. Drainage by incision is done when there is pointing with imminent rupture. An ugly scar may thus be prevented.

Abdominal tuberculosis

A randomized, controlled trial of short course chemotherapy in abdominal tuberculosis, demonstrated similar favorable responses at the end

of treatment (99% for 6R and 94% for 12E) in both patients randomized to receive 2HRZ/4HR (6R) and 2SEH/10EH (12E). A total of 193 patients aged 13-72 (135 had intestinal lesions, 84 peritoneal TB, 25 hepatic TB, 17 mesenteric TB, 2 retroperitoneal TB, 61 had combined lesions) were involved in the study. No one among the 147 patients who completed follow-up at 60 months developed relapse of abdominal tuberculosis.¹²⁰

2. *How effective are the other modalities of treatment for extrapulmonary tuberculosis?*

- The use of corticosteroids as adjunctive therapy is recommended for patients with tuberculous meningitis [Grade A] and pericarditis [Grade B].
- In tuberculous meningitis, adjunctive corticosteroid therapy with dexamethasone is recommended, particularly those with a decreased level of consciousness. The recommended regimen is dexamethasone with an initial dose of 12 mg/day for adults. The initial dose is given for three weeks then decreased gradually during the next three weeks. [Grade A]
- In tuberculous pericarditis, prednisone or prednisolone is recommended as adjunctive therapy. For adults, prednisone should be given at 60 mg/day for four weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks, and 5 mg/day on the 11th week. The equivalent dosages for prednisolone also follow this regimen. [Grade B]

Table XX. Adjunctive Treatment for Extrapulmonary TB

Site	Corticosteroids	Rating
Lymph node	Not recommended	Level 3
Bone and Joint	Not recommended	Level 3
Pleural disease	Not recommended	Level 1
Pericarditis	Recommended	Level 2
CNS TB including meningitis	Strongly recommended	Level 1
Disseminated disease	Not recommended	Level 3
Genitourinary	Not recommended	Level 3
Abdominal	Not recommended	Level 3
Pulmonary TB	Not recommended	Level 2

Summary of Evidence

Pericardial tuberculosis

In a randomized, double-blind, controlled trial involving patients in the effusive-constrictive phase, patients in the prednisolone group had a more rapid clinical resolution compared to those in the placebo group. Patients given prednisolone had a lower mortality (2/53, 4% versus 7/61, 11%) and less frequent need for pericardiectomy (11/53, 21% versus 18/61, 11%) but these differences did not reach statistical significance.¹²¹ In another RCT involving patients with effusive pericarditis, prednisolone reduced the need for repeated pericardiocentesis (7/76, 9% versus 17/74, 23% $p < 0.05$) and significantly lowered mortality (2/76, 3% versus 10/74, 14% $p < 0.05$). A combined analysis of both trials showed the prednisolone-treated patients had fewer morbid outcomes (although this was not statistically significant). These outcomes include the need for repeat pericardiocentesis (RR 0.45; 95% CI 0.20, 1.05), and the need for pericardiectomy (RR 0.85; 95% CI 0.51, 1.42).¹²² There were also fewer deaths in the prednisolone group but this reduction did not reach statistical significance (RR 0.65; 95% CI 0.36, 1.16).¹¹⁸

A small randomized clinical trial performed in 58 HIV seropositive patients, prednisone therapy was associated with lower mortality (5/29 vs. 10/29; $p = 0.004$).¹²³

Tuberculous Meningitis

Prasad et al, in a systematic review of six controlled trials (595 patients), showed that steroids is associated with a reduced incidence of death (RR 0.79; 95% CI 0.65-0.97) and/or disability (RR 0.58; 95% CI 0.38-0.88).¹²⁴

A recent large RCT of 545 patients with TB meningitis¹²⁵ likewise showed that adjunctive treatment with dexamethasone reduced the risk of death (87/274, 31.8%) in dexamethasone-treated patients (112/271, 41.3%) when compared to those not given the drug (RR = 0.69; 95% CI 0.52, 0.92). However, dexamethasone did not prevent severe disability (34/187, 18.2% versus 22/159, 13.8%, $p = 0.27$).

Pleural Tuberculosis

Lee et al., in a comparative study, found that patients with pleural TB who received prednisone had a more rapid resolution of symptoms (fever,

chest pain and dyspnea) and faster radiographic resolution of effusion. The mean duration from symptoms to relief was 2.4 days in the steroid-treated group, and 9.2 days in the placebo group ($p < 0.05$). Complete reabsorption of pleural effusion occurred in an average of 54.5 days in the steroid-treated group and 123.2 days in the placebo group ($p < 0.01$).¹²⁶

In a small double-blind, placebo-controlled randomized trial (where all patients included had complete drainage of effusion and received 6-months of anti-TB therapy), Weiser et al. demonstrated that drainage led to a rapid resolution of symptoms. Improvements in the visual analogue scale (VAS) scores were observed after complete drainage of the effusion. Differences in the degree of improvement in VAS scores between the two groups were, however, not statistically significant. No significant differences in residual pleural thickening, both on high-resolution CT scan and by chest x-ray, were also detected between patients who were given prednisone and those given placebo.¹²⁷

In a systematic review of 3 RCTs (including the above-mentioned studies), the evidence was insufficient on the effect of steroids as adjuncts to anti-TB drugs on the risk of death or lung function in patients with tuberculous pleurisy. Point estimates for secondary outcomes (residual pleural fluid {RR 0.28; 95% CI 0.06-1.34}, residual pleural thickening {RR 0.76; 95% CI 0.48-1.21} and adhesions {RR 0.30; 95% CI 0.03-2.66}) leaned towards a beneficial role, but none were statistically significant.¹²⁸ A large placebo-controlled trial is needed to evaluate death as an endpoint.

3. *What is the role of surgery in the management of extrapulmonary TB?*

In patients with tuberculosis of the thoracic or lumbar spine, surgery in addition to chemotherapy is indicated in the following situations:

1. those less than 25 years of age, in whom the initial angle of kyphosis is more than 30°
2. those who develop progressive kyphosis while on ambulant chemotherapy
3. children aged less than 10 years with destruction of the vertebral bodies who have partial or no fusion during the adolescent growth spurt
4. those with compression of the spinal cord whose neurological status deteriorates in spite of chemotherapy

In patients with abdominal tuberculosis, elective surgery is reserved for complications such as obstruction, fistula formation, and intractable ulceration.

Therapeutic lymph node excision is not recommended for TB lymphadenitis unless unusual circumstances arise (e.g. large fluctuant lymph nodes that are about to spontaneously drain).

Summary of Evidence

Spinal tuberculosis

A randomized controlled trial by Parthasarathy et al. recommended surgery (in addition to chemotherapy) for the following patient populations:¹²⁹

1. patients aged less than 25 years, in whom the initial angle of kyphosis is more than 30°;
2. patients started on ambulant chemotherapy who develop progressive kyphosis;
3. children aged less than 10 years with destruction of vertebral bodies who have partial or no fusion even during the adolescent growth spurt; and
4. patients with compression of the spinal cord in whom the neurological status deteriorates in spite of chemotherapy.

In the thirteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine (a 15 year assessment), randomized controlled trials demonstrated no additional benefit of open debridement over radical operations in terms of overall clinical outcome. The radical operation in Hong Kong gave more rapid healing with complete bony fusion and less deformity.¹³⁰

Gastrointestinal Tuberculosis

Elective surgery should be reserved for complications such as obstruction, fistula formation and intractable ulceration. In a randomized controlled trial assessing the efficacy of short course chemotherapy for abdominal tuberculosis, it was found that short course chemotherapy is adequate and that there is no role for routine surgery in the treatment of abdominal tuberculosis.¹³¹ When diagnosed before surgery, most lesions regress with appropriate antitubercular treatment and do not require excision as reported in retrospective studies.^{132,133}

Tuberculous Lymphadenitis

heh groups given cash per visit; and direct observation at a participant chosen site without cash incentive. observation at a dTherapeutic lymph node excision is not indicated unless unusual circumstances arise. For large lymph nodes that are fluctuant and appear to be about to spontaneously drain, aspiration or incision and drainage may be beneficial, although this approach has not been evaluated systematically [LEVEL 3].⁵

Tuberculous Meningitis

Pascual et al., in a review of 92 Filipino patients admitted for TB meningitis stages II and III, therapeutic lumbar punctures was helpful in the assessment of candidates for permanent CSF shunting, and in the relief of intracranial pressure for improving sensorium at the time of discharge. For later stages of the disease (with hydrocephalus), urgent ventriculoperitoneal shunting was recommended, with therapeutic lumbar CSF drainage as a temporary measure.¹³⁴

Tuberculous Pericarditis

The systematic review by Mayosi et al. also compared the outcomes between routine open surgical drainage for effusion and no open surgical drainage. Open surgical drainage was associated with fewer patients requiring pericardiectomy but this was not statistically significant (RR 0.39, 95% CI 0.08-1.91). The procedure prevents the occurrence of cardiac tamponade but confers no mortality benefit, and may be associated with a poorer clinical status at 24 months. There is no clinical trial information on which to base recommendations regarding the indications and the timing of pericardiectomy in TB constrictive pericarditis.¹¹⁸

Pleural Tuberculosis

In a randomized controlled trial, 30 patients who received pigtail drainage combined with anti-TB drugs were compared to 31 patients who received only anti-TB drugs. No statistical difference between the groups in terms of symptom scores, forced vital capacity, and incidence of residual pleural thickening were noted. The addition of pigtail drainage to an effective anti-TB regimen does not reduce the level of residual pleural thickening and does not provide additional clinical benefits.¹³⁵

However, surgical procedures like decortication may be needed in a select group of patients because of dyspnea resulting from pleural loculations and thickening despite anti-TB treatment. In a comparative study of different modalities, where 48 patients were randomly separated into 3 groups (control: repeated thoracentesis; catheter group: small bored catheterization; and urokinase group: catheterization with intrapleural urokinase instillation), better results were seen in the urokinase group in terms of the frequency of catheterization, frequency of obstruction, and the duration of catheterization.¹²²

Mammary Tuberculosis

In a retrospective study of 52 cases of tuberculosis of the breast, wherein all patients received anti-TB therapy, 24 patients needed surgical intervention, including excision of the mass, repeated aspirations from a cold abscess, excision of the sinus, and simple mastectomy. Surgical intervention is reserved for aspiration of cold abscesses, and excision of residual sinuses and masses. Simple mastectomy may be performed in refractory cases with destruction of the breast.¹³⁶

G. ADJUNCTIVE THERAPY FOR TUBERCULOSIS

1. *What is the role of immunomodulators as an adjunct in the management of TB?*

1. *Mycobacterium vaccae*, given as a vaccine, is not recommended as an adjunct to chemotherapy for treating tuberculosis [Grade A].
2. Single cytokine therapy (IL-2) is not recommended at this time as adjunctive therapy for TB [Grade B].

Summary of evidence

A Cochrane systematic review of 7 RCTs using whole, killed *Mycobacterium vaccae* for patients with TB receiving anti-TB chemotherapy concluded that *M. vaccae* does not benefit patients with TB. Four trials assessed the number of deaths in the treatment and control groups and the combined analysis of these studies did not demonstrate a difference in mortality (OR 1.09; 95% CI 0.79, 1.49). No consistent effect on sputum negativity or sputum cultures was found. Most immunotherapy recipients

experienced local adverse reactions (2 trials, OR 18.19, 95% CI 8.96, 36.95), some of which progressed to ulceration and scarring.¹³⁷

Results of the first large-scale RCT of adjunctive cytokine therapy for TB showed that recombinant human IL-2 did not enhance bacillary clearance after 1 and 2 months of anti-TB therapy. There were no differences in weight gain and improvement in fever, cough and chest pain between the placebo and treatment groups. The trial was conducted in Uganda among 110 HIV-seronegative adults in whom smear-positive drug-susceptible PTB was newly diagnosed.¹³⁸

Large RCTs are needed to confirm or refute the promising results of small studies using interleukin-2 and aerosolized interferon-gamma as adjunctive treatment for multidrug-resistant TB.^{139,140,141}

2. What is the role of micronutrient and vitamin supplementation in the management of TB?

Arginine, vitamin A and zinc are beneficial as adjuncts to standard anti-TB chemotherapy in HIV negative patients with smear-positive PTB. It can hasten sputum conversion, reduction of symptoms such as cough and promote weight gain [Grade B]

Summary of Evidence

A small community-based double-blind placebo controlled supplementation trial was conducted among Indonesian patients with PTB randomly to determine whether vitamin A and zinc supplementation improved the efficacy of anti-TB treatment in terms of clinical response and nutritional status. The micronutrient group (n=40) received 5000 IU vitamin A (as retinyl acetate) and 15 mg zinc (as zinc sulfate) daily for 6 months, while the other group (n=40) received placebo. Micronutrient supplementation resulted in earlier elimination of tubercle bacilli from sputum. After 2 weeks, the proportion of patients with negative sputum smears was significantly higher in the micronutrient group (23%) than in the placebo group (13%). This difference was maintained up to 7 weeks (p=0.01). The mean reduction in lesion area on the chest x-ray was significantly greater in the micronutrient group than in the placebo group after 2 months. In the micronutrient group, the increase in plasma retinol concentration was correlated with the reduction in mean lesion area after 6 months of anti-TB treatment. Plasma retinol concentrations were

significantly higher in the micronutrient group than in the placebo group after 6 months ($p < 0.05$). Plasma zinc concentrations were not significantly different between the 2 groups.¹⁴² Larger trials are needed to confirm these significant findings.

Another small double-blind placebo-controlled trial conducted in Ethiopia randomized 120 HIV negative smear-positive TB patients to receive either arginine or placebo for 4 weeks in addition to conventional anti-TB chemotherapy. Compared with the placebo group, patients in the arginine group showed significant improvement defined as increased weight gain, higher sputum conversion rate (arginine 100% vs placebo 84%) and faster reduction of symptoms, such as cough on the 2nd month of DOTS treatment. Arginine serum levels increased significantly in the arginine-treated group compared with the placebo group.¹⁴³

A third small RCT randomized 44 patients with active PTB to receive either a multivitamin-trace element supplement or a placebo-containing calcium in addition to the standard anti-TB regimen. At 2 months, the multivitamin-trace element group had a significant reduction in the number of sputum smear-positive individuals (2/22 compared with 7/22 in the placebo group; $p = 0.03$).¹⁴⁴

H. MANAGEMENT OF ADVERSE REACTIONS

1. *What tests should be done to monitor for adverse reactions?*

- Routine monitoring of liver or renal function or platelet count for patients being treated with first-line drugs is not recommended unless there were abnormalities at baseline or there are clinical indications or are at increased risk for hepatotoxicity (e.g. history of hepatitis B or C virus infection, alcohol abuse, elderly). [Grade B]
- Patients with stable abnormalities of hepatic and renal function at baseline should have repeat measurements early in the course of treatment to ensure that there has not been any worsening. [Grade B]
- Patients receiving ethambutol should be asked on visual disturbances at monthly intervals; monthly repeat testing of visual acuity and color vision is recommended for patients receiving an ethambutol dose > 15 -20 mg/kg and for patients receiving the drug for > 2 months. [Grade C]

Summary of Evidence

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do develop adverse effects and therefore clinical monitoring of all TB patients for adverse effects is important during treatment. Routine laboratory monitoring is not necessary under program conditions. Health personnel can monitor adverse effects of drugs by teaching patients how to recognize symptoms of common adverse effects and to report if they develop such symptoms. Health personnel can also ask about symptoms when patients come to collect their drugs.⁴

ATS/CDC/IDSA guidelines recommend that at the time treatment is initiated, measurements of AST, bilirubin, alkaline phosphatase, and serum creatinine and a platelet count should be obtained for all adults. Testing of visual acuity (Snellen chart) and color vision (Ishihara tests) should be performed when EMB is used. Patients who have stable abnormalities of hepatic or renal function at baseline should have repeated measurements early in the course of treatment, then less frequently to ensure that there has not been worsening.⁵

In a local review of 421 PTB patients treated at the Philippine General Hospital Out-patient Department, significant risk factors associated with adverse effects on bivariate analysis were age > 60 years old (OR 1.8; 95% CI 1.1, 2.9), history of hepatitis (OR 21.6; 95% CI 1.2, 398.3) and use of fixed-dose combination preparations (OR 3.0; 95% CI 1.7, 5.4). However, adjustment for confounders was not done in this study.¹¹³ The most common adverse effects noted were pruritus and exanthema (54.4%), nausea and/or vomiting (24.1%), hepatitis (9.7%) and headache (8.3%).

2. How should adverse reactions due to anti-TB drugs be managed?

General principles in the management of adverse reactions due to anti-TB drugs are as follows:

- a. Mild adverse effects can be managed with symptomatic therapy.
- b. For severe adverse effects, the offending drug or drugs must be discontinued. Single drug formulations should be used if the patient is receiving FDC.
- c. First-line drugs should not be stopped without adequate justification.
- d. Management of more serious adverse reactions requires referral to specialists.

3. *How should drug –induced hepatotoxicity be managed?*

- Patients diagnosed with drug-induced hepatotoxicity should be restarted on a **regimen without pyrazinamide** e.g. HRES, with gradual reintroduction of isoniazid and rifampicin. [Grade B]
- In the absence of symptoms, therapy should not be altered because of modest asymptomatic elevations of AST ($< 5\times$ normal), but the frequency of clinical and laboratory monitoring should be increased.
- For AST levels $> 5\times$ elevated with or without symptoms or $> 3\times$ elevated with symptoms, all hepatotoxic drugs should be stopped immediately and patient should be evaluated.

Summary of Evidence

Drug-induced hepatitis is the most serious and common adverse effect. It is defined as a serum AST level $> 3\times$ the upper limit of normal in the presence of symptoms or more than $5\times$ the upper limit of normal in the absence of symptoms. If hepatitis occurs, INH, RIF, and PZA, all potential causes of hepatic injury, should be stopped immediately. Serologic testing for hepatitis viruses A, B, and C (if not done at baseline) should be performed and the patient questioned carefully regarding exposure to other possible hepatotoxins, especially alcohol. Once the AST level decreases to less than two times the upper limit of normal and symptoms have significantly improved, the first-line medications should be restarted in sequential fashion. Close monitoring, with repeat measurements of serum AST and bilirubin and symptom review, is essential in managing these patients.

A small randomized trial conducted in Turkey compared the efficacy of 2 different retreatment protocols for newly diagnosed TB patients who developed anti-TB drug-induced hepatotoxicity. Patients in group 1 ($n=20$) were retreated with a drug regimen consisting of isoniazid, rifampicin, ethambutol and streptomycin administered by gradually increasing the number and dosage of the drugs. Patients in group 2 ($n=25$) received the same regimen of isoniazid, rifampicin, pyrazinamide and ethambutol in the same dosages throughout. This study demonstrated that the rate of recurrence of hepatotoxicity in the retreatment of TB is significantly lower when a regimen that does not include pyrazinamide is gradually reintroduced than when the full dose regimen containing pyrazinamide is given again ($p=0.021$). This finding is further supported by the fact that patients who had hepatotoxicity recurrence with the retreatment regimen containing

pyrazinamide showed no recurrence (even in a third period of anti-TB treatment) when they were gradually reintroduced to a regimen without pyrazinamide.¹⁴⁵

The incidence of pyrazinamide-induced hepatotoxicity and rash during treatment for active TB is substantially higher than with other first-line anti-TB drugs as reported in cohort studies, in contrast to reported rates in RCTs [HongKong Chest Service, BMRC 1987].¹⁴⁶ For instance, Yee et al in a cohort study of 430 patients, reported the incidence of adverse effects for pyrazinamide was 1.48 per 100 person months of exposure (95% CI 1.3, 1.6) compared to 0.49 (95% CI 0.42, 0.55) for isoniazid, 0.43 (95% CI 0.37, 0.49) for rifampicin and 0.07 (95% CI 0.04, 0.10) for ethambutol.¹⁰⁷ These results are in agreement with previous cohorts of patients treated in specialized centers in Britain.^{108, 109, 110, 111} In these studies, pyrazinamide was the most common causative agent for all side effects, hepatitis^{109,110} and rash.¹⁰⁸

4. *How should gastrointestinal reactions be managed?*

- AST and bilirubin levels should be measured in patients with gastrointestinal reactions. If AST level is < 3x normal, symptoms are assumed not to be due to hepatic toxicity. If AST level is 3 or more times elevated, GI symptoms are assumed to represent hepatic toxicity. [Grade C]
- For GI symptoms not due to hepatotoxicity, the timing of drug administration should be varied. Taking anti-TB drugs with food may minimize symptoms. Patients under directly observed therapy should take meals coinciding with drug intake. Patients who self-administer medications may take medications at bedtime. However if GI intolerance persists, all medications should be taken with meals. Administration with meals is preferable to splitting the dose or taking second-line drugs. [Grade C]

Summary of Evidence

There are no clinical trials on the management of gastrointestinal adverse reactions.

5. *How should hypersensitivity reactions be managed?*

- For minor rash, affecting a limited area or predominantly manifesting as pruritus, antihistamines should be given for symptomatic relief. All drugs can be continued.
- Petechial rash may suggest thrombocytopenia in patients taking rifampicin. Check platelet count and if low assume rifampicin hypersensitivity as the cause. Discontinue rifampicin and monitor platelet count until it returns to baseline.
- If with generalized erythematous rash, especially if associated with fever and/or mucus membrane involvement, stop all drugs immediately.
- When the rash has improved, medications can be restarted one by one at intervals of 2-3 days. Start with rifampicin followed by isoniazid and then ethambutol or pyrazinamide with gradually increasing doses. If the rash recurs, the last drug added should be stopped. If no rash appears after the first three drugs have been restarted, the fourth drug should not be restarted unless the rash was relatively mild and the fourth drug is considered essential for therapy.

Summary of Evidence

There are no clinical trials on the management of hypersensitivity reactions due to anti-TB drugs. The idea of drug challenging is to identify the drug responsible for the reaction. Drug challenge starts with the drug least likely to be responsible for the reaction. The rationale for starting with a small challenge dose is that if a reaction occurs, it will be less severe than the reaction to a full dose. The dose is gradually increased over the next 3 days. The procedure is repeated adding in one drug at a time. A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction. There is no evidence that this challenge process gives rise to drug resistance. If the drug responsible for the reaction is pyrazinamide, ethambutol or streptomycin, TB treatment is resumed without the offending drug. If possible, the offending drug is replaced with another drug. It may be necessary to extend the treatment regimen. This prolongs the total duration of treatment but decreases the risk of relapse.

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Chapter 5: Control and Prevention of Tuberculosis in the Philippines

I. The Clinician and his Role in the Control of Tuberculosis

An extensive discussion on the Current State of Tuberculosis in the Philippines is included in the first chapter of this document. Three important players have been identified as key components to achieve control of tuberculosis in the country: the Patient, the Health Provider, and the National TB Program. Although the rates of case detection and treatment success have improved in the last few years, particularly in the public sector, there remain many several obstacles to be hurdled for adequate TB control.

Being a clinical practice guideline, this chapter on Control and Prevention of Tuberculosis in the Philippines is written having in mind the health provider as a professional seeing patients with TB in his everyday clinical practice with other multiple tasks in our society. Thus the focus of recommendations is not possible solutions to problems of the national TB program. Instead it will be directed in helping each and every practicing physician, whether in government or in the private sector, whether in the rural or urban areas or in teaching institutions to coordinate individual efforts to the improvement of care of each and every TB patient for the common good.

II. Outline of Issues on Control and Prevention

- A. How can physicians contribute to the control and prevention of TB in the Philippines?
- B. How helpful is active case finding in detecting other individuals infected with TB?
- C. How useful is the tuberculin skin testing in the diagnosis of tuberculosis?
- D. Do we manage latent tuberculosis?
- E. What is the role of vaccination in the prevention of TB?
- F. What are the infection control measures appropriate for TB in the hospital setting?

III. Recommendations for the Control and Prevention of Tuberculosis in the Philippines

How can physicians contribute to the control and prevention of TB in the Philippines?

The control and prevention of tuberculosis in a high-burden country such as in the Philippines can be achieved primarily by correct management of each and every case of active and infectious TB disease through DOTS. Clinicians should employ best practices in the diagnosis and treatment of TB as outlined in this clinical practice guideline within the context of a directly observed treatment short course (DOTS) program.

How helpful is active case finding in detecting other individuals infected with TB?

As an extension of the DOTS strategy, active case finding in family members and close contacts of patients with tuberculosis can facilitate reduction in the morbidity and mortality attributed to the disease.

Summary of Evidence

Strategies to promote active case findings in the family members and the close contacts of TB patients have yet to be formulated in the local setting. But this will be a helpful tool, as it can lead to earlier detection and immediate treatment of active cases, resulting in decreased morbidity and mortality rates. Four active case finding strategies were evaluated in a study with the goal of expanding the WHO tuberculosis control program. The study showed one twelve year cycle of active case finding based on a symptomatic screen could reduce the number of new cases of tuberculosis between 1998 and 2050 by 17 million, and the number of deaths by 7 million.¹ Social support offered by families has been identified with positive health seeking behavior and treatment adherence.²

How useful is the tuberculin skin test in the diagnosis of TB?

In the general population, the tuberculin skin test (TST) is not useful for detecting tuberculosis infection. TST is recommended for asymptomatic individuals with an increased risk for tuberculosis and are likely to benefit from treatment of latent tuberculosis infection (LTBI).

Summary of Evidence

A major concern of TB prevention strategies is the identification of asymptomatic *M. tuberculosis* infection. Presently, only the tuberculin skin test (TST) administered by the Mantoux method is recommended for detecting asymptomatic tuberculosis – despite its low pooled sensitivity (60% at 95% CI; range 38% - 82%) and pooled specificity (78% at 95% CI; range 59% - 97%).³ Test sensitivity approaching 100% if it is administered in patients with latent tuberculosis infections and normal immune responses. However, false positive reactions from non-tuberculous mycobacteria may complicate readings.

Currently, no other diagnostic test has been found to accurately identify TB infection among asymptomatic individuals. A method known as the multiple-puncture technique has been cited, but was found to have even poorer sensitivities and specificities compared to the Mantoux test; it is thus not recommended even for children or infants.⁴

The Mantoux technique is the intradermal injection of tuberculin, the most widely used of which is purified protein derivative (PPD) from cultures of *Mycobacterium tuberculosis*. The size of the Mantoux reaction is correlated with future risk of tuberculosis development, but no correlation between the sizes for current active disease has been established. The recommended cut-off for a positive tuberculin skin test among Filipinos is 8 mm.⁵

An initial two-step tuberculin skin test has been recommended for high-risk individuals (e.g. health care workers, employees in health care facilities, and residents of nursing homes). This two-step technique is recommended when there is a need to determine a true baseline reading. The second injection step is made when the initial test reads negative; this is administered a week after the first test.

The two-step tuberculin skin testing is also recommended for individuals who are candidates for serial testing as part of surveillance programs, for example, health care workers who are in contact with people with active disease. The procedure is also advocated for individuals who intend to travel to places with a high incidence of tuberculosis infection.⁶

Other uses for the tuberculin skin test include monitoring recent converters in institutions where TB outbreaks are common, and screening immunosuppressed patients and other high-risk groups. Monitoring recent converters in institutions like hospitals, prisons, homeless shelters, workplaces, schools and other areas where people repeatedly congregate

(bars, clubhouses) allows reductions in morbidity as the TB infection usually initiated in these places frequently progress to active cases.⁷ Performing TST on HIV/AIDS victims, patients with diabetes mellitus, persons undergoing regular dialysis, and other high-risk immunosuppressive individuals has been proven cost-effective and has been recommended by the American Academy of Pediatrics (AAP), the Advisory Committee for Elimination of Tuberculosis of the Centers for Disease Control, and the American Thoracic Society (ATS).⁸

For a more extensive discussion of the tuberculin skin testing, please refer to the recently released statements of the PCCP Council on Tuberculosis “Guideline on Tuberculin Skin Testing in Adult Filipinos”¹⁵.

Do we manage latent tuberculosis?

At this time, the treatment of patients with LTBI is not a priority in the Philippines. While TB remains uncontrolled, resources must be focused on the “source” case. If and when targets have been achieved and sustained, strategies can then be shifted from control to elimination.

Summary of Evidence

At present, the focus of management remains on the “susceptible” infected individual.⁹

For high-risk groups, i.e., those who are likely to have progression of active disease, chemoprophylaxis or treatment of Latent TB Infection (LTBI) may be needed, as recommended by the American Thoracic Society, American Academy of Pediatrics, the Advisory Committee for Elimination of TB of the Center for Disease Control and Prevention, and the Philippine Guidelines on Periodic Health Examination. These high risk groups include childhood contacts of active cases of TB, and persons with positive TST and risk factors for TB: diabetics on immunosuppressive treatment, patients on hemodialysis presenting with fibrotic lesions, health care workers who convert from negative to positive, and patients with HIV infection. However, emphasis should be placed on adequate screening, close monitoring and observation, and appropriate treatment once these patients show signs of active disease.

What is the role of vaccination in preventing TB infection?

Bacille bilié de Calmette-Guérin (BCG) vaccination is not recommended for adults because it does not confer protection. There is currently no available effective vaccine against tuberculosis though several trials are underway.

Summary of Evidence

Bacille bilié de Calmette-Guérin (BCG), a live attenuated vaccine developed from virulent strains of *Mycobacterium bovis*, was first used in 1921 to control tuberculosis. Despite an estimated global vaccine coverage of 80%, its efficacy greatly varies (reports range from 0% to 80%).^{10,11} Even if studies have established the vaccine's efficacy against childhood TB, this tends to decrease with time; and adults, thus, have no sufficient protection against pulmonary tuberculosis. BCG revaccination does not confer protection against development of tuberculosis.¹²

The variability in BCG's efficacy is generally attributed to (1) strain variation in BCG preparation (absence of ESAT-6 and CFP-10, MPT64 or unexpression of MPB70 and MPB83 - proteins that are present in the parental strain), (2) exposure to environmental mycobacteria and chronic parasite infections, and (3) suboptimal delivery of vaccine.

New tuberculosis vaccine candidates that have entered phase 1 clinical trials in 2004 include: recombinant BCG (rBCG30), vaccinia-vectored vaccines (MVA85A), subunit and fusion proteins formulated in novel adjuvants (ESAT-6, Ag85B, HSP60 and Mtb32). Live mycobacterial vaccines, DNA vaccines and killed BCG and *M. bovis* are the newer type of vaccines that are still undergoing modification and further investigations.^{13,14}

What are the infection control measures appropriate for TB in the hospital setting?

The following are general recommendations to reduce the risk of spread of TB infection in the hospital setting. For more thorough discussion, the reader is referred to pertinent documents of the US Centers for Disease Control.^{15,16}

- ❖ TB is a highly communicable illness transmitted by airborne route. If a TB patient requires hospitalization, it is best if the patient can be admitted to designated isolation rooms with negative pressure systems or at least a single private room.

- ❖ Isolation rooms meant to function as source isolation for infectious cases should be constructed with the recommended ventilation of 12 air exchanges per hour.
- ❖ Cohorting of many TB patients can be done in general wards housing several patients with the same illness is allowed. These wards without partitions are best maintained with natural ventilation.
- ❖ Areas that opt to shift from natural ventilation to mechanical ventilation/ centralized airconditioning should still consider the necessary air exchanges and air flow route as well as the anticipated burden of communicable illnesses so that infection to staff and other patients is still minimized.
- ❖ Efficient diagnosis and management of TB should include the following strategies:
 - ✓ Early detection with low threshold of suspicion for a possible diagnosis of TB
 - ❖ Patients with active pulmonary or laryngeal TB are the most infectious during the period they are still undiagnosed, not isolated and not on any anti-TB medications.
 - ❖ Other cases of extrapulmonary are not as infectious unless there is concomitant pulmonary TB
 - ✓ Early initiation of TB diagnostic work-up and efficient release of sputum microscopy results
 - ❖ Patients should expectorate to collect specimen for microscopy at designated sputum induction rooms.
 - ✓ Early initiation of Adequate Quadruple anti-TB meds
 - ❖ Availability of 1st line anti-TB medications at all times in tablet and suspension forms.
 - ✓ Isolation of suspected or confirmed TB for at least one week, preferably two weeks
 - ❖ **All patients suspected or confirmed to have active TB should be asked to purchase and wear a surgical mask if their pulmonary status can tolerate.** This act alone, whether patient is in the isolation room or in the general ward is a good isolation measure.
 - ❖ Patients in isolation suspected to have MDR-TB should remain in Isolation until discharged or until

conversion of sputum AFB to negative or significant improvement in the CXR.

- ✓ Engineering Controls thru Proper Ventilation
 - ❖ Isolation Rooms should have its own ventilation source and exhaust. Air that comes from Isolation rooms should NOT recirculate into the general air circulation.
- ✓ Proper use of Personnel Protective Equipment (PPE)
 - ❖ Use of PPE should be regarded only as second line precaution especially in situations where the above cannot be properly implemented. In the long run wide non-judicious use of PPE is probably going to be more expensive and not-sustainable.
 - ❖ PPE for active TB include mainly the N95 mask.
 - ❖ The N95 masks should be well-fitting and produce a seal over the face. It can be used for TB as long as it is physically intact, dry and not visibly soiled. N95 should not be shared between personnel and kept in a manner that the shape is not distorted.

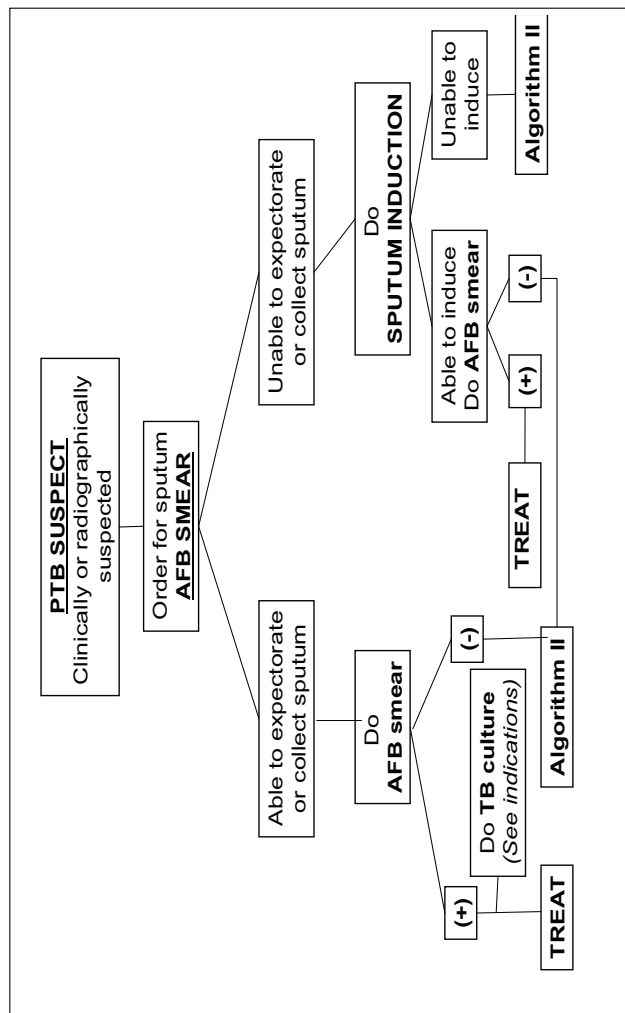
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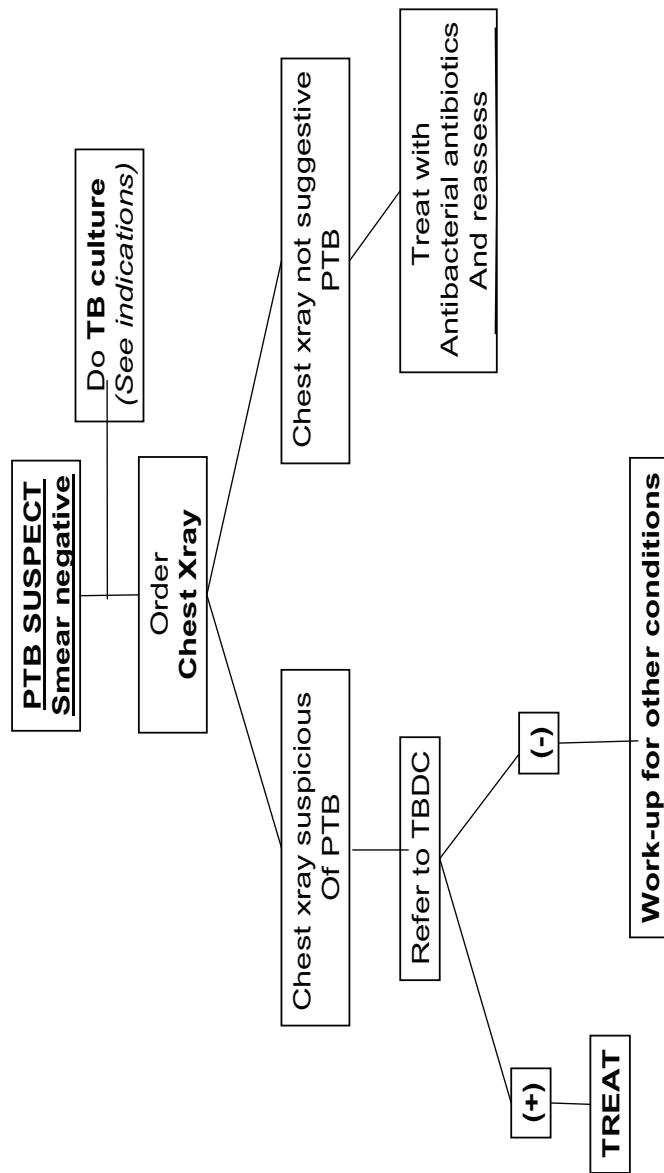
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CHAPTER 6: ALGORITHMS

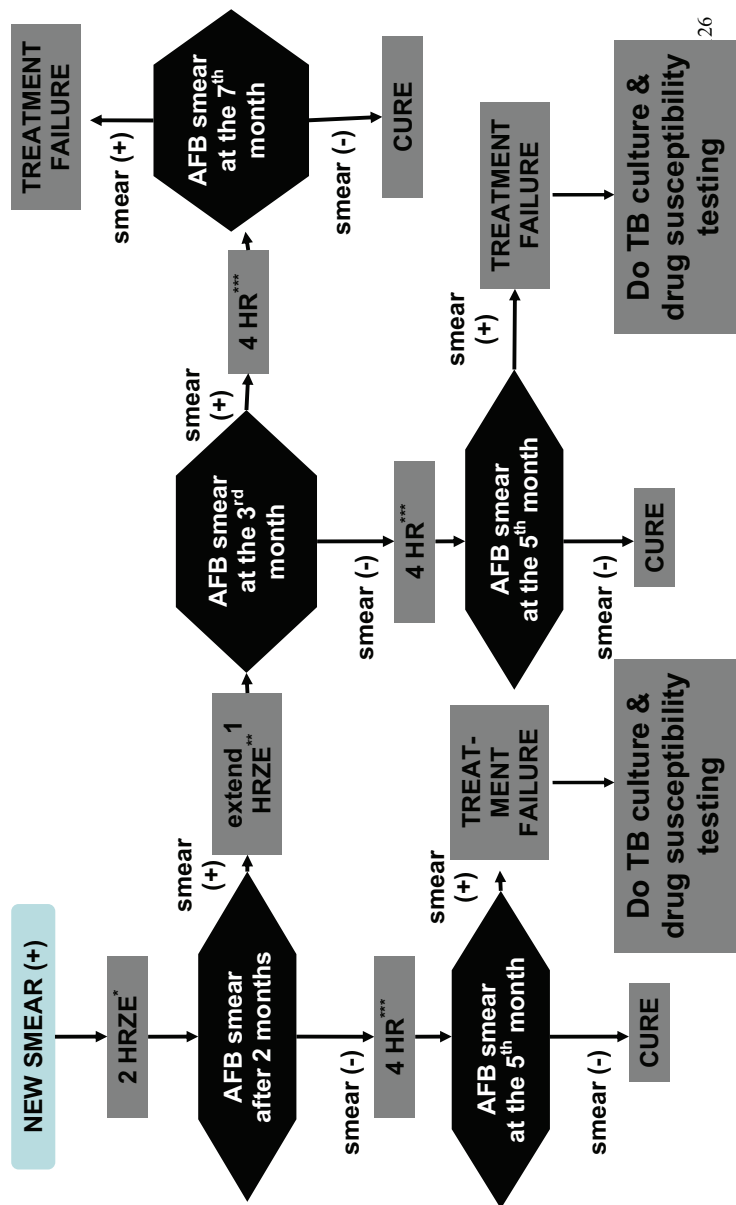
DIAGNOSIS ALGORITHM 1: Work-up of PTB Suspect



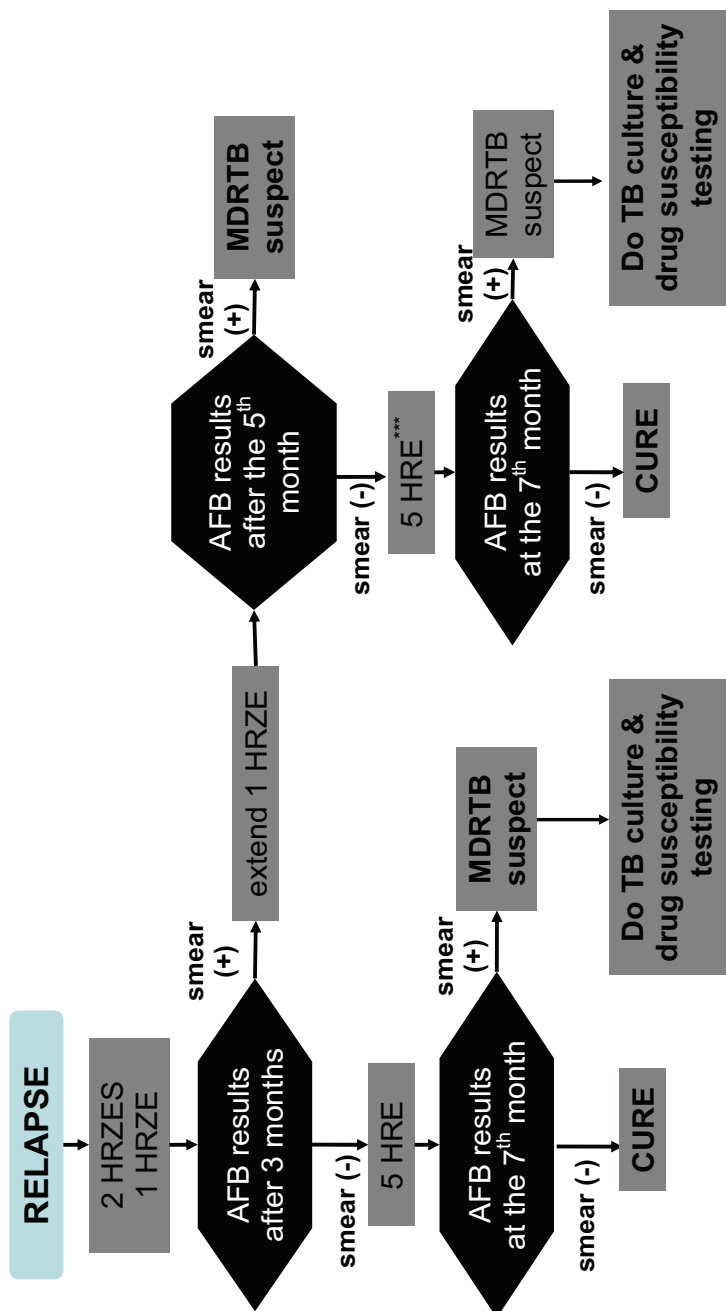
DIAGNOSIS ALGORITHM 2: Work-up of Smear negative PTB suspects



Treatment Algorithm 1 – Newly Diagnosed, Smear (+) Patients



Treatment Algorithm 2 – Relapse



Summary Algorithm for Treatment

