Is TB recurrence in Treated TB-HIV Co-Infected Patients Relapse or Re-infection? 
The TRuTH Study 
(TB Recurrence upon Treatment with HAART)

A research protocol prepared by:

The Centre for the AIDS Programme of Research in South Africa
FUNDED BY THE HOWARD HUGHES MEDICAL INSTITUTE AND CENTRE FOR DISEASE CONTROL

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CAPRISA 005 is a protocol of the KwaZulu-Natal Research Institute for TB-HIV (K-RITH)
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**PROJECT OVERVIEW**

**Title:** Is TB recurrence in treated TB-HIV co-infected patients relapse or re-infection?

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This study is being conducted by CAPRISA (Centre for the AIDS Programme of Research in South Africa) in Durban, South Africa as part of K-RITH (KwaZulu-Natal Research Institute for TB-HIV). All enrollments and follow-ups are scheduled to take place at a single site, the CAPRISA eThekwini Clinic 1, at the Prince Cyril Zulu Communicable Disease Centre (PCZCDC).

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### Acronyms

<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>AFB</td>
<td>acid-fast bacilli</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immuno-Deficiency Syndrome</td>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<tr>
<td>BREC</td>
<td>Biomedical Research Ethics Committee</td>
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<tr>
<td>CAT</td>
<td>CAPRISA AIDS Treatment Programme</td>
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<tr>
<td>CBO</td>
<td>Community Based Organization</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>CRSG</td>
<td>Community Research Support Group</td>
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<td>DoH</td>
<td>Department of Health</td>
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<tr>
<td>DOT</td>
<td>Directly Observed Therapy</td>
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<td>DST</td>
<td>Drug Susceptibility Test</td>
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<tr>
<td>EPTB</td>
<td>Extra-pulmonary Tuberculosis</td>
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<tr>
<td>ETH</td>
<td>Ethambutol</td>
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<td>FBO</td>
<td>Faith-based organization</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
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<td>HLA</td>
<td>Human Leukocyte Antigen</td>
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<td>Human Subjects Protection</td>
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<td>Hypersensitivity Reactions</td>
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<td>MTB</td>
<td>Mycobacterium Tuberculosis</td>
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<td>PCZCDC</td>
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<tr>
<td>PLWHA</td>
<td>People living with HIV and AIDS</td>
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<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
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<td>RFLPs</td>
<td>Restriction Fragment Length Polymerization</td>
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<td>RIF</td>
<td>Rifampicin</td>
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<tr>
<td>SANCTR</td>
<td>South African National Clinical Trials Register</td>
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<tr>
<td>SAPIT</td>
<td>Starting AIDS treatment at three Points in TB treatment</td>
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<tr>
<td>START</td>
<td>Starting Tuberculosis and Antiretroviral Therapy</td>
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<td>T.BILI</td>
<td>Total Bilirubin</td>
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<td>TB</td>
<td>Tuberculosis</td>
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<td>University of KwaZulu Natal</td>
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<td>VCT</td>
<td>Voluntary Counseling and Testing</td>
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<td>WHO</td>
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1. INTRODUCTION

1.1 Literature Review

South Africa has the highest number of notified TB cases in the world, and has been ranked ninth among the 22 high burden TB countries [1]. The annual number of TB cases reported in this country has quadrupled from 61,486 in 1988, to 279,260, in 2004. The TB case fatality rate has also risen from 3% in 1993 to 7.4% in 2003. In 2004 the TB notification rate was 551/100,000 population and within the province of KwaZulu Natal the notification rate was 723/100,000 population demonstrating the largest number of newly diagnosed cases of all the provinces [1]. HIV infection has added considerably to the TB burden in the country. South Africa is home to the largest number of people living with HIV estimated at 5.3 million people [2]. In 2004, 8% of global HIV-related deaths were estimated to be caused by TB. Autopsy studies have shown that the rates of TB were over 33% among people dying of Acquired Immuno-Deficiency Syndrome (AIDS) [3, 4]. TB is the most common opportunistic infection and the most common cause of HIV related morbidity and mortality in South Africa.

In a study conducted in South Africa, it was demonstrated that initiation of antiretroviral therapy (ART) at CD4<200 cells/mm³ or at WHO Stage 4 HIV disease, is associated with high incidence of TB in ART programmes [5]. This study showed that while TB incidence is reduced during HAART, the TB incidence rate remains unacceptably high among HIV-infected patients. HIV-infected patients on HAART, have a TB incidence rate of 4.6 cases/100 patient-years, this is approximately 10-fold higher than the TB incidence rates of HIV negative patients in the same community [6].

The question of when to begin ART in TB patients is still unanswered. Currently, there is no randomized, controlled clinical trial demonstrating TB treatment outcomes in HIV-infected patients with TB, in countries where both diseases are endemic. One of the issues related to management and care of HIV-TB co-infected individuals is how to effectively treat HIV-TB co-infection to reduce mortality and TB recurrence. The SAPIT (Starting AIDS treatment at three Points in TB treatment) trial addresses the question of timing of HAART initiation on mortality and incidence of AIDS but does not address a key public health question of impact on TB recurrence.

Recurrent TB accounts for the majority of TB cases in countries with a high TB incidence rate [7]. Literature has shown that TB scarring, cavities, regimens used for the initial episode and a low CD4 count are all risk factors for recurrent TB. There is a consensus among authors that HIV-infection is a major risk factor for TB recurrence [8-10]. A study of South African gold miners demonstrated that TB recurrence was 5 times more likely in HIV positive people [11].

KwaZulu-Natal, one of the epicenters of TB infection currently has, 2 known circulating subspecies of Mycobacterium tuberculosis (MTB) namely the Beijing, and KZN subspecies. Multiple circulating strains are found to be part of the Beijing or KZN subspecies. A strain is a single isolate of a characteristic pattern that belongs to a specific subspecies. The exact number of strains belonging to each of these subspecies is undetermined and due to the sheer burden of disease this will likely never be known. The likelihood of individuals who have been infected with the same MTB subspecies, having infection by the identical strain is 15-20%. A number of unique isolates have also been identified in our setting which do not group into any of the known subspecies and hence have been termed unique or non-clustering. For reasons that remain
unknown, these strains have not been or very rarely been shown to infect more than one individual [30, 31].

There is a paucity of information regarding incidence rates of and risk factors for recurrent TB in a HIV infected population enrolled onto ART [11]. The few studies that have examined rates of TB recurrence have had major limitations including, small sample sizes and the restriction of investigations to special populations of people, such as, gold miners, and have not been specific to HIV infected populations on [10-12].

TB recurrence due to either re-infection or relapse has important implications for TB control and the impact on the emerging drug resistant TB epidemic. TB recurrences increase the pool of infectious TB cases in the community and pose an added risk of increased TB transmission to people living with HIV/AIDS (PLWHA). In settings with high rates of TB, rapid HIV disease progression has been shown to be an important factor in TB re-infection [7]. A study conducted in a high TB incidence area in South Africa demonstrated that rates of TB re-infection after successful treatment could be higher than rates of new episodes of TB[12]. Of the 612 patients in the sample, 18% had recurrent TB. The re-infection disease rate was estimated at 2.2 per 100 person-years and the study concluded that TB attributable to re-infection after successful treatment was 4 times that of new TB. A major limitation of the study was that the HIV status of the participants was not known and it did not address the key question of recurrence of TB in patients on HAART.

1.2 Justification for the study
South Africa is a high TB burden country, and has the largest HAART rollout in the world. There is a pressing need to examine TB recurrence in patients on HAART and the impact of ART provision on the incidence of recurrent TB [13]. With increasing numbers of patients on HAART spending long hours in inadequately ventilated waiting rooms in AIDS clinics and where limited infection control activities are taking place, the roles of relapse and re-infection, especially with drug resistant TB, need to be investigated. There are important public health and programmatic implications of the relative contributions of relapse versus re-infection in TB recurrence. If the predominant form of TB recurrence is as a result of TB re-infection, this has implications for directing increased effort and resources aimed at environmental control of TB, including direct infection control measures targeted at nosocomial transmission of TB in health facilities, as well as community and household based infection control measures. Most importantly, from a public health perspective, if re-infection is the predominant form of TB in HIV infected patients, then integration of TB and HIV care can occur only up to the end of TB therapy. Patients who complete TB therapy in facilities that integrate TB HIV care will need to be referred out to reduce the likelihood of TB re-infection. If the predominant form of TB recurrence is due to TB relapse, this would provide evidence to inform public health interventions which includes the roll-out of IPT to all HIV positive patients on completion of TB therapy, and will also raise questions of the possibility of lengthening the duration of TB therapy, and will underscore the need for nutritional support in HIV infected patients to reduce the likelihood of TB relapse disease.
1.3 Rationale for Focusing on TB Participants Co-Infected with HIV on ART as a Target Population for Investigating TB Recurrence

1.3.1 Efficient Strategy for Identifying Participants likely to experience TB recurrence

Despite efforts to improve immunity and reduce morbidity in the HIV infected by enrolling eligible patients onto ART, incomplete immune restoration against TB [14], creates a persistent risk of TB disease in patients on antiviral therapy at all CD4 levels. Patients who are currently in care within HIV treatment programmes, who have had at least one previous episode of active TB, provides an efficient mechanism for identifying individuals with HIV who are on ART and are likely to experience recurrent TB.

1.3.2 HIV-Related TB has a High Case Fatality Rate

Despite the availability of appropriate TB chemotherapy, HIV-related TB is associated with higher case fatality rates, and ART may have a substantial beneficial impact on HIV-related TB. Thus, a significant impact may be achieved due to the potential effectiveness of the HAART in the large populations co-infected with HIV and TB.

1.3.3 Patients with TB Receive Treatment through an Established Infrastructure

In many developing countries, an established, acceptable, and familiar infrastructure is available to provide treatment for patients with TB. TB patients receive ongoing clinical care, have secure access to medications, and most receive treatment through Directly Observed Therapy (DOT) programs. Staff at health facilities are trained to identify TB, manage the patients, and provide the appropriate linkages and support to ensure completion of and adherence to treatment. National guidelines exist to guide and monitor TB treatment and its outcomes.

1.3.4 Role of host genetic factors in susceptibility to tuberculosis

Certain populations have been described as having an increased susceptibility to TB and in many cases this susceptibility is modulated by the Human leukocyte Antigen (HLA) II [15]. One study demonstrated that Mycobacterium tuberculosis (MTB)-specific CD8+T cells were found in high frequency in infected individuals and were predominantly HLA-B allele restricted [16]. The presence of the HLA-DRB1 allele was demonstrated to be a significant factor influencing host humoral and cellular responses. In the presence of the allele in pulmonary tuberculosis (PTB) positive patients a significantly lower level IFN-γ was produced than in healthy individuals with the allele present. In contrast both groups with the allele present produced significantly lower levels of IFN-γ than healthy individuals without the allele. In addition, the presence of HLA-DRB1 appears to drive and unfavorable Th2 cellular and cytokine response [17]. The HLA-DQB1*0503 allele was shown to be significantly present in 78 patients with TB but none of the 49 controls [15]. Depending on HIV-1 status, HLA-A and -C were shown to be associated with an increased risk of developing active TB. Among HIV positive subjects, HIV load was independently associated with increased risk of developing PTB. HLA-DRB1 homozygosis among HIV-positive subjects was associated with reduced risk of developing PTB but increased risk of rapid progression to pleural effusion TB. These observations indicate that HLA is significantly associated with the development of symptomatic TB at various stages of disease and that these effects are modified by HIV co-infection [18]. Observations from studies conducted in developed countries indicate that HLA alleles are significantly
associated with the development of symptomatic TB at various stages of disease and that these effects are modified by HIV co-infection [32]. HLA typing for class I and class II alleles will be carried out on all study participants to investigate whether a particular HLA type predisposes or protects patients in our setting from symptomatic recurrent TB.

### 1.3.5 Role of cellular immune responses in recurrent and relapse TB cases

Control of infection with TB relies heavily on the cellular immune system [16]. Immune restoration syndrome induced TB is common for those on HAART therapy. This has posed important questions as to the timing of HAART therapy. Findings independent of viral load, CD4 cell counts or time of HAART showed that an acute exacerbation of Th1 responses to mycobacterial antigens appears to cause immune restoration syndrome in patients co-infected with HIV and TB [19]. In addition immune analysis may serve as useful tools in determining the most appropriate time for preventative TB therapy particularly in HIV infected patients. A study on B cell and antibody responses showed that the presence of antibodies was unreliable in the determination of active TB yet; the presence of short lived MTB specific B cells on the other hand was reliable for the determination of active replicating TB in HIV infected individuals [20]. Local immune responses have also been described as potential factors affecting the clinical presentation of TB in HIV infected patients. Studies comparing TB smear negative with smear positive with culture positive samples showed differences in pro-inflammatory and immunomodulatory cytokines, with these being higher in patients positive for TB in both smear and culture [21]. Analysis among controlled trials demonstrated overall recurrence rates (per 100 000 person-years) were respectively 3010 (95%CI:2230–3970) and 2290 (95%CI: 1730–2940) at 6 and 12 months after treatment completion. Among those with HIV, recurrent TB was associated with a low initial CD4 count and receiving less than 37 weeks of anti-TB treatment [22]. Relapse TB cases were noted to be minimal if the HIV infected patient stayed on anti-TB prophylaxis for a period of 9 months while simultaneously achieving an undetectable viral load with an associated increase in CD4 cell counts [23]. Of the published TB studies, only one study adequately distinguished second episodes of TB in HIV infected as due either to relapse or re-infection [24]. A prospective cohort study in South Africa demonstrated that in HIV infected individuals, TB recurrence was significantly associated with re-infection but not relapse [11]. Von Reyn et al (2006) in a commentary raised a significant possibility that culture- positive TB cases represent a group genetically susceptible to re-infection, but that culture-negative cases reflect a stronger adaptive immune response with reduced susceptibility to re-infection [25].

The study provides us with an opportunity to establish if the longitudinal characterization of immunodominant epitopes and functionality of MTB-specific T cells determine TB relapse from reinfection. A longitudinal assessment of both immunodominant T cell epitopes and functionality of MTB-specific T cells may enable us to distinguish between MTB relapse and reinfection. Individuals who progress to active TB as a result of reactivation of a pre-existing infection may target similar T cell targets over time whereas in individuals who are reinfected we may observe a new pattern of T cell epitopes Differences in the functionality of MTB-specific T cells may also be apparent between the two groups as T cells that have been stimulated by antigen for a prolonged period of time may display severe immune defects compared to newly primed/less stimulated populations. Essentially, individuals who display severe MTB-specific T cell immune dysfunction may be more susceptible to the development of reactivation TB.
1.3.6: Assessment of innate immunity in determining relapse from re-infection

Macrophages play a critical role in the innate immune response to TB (Kaufmann, Cole et al. 2005). These cells express an array of pathogen-sensing receptors, including Toll-like receptors (TLR), which allow these cells to respond to pathogens. It is now well-established that TLR2 and TLR4 are involved in the recognition of Tb by macrophages, and in the initiation of the TB-specific immune response, while HIV-1 can be sensed by TLR7 and TLR8 (Russell and Yates 2007). Based on recently published studies, the activation of one TLR pathway on a cell has a significant impact of the ability of that cell to respond to consecutive stimulation. Impaired responsiveness of macrophages to Tb-encoded TLR ligands in the setting of HIV-1 infection might therefore represent one of the mechanisms that render HIV-1 infected individuals more susceptible to Tb infection, even at early stages of infection when CD4+ T cell counts are still high. Furthermore, NK cells play a critical role in the innate immune response in HIV-1 disease (Alter and Altfeld 2009) and to other opportunistic infections including TB (Schierloh, Aleman et al. 2005). Impaired responsiveness of macrophages and NK cells in the setting of HIV-1 infection might therefore represent one of the mechanisms that render HIV-1 infected individuals more susceptible to Tb infection, even at early stages of infection when CD4+ T cell counts are still high. This study will help us to identify the immunological mechanisms that are responsible for the increased risks of MTB infection and TB disease progression in HIV-1 infected individuals, even before their immune system is compromised to levels at which other opportunistic infections occur.

1.3.7 Restriction Fragment Length Polymerization (RFLPs)

*IS6110* RFLP typing has become the most widely used molecular typing technique for *M. tuberculosis*, since the internationally accepted standardized protocol was published in 1993 [26, 27]. The principle of the technique hinges on the difference in *IS6110* copy number within an *M. tuberculosis* strain [27]. This ranges between 0 – 25 copies [28]. While the sequence is found in almost all strains of *M. tuberculosis* it is not known to be found in any other organism. Today this technique forms the gold standard for *M. tuberculosis* typing [26-28].

1.4 Intended/Potential Use of Study Findings

The data emanating from this study has the potential to inform public health interventions. Depending on which is the predominant form of TB recurrence (relapse or reinfection), public health policy can be informed as to what the future priorities of TB disease control policy should be. The implications of these study findings will also help direct TB research priorities such as TB vaccine development. If TB re-infection is predominant, then vaccine development needs to be directed toward prophylaxis to reduce the risk of TB disease. If TB relapse is predominant, then TB vaccines need to be adjunctive, i.e. used with TB therapy, to enhance the efficacy of TB therapy. The TRuTH study has the potential to provide evidence to inform all of the above.
1.5 Study Design and Location: The Prince Cyril Zulu Communicable Diseases Centre (PCZCDC)

This study is a prospective cohort study which will determine the rate at which TB recurrence occurs in a cohort of patients who have completed TB therapy for PTB and are on HAART. PCZCDC is the designated clinic for the diagnosis and treatment of TB cases from North and South Central Durban. The clinic serves mainly the local community and is staffed by medical officers who provide examinations and treatment. Patients are either referred from primary health care centers and hospitals with a diagnosis of TB or are self-referred and considered “walk-in” patients. Upon arrival to the clinic, self-referred patients are screened by a clinic attendant and are directed to a professional nurse. The nurse will assess the patient by asking a series of screening questions to ascertain whether patients have signs and symptoms of TB. Patients who have had a cough for six weeks or more, show other constitutional symptoms of TB, and are from within the Durban metropolitan region are admitted into the system.

With regard to Design and Location, Section 1.5 has been amended to include: The PCZCDC currently provides the community with TB testing, TB treatment, hospital referrals, and HIV voluntary counseling and testing (VCT). It is a natural extension for this clinic to provide the next logical step in a continuum of care, specifically HIV treatment. The PEPFAR-funded CAPRISA AIDS Treatment (CAT) Program was initiated in June 2004 and currently provides an integrated package of prevention and treatment services. The program provides an innovative method of providing ART by integrating the tuberculosis (TB) and HIV care as well as counseling and testing, family planning, sexually transmitted infections (STI) treatment, prophylaxis and treatment for opportunistic infections (OIs), and other HIV associated conditions. The CAPRISA eThekwini Clinical Research Site is an urban facility attached to the PCZCDC. HAART provision at this clinic integrates TB and HIV care into the existing TB control program. Patients are either self referred, or enter the HIV care continuum via the adjoining TB or STI services.

In 2004, 8,580 new patients were diagnosed with TB at the PCZCDC (an average of 715 per month). Of these, 5,390 (63%) patients were self referred, and 3,190 were referred from other clinics or hospitals. Of the self referred patients, 4,532 (84%) had pulmonary TB (377 per month). A total of 3,568 (79%) were smear positive, 542 (10%) were smear negative but culture positive and the remainder were smear and culture negative; 65% of patients had no past history of TB. The majority (91%) of TB patients are black Africans, 39% are women, and the median age is 33 years (range 5 to 72 years). The majority of patients (53%) are unemployed. The HIV prevalence among TB patients who agreed to be tested is approximately 65%. In 2008, 4179 TB patients were managed at the clinic and of these, 2204 had smear positive TB.

DOT remains the cornerstone of TB management, and all patients are encouraged to receive their medication under supervision. Newly diagnosed TB patients are counseled on the importance of completing treatment and given options for treatment support. They choose from a range of medication supervisors, including supervision by staff at the PCZCDC, workplace-based supervisors or community-based supervisors (neighbors, shopkeepers, and friends).

Ninety-one percent of patients who were supervised by the Prince Cyril Zulu CDC reported being compliant to their treatment regimen at 6 months. TB management at the Prince Cyril Zulu CDC is in
accordance with the National and Provincial Tuberculosis Programme guidelines as set out by the Department of Health and entails the daily administration of isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months of TB treatment, and isoniazid and rifampicin for the duration of TB treatment.

The PCZCDC currently provides the community with TB testing, TB treatment, hospital referrals, and HIV voluntary counseling and testing (VCT). It is a natural extension for this clinic to provide the next logical step in a continuum of care, specifically HIV treatment.

1.6 Challenges Associated with use of ART during Anti-TB Therapy

1.6.1 Side Effects and Toxicities

The treatment of TB requires intake of 2-4 medications on a daily basis while the treatment of HIV requires intake of 3 medications on a daily basis. Each of these regimens may be associated with adverse events. These include Gastrointestinal (GI) intolerance, hepatitis, pancreatitis, Hypersensitivity reactions (HSRs), peripheral neuropathy, rash, and neuro-psychiatric difficulties. The combination of both regimens may result in additive toxicity and side effects. Some studies suggest that HIV-infected patients have a higher rate of adverse events while other studies do not support these findings [29]. Notwithstanding, the concern about additive side effects and toxicities warrants collection of detailed toxicity and tolerability data in future studies of combined therapy.

1.6.2 Complexities associated with the co-management with HAART and Anti-TB therapy

When patients with HIV develop TB, the question of when to initiate HAART treatment is still to be answered. The immune recovery associated with use of HAART is likely to enhance recovery from TB. On the other hand, vigorous immune reconstitution can also be associated with transient increase in symptoms. The co-administration of HAART during TB treatment may alter the pharmacokinetics of both anti-TB and HAART medications and increase side effects and toxicities.

Despite the availability of appropriate TB chemotherapy, HIV-related TB is associated with higher case fatality rates, and ART may have a substantial beneficial impact on HIV-related TB. Thus, a significant impact may be achieved due to the potential effectiveness of HAART in the large populations co-infected with HIV and TB.

2. OBJECTIVES

2.1 Primary objective

The primary objective of this study is to determine the incidence of TB recurrence in patients on ART. The proportion of TB recurrence due to relapse vs re-infection will be established via RFLP. The objective is to determine whether relapse or re-infection is the primary driver of TB recurrence.

2.2 Secondary objectives
i. To identify risk factors for TB recurrence.
ii. To identify risk factors for TB recurrence due to re-infection.
iii. To identify the risk factors for TB recurrence due to relapse.
iv. To describe the presentation at TB recurrence of TB relapse versus re-infection. This will include clinical, virological (viral load), microbiological, radiological and immunological (CD4 count) characteristics at the time of TB recurrence;
v. To describe the time to TB recurrence from first TB diagnosis
vi. To describe the time to TB recurrence from HAART initiation
vii. To describe the time to TB recurrence from TB treatment cure/completion;
viii. To investigate the host genetics, including Human Leukocyte Antigen (HLA) profiles in patients with TB recurrence
ix. To describe immune responses to TB and HIV before and after TB recurrence

2.3 Hypotheses /Questions

No hypotheses will be tested in this study; however, the primary study question will determine the proportion of TB recurrence due to relapse vs. re-infection.

2.4 General Approach

The general approach adopted in this study is exploratory.

3. PROCEDURES AND METHODS

3.1 Study Design

This is a prospective cohort study investigating the rate of TB recurrence in adult patients who have completed TB therapy for PTB and are on HAART. The study will be conducted at the CAPRISA eThekwini clinic, which is adjacent to the PCZCDC, a major urban TB clinic, in Durban, South Africa. This study will involve follow-up of patients who have completed the SAPIT (see Appendix I for SAPIT study schema) and START trials (see Appendix II for START study schema), some of whom are enrolled into long term care within the CAPRISA AIDS Treatment (CAT) programme.

As ex-SAPIT and START patients enter into CAT, they will be screened for the TRuTH study and after obtaining informed consent enrolled onto the study. Patients will be followed up for a period of 3 years. In order to detect recurrences of TB, patients will be administered a sputum smear at study entry (Baseline) and 3-monthly sputum smears thereafter. Patients will undergo chest X-rays and blood draws at baseline and then at every 6 month intervals. At every study the patient will be administered a TB symptom checklist (Appendix III) which assesses the patient’s symptoms and risk factors for TB, in addition to a thorough medical history and clinical examination.
Comparisons will be made between those patients who have recurrence of TB due to relapse and TB recurrence due to reinfection in order to determine which will have the larger contribution to TB recurrences.

3.2 Audience and Stakeholder Participation

As the outcome of this study can potentially inform public health interventions, the primary audience for this study will be public health policy makers, in this instance being the Department of Health (DoH), and local authority. Additional stakeholders include trial participants, representatives from Faith-Based Organizations, Non-Governmental Organisations, PLWHA, as well as political and civil society leadership and community leaders. Currently the needs and views of the community in which this study is being implemented, is well represented by the CAPRISA Community Research Support Group (CRSG). The CRSG consists of representatives from the community who monitor the rights and well-being of research participants in all CAPRISA research activities.

3.3 Study Time Line

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4. STUDY POPULATION

4.1 Description and Source of Study Participants

A concerted effort has been made in the SAPIT and START studies, to access a study population that was reflective of the larger population of South and sub-Saharan Africa. SAPIT and START recruitment activities targeted participants who attended the Prince Cyril Zulu CDC for services. This study population comprises a cross-section of different races, ages, and genders in South Africa. Participants from throughout the greater Durban area who may have TB are routinely evaluated at this health center. They may be referred from several sources, i.e., self-referral, from a physician, from a local treatment clinic, from a hospital setting, or from a local “traditional” healer. The Prince Cyril Zulu CDC does not treat complex cases of TB, including TB meningitis and miliary TB. Complex cases are referred to King Edward VIII and King George V Hospitals for management and are not eligible for this study.

4.2 Enrollment of ex-SAPIT and START patients into the TRuTH study

Once SAPIT (CAPRISA 003) and START (CAPRISA 001) patients have completed study follow up in these two trials, they are transitioned into the CAPRISA AIDS Treatment (CAT 053) programme for continued care and treatment. It is at entry into the CAT programme that patients will be introduced to the TRuTH study. We have succeeded in implementing a smooth transition procedure for these patients as outlined in Section 5.1 below.

4.3 Case Definitions

The following definitions/descriptions will be used in the study in accordance with the South African National Tuberculosis Guidelines, 2007 (Draft 1) (Appendix IV):

**Diagnosis of Tuberculosis:** The presence of either two positive acid-fast bacilli (AFB) sputum smears or one positive sputum smear with a clinical picture consistent with tuberculosis (TB).

**Intensive Phase of TB Therapy:** In accordance with the South African National Tuberculosis Guidelines, 2007 (Draft 1) (Appendix II), the intensive phase of TB therapy is the period during which 4 anti-TB drugs are administered. This phase usually lasts 2 months but may be extended.

**Continuation Phase of TB Therapy:** The continuation phase begins immediately after the intensive phase ends and comprises a period during which 2 anti-TB drugs are administered. This phase usually lasts 4 months but may be extended.

**Uninterrupted TB Treatment:** Defined as at least 130 TB directly observed therapy (DOT) doses within 9 calendar months (approximately 274 days since initiation of TB therapy). Participants must receive at least 43 intensive phase DOT doses within 3 calendar months with no interruptions of 14 or more consecutive days and at least 87 continuation phase DOT doses within 6 calendar months.
**TB Cure:** Completion of TB treatment with protocol-defined uninterrupted TB treatment; and at least two consecutive negative sputum cultures at or beyond 2 months of TB therapy with one of the cultures at or beyond 5 months of TB therapy.

**Successful TB Treatment Completion ("Clinical Cure"):** Completion of TB treatment based on protocol-defined uninterrupted TB treatment, with a clinical and radiologic response to TB treatment without two adequate sputum samples obtained at or beyond 2 months, including one at or beyond 5 months of treatment.

**TB Treatment Failure:** The presence of a positive smear or culture obtained at or beyond 5 months after initiating treatment.

**Clinical TB Treatment Failure:** Clinical or radiological evidence of failure to respond to therapy but without a positive culture or smear obtained at or beyond 5 months after initiation of treatment.

**Other, Non-Specified TB Outcomes:** All Participants who did not qualify as a “cure,” “successful TB treatment completion,” “treatment failure,” or “TB recurrence.”

**TB Recurrence:** The diagnosis of TB following TB cure or successful TB treatment completion. This includes culture proven TB relapse and TB re-infection (both based on the RFLP pattern, see below), culture and smear-positive recurrences without a conclusive RFLP pattern, and clinical recurrence diagnosed on the basis of clinical or radiologic evidence without a positive culture or smear.

**TB Relapse:** The diagnosis of TB following TB cure or successful TB treatment completion with isolation of an organism having a RFLP pattern similar to that isolated from the previous TB episode.

**TB Re-infection:** The diagnosis of TB following TB cure or successful TB treatment completion with isolation of an organism having a different RFLP pattern compared to that isolated from the previous TB episode.

**Progression of HIV Disease (AIDS Diagnosis):** A World Health Organisation (WHO) Clinical Stage IV AIDS-defining opportunistic infection or malignancy, excluding extra pulmonary TB.

**Virologic Failure:** HIV-1 RNA ≥ 1,000 copies/ml on two consecutive measurements obtained after completion of 16 weeks or longer of study treatment.

### 4.4 Participant Inclusion and Exclusion Criteria

#### 4.4.1 Inclusion criteria

- Adult patients (≥ 18 years) who were diagnosed as co-infected with TB and HIV and previously enrolled in the SAPIT and START trials
- Willing to consent to participate in this study and contribute specimens to the K-RITH repository for future investigations

*Note Past Mother to Child Transmission (MTCT) and Post Exposure Prophylaxis (PEP) prevention treatments are allowed*

#### 4.4.2 Exclusion criteria
- Patients with Extensively drug-resistant (XDR) TB will not be eligible.
- Patients who refuse consent

4.5 Sample size calculation

The sample for the TRuTH study will be 550 as this will include patients enrolled in the SAPIT and START trials who have stored sputum cultures at baseline, many of whom have enrolled into long term care in the CAT programme. The follow up period will be 3 years, but may be extended in order to obtain a minimum of 76 cases of TB recurrence. The target of 76 has been set to ensure a minimum of 30 cases of relapse for sufficient sample size for meaningful comparisons between cases of TB relapse and TB re-infection.

The annual TB incidence in HIV positive patients is 4.6 cases /100 person-years [6]. If we enroll 550 participants in this study, a 3 year long study would generate 76 incident cases of TB. It is assumed that 10% of the recurrences would be due to relapse and 90% will be due to re-infection. With 76 incident cases of TB recurrence, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.067 from the observed proportion for an expected proportion of 0.3. This means that, if the true proportion of recurrence due to re-infection is indeed 90%, we would have a confidence interval of 83 % to 96.7%

5. STUDY PROCEDURES

5.1 Recruiting SAPIT and START patients into the TRuTH Study

In the SAPIT trial patients are required to remain in the study for 24 months of follow-up. At their Month 24 visit (the last SAPIT study visit) they are allocated a Patient Identification (PID) number for readiness into the CAPRISA AIDS Treatment (CAT) programme. This number is distinctly different from their SAPIT number. The new CAT PID is recorded in a register/log with the patient’s corresponding SAPIT PID. This log will be maintained by the TRuTH study coordinator. The purpose of the log is to have a link to the patient’s SAPIT clinical information in order to ensure continued care and treatment of the patient in the TRuTH study.

Similarly START patients were transitioned into the CAPRISA AIDS Treatment Programme and assigned a CAT PID. Ex-START who are currently active in CAT will be recruited for the TRuTH study.

SAPIT and START clinicians complete a clinical summary form (Appendix IV ) which provides in-depth patient clinical information including a patient TB history, dates of TB diagnosis and HAART initiation, HAART regimen switches and any adverse events that were experienced by the patient. This clinical summary is filed in the patient’s new CAT file. In addition, safety blood results, contraception history logs, vitals logs are transferred to the new CAT file, in order to ensure continuity of information for proper care and treatment. All SAPIT and START PIDs are deleted /blackced out of documents transferred to the new CAT files.
5.2 Screening ex-SAPIT patients and administering informed consent

At the patients’ first CAT visit, they will be introduced to the TRuTH study and after obtaining informed consent patients will be enrolled onto the study.

Once a suitable study participant has been identified, the study nurse will introduce the patient to the study and he or she will be asked to read and sign BREC approved informed consent and specimen storage consent forms. A study clinician will assess the patient at the screening visit making sure that all inclusion and exclusion criteria are adhered to.

5.3 Enrolment into the study

- **Study patients will be seen at the entry visit and at Month1 and Month 3 on the study. Thereafter all study patients will be placed on a 3 monthly schedule, for routine clinic visits and ART services.** As part of the daily Health Education group sessions currently being conducted for patients, all patients will be educated on signs and symptoms of possible TB recurrence.

- At each of these visits patients will be screened for TB recurrence by:
  - Conducting 3 monthly TB symptom checks (see Appendix III for TB symptom checklist)
  - TB specific investigations dependant on symptoms and signs e.g., FNAB, histology etc for extra pulmonary TB (EPTB)
  - TB Sputum cultures will be conducted 3 monthly from the enrollment visit.
  - Chest x-rays conducted on a 6-monthly schedule
  - Sputum smears for TB – if positive then cultures will be performed. All culture positive smears will have drug susceptibility test (DST) performed
  - RFLPs will be conducted retrospectively on diagnosis of TB recurrence with a comparison of DNA fingerprint from sputum from the recurrent TB episode, with that from sputum collected at the baseline TB episode.

- At all visits patients will have a full med history, clinical exam, treatment for intercurrent illness, HIV and ART review, and dispensing of ART’s

- Patients will also have periodic blood draws for safety and cd4 and viral load monitoring

A study scheme, depicting the transition of patients from the SAPIT trial to the TRuTH study and the clinical assessment of TB recurrence is provided in Appendix V

5.4 Laboratory evaluations

5.4.1 Safety Evaluation

The DAIDS table for grading the severity of Adult and Paediatric Adverse Events, 2004, shall be employed to determine the severity grade of laboratory values. Laboratory evaluations will include the following:

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• **Hematology**: Hemoglobin, hematocrit, white blood cell count (WBC) differential, absolute neutrophil count (ANC), and platelets will be tested.

• **Serum Chemistries**: Creatinine will be tested. Participants on tenofovir will also have serum phosphate evaluated.

• **Liver Function Tests**: Total bilirubin (T. BILI), (Aspartate aminotransferase) AST (SGOT), and ALT (Alanine aminotransferase) (SGPT) will be tested.

• **Pregnancy Test**: For women with reproductive potential, urine β-HCG (urine test must have a sensitivity of ≤ 50 mIU) will be tested monthly during ART therapy.

• **CD4+/CD8+ Cell Count**: CD4+/CD8+ cells counts (both absolute and subset percentage counts) will be performed throughout the study at the CAPRISA Laboratory. Each time a CD4+/CD8+ cell count is obtained, the local laboratory will perform a White Blood Cell count and differential from a sample obtained at the same time.

5.4.2 Determining relapse from re-infection

The following analysis will be performed to determine cellular and innate immune responses to TB and HIV after TB recurrence; and to determine relapse from re-infection:

**Determining cellular immune responses in recurrent and relapse TB cases**

Comprehensive longitudinal IL2/IFN-gamma Elispot assays will be carried out using overlapping MTB peptide pools. The antigens for which we have overlapping peptides include ESAT-6, CFP-10, Ag85A and TB10.4 (all shown to be highly immunogenic in the Durban Sinikithemba cohort) (Day, Mkhwanazi et al. 2008), an additional RDI antigen Rv3879c [incorporated in the newly developed ELISpotPLUS; Oxford Immunotec; Oxford, UK](Dosanjh, Hinks et al. 2008), and Rv2029c (a highly expressed protein from the Dormancy regulon)(Leyten, Lin et al. 2006). We are also in the process of identifying and obtaining other key antigens. ICS multi-color flow experiments (following in-vitro stimulation of PBMC or ex-vivo if possible) will be used to identify the cell subset (i.e. CD8+ vs. CD4+) producing IL-2 and IFN. Key immunodominant antigenic targets (as determined by targeting frequency) will be further dissected to the level of optimal epitope and restricting HLA in order to generate HLA-peptide-tetrameric complexes. These will be used for single-cell visualization of immune effector cells. ICS multi-color flow will be used to assess the cytokine secretion profile of MTB-specific T cells for IFN-gamma, TNF-alpha, MIP-1B and IL2. CFSE proliferation assays will be carried out as a further read-out of antigen-specific functional capabilities.

**Assessment of innate immunity in determining relapse from re-infection**

An evaluation of the phenotypic and functional characteristics of innate immune cells, in particular monocytes and NK cells, will be conducted, to determine innate immune responses to TB and HIV after TB recurrence and to determine relapse from re-infection. We will use multi-parameter flow cytometry to characterize monocytes activation following stimulation with TLR
ligands, as well as their phagocytic activity. Furthermore, we will assess differences in the
phenotype and function of NK cells in response to classical NK cell stimuli, such as K562 cells
and PMA, as well as macrophages loaded with TB antigen.

**Immune Parameters:** In each study participant who has recurrent TB, innate and adaptive cellular
immune responses will be assessed to compare immune responses in TB relapse and re-infection.
Furthermore, a CD4+/CD8+ cell count matched subgroup of individuals (n = 50) that do not develop
TB will be studied to identify the immunological predictors of TB relapse versus re-infection. The
following studies of the innate and adaptive immune response will be performed:

5.5 **Immunologic studies**

The following analysis will be performed to determine immune responses to TB and HIV after TB
recurrence:

- **CD4+/CD8+ Cell Count:** CD4+/CD8+ cells counts (both absolute and subset percentage
counts) will be performed throughout the study at the CAPRISA Laboratory. This laboratory
participates in an external proficiency testing program (UKNEQAS/IQA). Testing will be
conducted in “real time”. Each time a CD4+/CD8+ cell count is obtained, the local laboratory
will perform a WBC and differential from a sample obtained at the same time.

- **Immune Parameters:** Additional assays will be performed. Blood will be collected for
peripheral blood mononuclear cells (PBMCs), to assess immune parameters. Each study
participant who has recurrent TB will be assessed by IFN gamma ELISPOT assay to compare
CTL immune responses in TB relapse and re-infection. Additional immune parameters that may
be studied include: CD4+ and CD8+ memory and naïve cells, and other pro-inflammatory and
immunomodulatory cytokine production such as IL-10, IL-2, and IL-12.

- **Stored Plasma/Serum/PBMCs:** Participants who consent to have additional samples stored for
future testing will have serum, plasma and PBMCs stored. Possible uses of plasma include
assessment of host genetics profiles, including HLA profile, additional viral load assays.
Possible uses of serum include additional safety serology and evaluation of suspected IRIS on
participants where indicated. The PBMCs will be used to test for IRIS/PR when suspected.
Other potential tests that may be performed on the stored specimens include new generation
assays of immunity. **For our proposed immunological studies 3 monthly blood draws are
essential. Assessing both adaptive and innate immune responses just twice a year makes it
difficult to monitor the trends and kinetics of particular immune responses and therefore
harder to identify cause versus effect**
5.6 Recurrent TB Evaluation

Sputum Testing

- **Sputum Smear, Culture:** Sputum will be collected 3 monthly for TB smear and culture diagnostics. Smears will be processed at the PCZCDC TB laboratory. Results of sputum smears will be accessed from the clinical digital records at the Prince Cyril Zulu CDC to confirm diagnosis of TB. All sputum samples will undergo further MTB culture and DST testing. On TB diagnosis further TB smear and culture will be obtained at month 2 and month 6 after the initiation of TB therapy and at the completion of TB therapy. Additional cultures that will be performed when patients present with TB symptoms or abnormal chest radiograph.

- **M. tuberculosis Susceptibility Testing:** *M. tuberculosis* susceptibility testing will be performed on each positive culture to assess for drug resistance.

- **Restriction Fragment Length Polymorphism Analysis (RFLP) Testing:** RFLP testing will be performed from stored bacterial isolates on all positive cultures in which recurrence is suspected and compared to the initial positive culture used to diagnose the TB initially. This technique utilizes the differential distribution of genetic markers in different strains of *M. tuberculosis* to identify specific strains of *M. tuberculosis*. These results will allow differentiation between re-infection and relapse. Isolates of *M tuberculosis* cultured from sequential sputum specimens of patients at baseline and subsequent follow-up visits will be stored at -70°C in storage media. These will be retrieved from storage and grown to confluence under standard conditions, harvested and heat inactivated. DNA fingerprints of sequential isolates will be generated by the IS6110- RFLP technique (Van Embden et al 1993). Briefly, this involves DNA extraction using CTAB, DNA restriction with restriction endonuclease *PvuII*, separation of restricted fragments by electrophoresis, immobilization of the restricted fragments by vacuum blotting, followed by hybridization with a 245 bp fragment of IS6110 and detection with enhanced chemiluminescence. A second hybridization will be performed using the same membrane to detect internal sizemarkers that will assist in the analysis of the RFLPs by a specialized software, Bionumerics.

5.7 Chest Radiograph

Chest Radiographs will be obtained 6 monthly from participants. Digital CXR imaging will be performed using the facilities at the PCZCDC.

Below is Table 1, which illustrates the study schedule of evaluations.
### Table 1: Study Schedule of Evaluations

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Screening</th>
<th>Baseline</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 12</th>
<th>Month 15</th>
<th>Month 18</th>
<th>Month 21-36 (3 monthly)</th>
<th>Month 24-36 (6 monthly)</th>
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<tbody>
<tr>
<td>Visit number</td>
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<td>5</td>
<td>6</td>
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<td>9</td>
<td>10</td>
<td>11,12,13</td>
<td>14,15,16</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
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</table>
5.8 Study Cohort Management (Tracking)

The DATAFAX system will serve as an electronic tracking system to provide study staff with a means for monitoring and tracking participants who have missed scheduled study visits. A follow-up team (two full-time fieldworkers) will be responsible for ensuring follow-up, conducting home visits when participants do not arrive for their scheduled appointments, and for assisting those who require transport for follow-up. **When acquiring patient locator information, the team informs the patient that home visits will form part of the care provided by the clinic.** The patient is requested to provide the contact details of people to whom he/she has disclosed his/her HIV status. The tracking team contacts only persons that the patient has identified. The tracking team is careful to identify themselves as TB health care workers when addressing the contacts of patients. Aside from home visits, the tracking team is also able to visit patients at other locations which they maybe more comfortable with (work, public venues etc.) Patient will have the option of opting out of the home visits

**Tracking and Follow Up Plan**

- Day 1 after missing appointment - Attempt telephone contact with the participant
- Day 2 after missing appointment - Contact persons listed on the locator form
- Day 3 after missing appointment - Send a field worker to the site identified based on updated locator information

Additional measures that will be in place to assist the study staff with retention and follow-up include:

- Computer generated reminder list on site and at the data management center, and internal quality assurance (QA)/quality control (QC) reports will be used for tracking purposes
- Attempts will be made to re-contact and re-schedule missed appointments within 24 hours (preferably on the same day).
- Study staff will pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window

Study staff will emphasize the value of the participant’s involvement in the study during the study informed consent process and subsequently at follow-up visits.
6. HUMAN SUBJECTS CONSIDERATIONS

6.1 Regulatory and ethical review

The study will be conducted under the oversight of the University of KwaZulu-Natal, Nelson R Mandela School of Medicine Biomedical Research Ethics Committee (BREC). The study protocol will be submitted to the ethics committee by the Principal Investigator and reviewed and approved by the ethics committee prior to study initiation. The investigator will provide progress reports and all other information required by the ethics committee to conduct its reviews. On approval of the study we will register the study with SANCTR (South African National Clinical Trials Register). We will also seek approval for the study from the eThekwini Municipality.

Patients who participated in the SAPIT trial were under the oversight of the UKZN BREC. Ethics no. E107/05.

6.2 Informed consent process

Written informed consent will be obtained from each study participant prior to enrollment (see Appendix VI). Written informed consent will also be obtained for long-term specimen storage and possible future testing (see Appendix VII). However, consent for specimen storage is not a precondition for study participation. Participants will be provided with a copy of their informed consent forms if they wish to receive them. In addition, a Patient Information Leaflet will be made available to patients. This is a brief but informative document that describes the objectives of the study and can be taken away by the patient if he/she needs more time to consider their participation in the study (Appendix VIII).

Study informed consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The informed consent forms will also be translated into isiZulu and the accuracy of the translation will be verified through independent back-translation.

The study consent process will include an assessment of each potential participant’s understanding of the study and the risks and benefits of study participation, which are essential for an informed decision. Participants who are not able to demonstrate adequate understanding of key concepts will not be enrolled in the study.

6.3 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ethics committee or the sponsor’s designee.
7. VARIABLES

7.1 Categories of variables

7.1.1 Demographics and Household Information

We will collect patient demographic and household information at the enrollment visit. This information will consist of patient characteristics such as: age, gender, occupational status, marital status and household information including access to basic services, number of people who live in the home and sources of income. These patient characteristics will allow us to understand and describe our patient cohort. The Demographics and Household Information Tool can be found in Appendix VIII.

7.1.2 Physical Examination

At every clinic visit, patients will undergo a physical exam by the study clinician. Patient clinical data will be captured onto the Physical Examination Form (Appendix IX). This form captures: vitals (weight, pulse, temperature, blood pressure) and an array of possible medical examination findings as per organ system.

7.1.3 Safety Bloods

Blood draws will occur on a 6-monthly schedule. These results will be transcribed onto the Safety Bloods Form CRF (Appendix X). This form will capture results for hemoglobin, platelet count, Leucocyte count etc.

7.1.4 Cd4 AND Viral Load Assessments

Similarly, a CD4 count and viral load will be conducted on a 6-monthly schedule. These results will be transcribed by study staff onto the ART Efficacy Monitoring Form (Appendix XI).

7.1.5 TB Recurrence

Episodes of TB recurrence, when detected, will be recorded onto the TB Recurrence form (Appendix XII). This form will record the date of diagnosis of the TB recurrence, whether or not sputum for RFLP testing was collected, as well as the site of the TB.

7.1.6 Baseline Chest X-ray and Sputum

The Baseline Chest X-ray and Sputum results are accessible to study staff via the Prince Cyril Zulu Communicable Disease Centre electronic data system. Chest X-ray and sputum findings will be transcribed on to this form (Appendix XIII). Similar information will be transcribed from follow-up Chest X-ray and sputum results (appendix XIV).

7.1.7 Sputum Culture and Susceptibility
Sputum cultures and susceptibility to TB drugs will be recorded. Clinicians will access results from the PCZCDC and transcribe these onto the Sputum Culture and Susceptibility form (Appendix XIV). This form captures data on resistance or susceptibility to Isoniazid (INH), Rifampin (RIF) Ethambutol (ETH), Moxifloxacin/Ofloxacin, Kanamycin and Ethionomide.

7.2 Training for all study personnel

7.2.1 Good Clinical Practice (GCP) and Human Subjects Protection (HSP) training

It is an essential requirement for all staff that work on the study to obtain training and certification on Good Clinical Practice (GCP) and Human Subjects Protection (HSP). The study coordinator is responsible for ensuring that all study staff are in possession of valid GCP/HSP certification.

7.2.2 In house training on data collection forms

All study staff will be trained on completing the data collection tools. Study nurses will be trained on administering the informed consent documents.

7.2.3 Protocol and Standard Operating Practices Training

Study staff will be trained on the study protocol as well as all standard operating practices within the study. The study coordinator and other senior members of the study team will be responsible for training staff on all aspects of the study.

8. DATA HANDLING AND ANALYSIS

This study will use a purposive sampling method. Patients who have completed and exited the SAPIT and START study will be selected for enrollment into the study. Upon obtaining informed consent for the TRUTH study enrolment, all participant data that was collected during follow-up within the SAPIT and START trial will be merged with prospectively collected data obtained during follow-up of the TRuTH Study. This will be done to minimize the loss of endpoint data.

8.1 Data Analysis Plan

The incidence of TB recurrence in patients on ART will be determined. Person time at risk of TB recurrence will be calculated from the time of enrolment into this study. 95% confidence intervals will be calculated for the rate of TB recurrence assuming a Poisson distribution. The incidence of recurrence due to relapse or re-infection will be calculated in a similar manner.

The proportion of all cases of TB recurrence due to relapse and re-infection respectively will be determined. The proportion of TB recurrence due to IRIS will be given, with 95% confidence intervals calculated using the Poisson distribution.
Risk factors for TB recurrence will be determined through multivariate logistic regression. Possible variables that will be included as potential risk factors will include demographic variables (like age and sex), nutritional status, sociological, clinical (including BMI, WHO status, viral load), immunological (CD4 count at baseline and at time of recurrence), biochemical, number of doses of TB treatment received, duration of ART. The same analysis will be repeated to identify risk factors for TB recurrence due to re-infection and due to relapse, respectively.

The clinical, virological (viral load), microbiological, radiological and immunological (CD4 count) characteristics at the time of TB recurrence will be described. Categorical variables will be described in contingency tables and continuous variables will be described using means, medians, standard deviation and interquartile ranges, as applicable.

Kaplan-Meier curves will be drawn for the time to TB recurrence. The time to TB recurrence will be calculated from the date of first TB diagnosis (in SAPIT or START), date of enrollment into the study, date of ART initiation and date of TB treatment outcome (first instance) respectively. The curves will be drawn to the first instance of TB recurrence. Participants who do not have TB recurrence will be censored at the time they are lost to follow-up, die or withdraw from the study for any other reason.

Host genetics, including HLA profiles, will be given for those participants who have TB recurrence and those who do not. Any differences between the two groups of participants will be investigated, using logistic regression.

Immune responses to TB and HIV, before and after TB recurrence will be summarised. In addition, repeated measures analysis will be done to show how immune responses within individuals change after TB recurrence.

8.2 Data Collection and Methods

Case Report Forms (CRFs) will be provided for each patient. Participants will be identified by a patient identification number (PID) provided by the CAPRISA Data Management Center upon enrollment. This PID is used on all CRFs to identify the participant for the duration of the study.

Data will be collected at scheduled clinic visits. Patients will be required to attend at the clinic for a screening visit and if found to be eligible, informed consent will be administered and the patient will be enrolled into the study. Thereafter the patient will be required to visit at the clinic every month for the next 3 months. Thereafter the patient will present at the clinic 3-monthly for routine HAART follow-ups as well as TB screening and investigations.

8.3 Information management and analysis software

CAPRISA uses the DATAFAX system to store data electronically. The current version of DATAFAX use is Version 3.7

Statistical Analysis Software (SAS) is used for analysis purposes. The current version in use is version 9.1.3
8.4 Data entry, editing and management, including handling of data collection forms, different versions of data

Instructions concerning the recording of study data on CRFs will be provided by the CAPRISA Data Management core dealing with data management. Completed CRFs must be checked by the designated on-site Quality Assurance person and upon approval, must be faxed to the CAPRISA DataFax system at the University of KwaZulu-Natal. The data must be verified in the DataFax system, QC reports produced, and approved data then added to the study database according to CAPRISA data management (SOPs) Study Operating Procedures.

It is the responsibility of the CAPRISA data management core to assure the quality of computerized data for the study. Study staff will be trained in source documentation requirements in accordance with the DAIDS SOP for Source Documentation and in proper forms completion techniques.

Database files will be password-protected, and access to the files will be limited to authorized study staff members only. Quality control and validation checks will be performed and data cleaning steps will be undertaken prior to finalizing the study database for analysis. Analyses will be conducted by study statisticians.

8.5 Data Storage

Original and DataFax electronic copies of study CRFs and related documents will be stored securely both during and after study completion. During the study, the original completed forms for each participant will be kept on-site at the PCZCDC. The forms will be stored in an access secured, double-locked, fire and waterproof room. Upon completion of the study, and finalization of the database for analysis, the original forms will be bound and kept off-site (separate site) for long-term storage. CAPRISA has a standing agreement with Metrofile to archive large amounts of documents. CRF data on the DataFax server will be accessible to the study staff and the statistician in a read-only mode. The data management team will have write-access, with access being restricted by passwords and validation levels. Study staff that has access to the data on the computer systems will be trained in how to access the system and the importance of system security. All information will be backed-up at regular intervals, and backups will be stored in file cabinets or secure areas with limited access.

8.6 Quality control/assurance

A quality check of the study forms will be conducted before the forms are data faxed. The QC procedures will specify the following types of checks:

- There are no illegible handwritten items, spelling errors, etc.
- Responses are clearly within designated spaces.
- All fields are completed with participant data or reason for no data is noted in or near the field.
- The participant's PID is recorded on all pages of the forms.
• The designated on-site QA person will initial each page to confirm that the form has been checked.

• The CAPRISA laboratory manager will also be responsible for checking that all the laboratories involved in the study are complying with QA procedures. The CAPRISA pharmacist will check that all drug related documentation meets Good Clinical Practice (GCP) requirements for drug accountability.

• QA/QC of data will be undertaken according to the SOPs.

8.7 Bias in data collection, measurement and analysis

Some bias will be introduced into the study in that some patients who would have been eligible for the TRuTH study have become lost to follow-up, withdrew or demised in the START and SAPIT study.

8.8 Intermediate reviews and analyses

The CAPRISA Scientific Review board conducts preliminary analyses and safety reviews on a regular basis. Semi-annual and Annual reports will be generated, which will be distributed to the relevant stakeholders including the funder.

8.9 Limitations of the study

The limitations of the study include the following:

• Failure to diagnose TB in those patients who demised in the SAPIT study. Autopsies are not routinely performed.

• Migrancy within the patient cohort makes tracking efforts a challenge. Most patients leave their rural dwellings and arrive at the city for diagnosis and treatment of illnesses. When they are well again, patients often return to their homes.

• Some patients within the SAPIT study have become lost to follow up.

• Laboratory – Baseline sputum of the first case of TB have been cryopreserved. There remains some uncertainty about the yield of stored samples to conduct RFLP genotyping and whether variable length of freezing will impact on the yield.

9. HANDLING UNEXPECTED or ADVERSE EVENTS

9.1 Identifying, managing and reporting adverse events

The definition of an adverse event for this study will be the same as for investigational agents, i.e., an adverse event is defined as any untoward medical occurrence in a clinical research participant. The current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events will be
used for grading toxicities. Periodic summary/reports of adverse events will be submitted to the ethics committee.

9.2 Adverse event reporting

Periodic summary/reports listing all adverse events will be submitted to the ethics committee on a semi-annual basis.

9.3 Study Discontinuation

This study may be discontinued at any time by the IRB/IEC, or other government agencies as part of their duties to ensure that research participants are protected.

10. TREATMENT REGIMENS

10.1 Anti-TB regimens

The anti-TB regimen will be considered background therapy, and therefore not considered the study regimen in this study.

All participants, regardless of treatment regimen, will receive their TB therapy in accordance with the National TB Control Programme Guidelines. For the first 2 months of TB therapy, the regimen consists of rifampicin/isoniazid/pyrazinamide/ethambutol fixed-dose combination tablets at dosages determined by patient weight. After approximately the first 2 months of TB therapy, participants will receive specified doses of rifampicin and isoniazid for the duration of TB therapy. Administration of TB therapy will occur under supervision via DOT at the Prince Cyril Zulu CDC. Current MDR treatment Regimen used in KZN: Kanamycin OR Amikacin, Ofloxac in, Ehionamide and Cycloserine or Terizidone, Pyrazinamide and Ethambutol for 18 months post sputum conversion, or a minimum of 2 years.

10.2 ARV drug regimens and formulation

In general all patients are on a first line regimen of Didanosine, Lamivudine and Efavirenz with dosage based on weight. In cases of treatment-limiting toxicities or associated conditions, the first-line combination of ART drugs may be changed by the study clinicians. The entire regimen may be switched or individual drugs may be substituted depending on the nature of the treatment-limiting toxicity or condition. Treatment-limiting toxicities or conditions include:
- Severe or recurring toxicities
- Concomitant conditions or required medications for which first-line options are contraindicated
- Pregnancy
- ART failure
11. CLINICAL MANAGEMENT OF STUDY ENDPOINT

11.1 Management of TB Recurrence

Cases of TB treatment recurrence identified during the study will be referred to the PCZCDC clinic for further management of the TB. Guidelines for management as per National Tuberculosis Control Programme guidelines. Patients will continue care and follow-up in the study.

12. BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens and TB can occur through contact with contaminated needles, blood, blood products, and sputum, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

13. PUBLICATION OF RESEARCH FINDINGS

Presentation and publication of the results of this study will be governed by CAPRISA publication policy (available at www.CAPRISA.org). All presentations, abstracts, and manuscript will be made available to the CAPRISA Scientific Review Committee for review prior to submission.
14. STUDY BUDGET

PERSONNEL

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TOTAL PERSONNEL COSTS: $194,609

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TOTAL TRAVEL COSTS: $9,846

SUPPLIES

<table>
<thead>
<tr>
<th>Items</th>
<th>#</th>
<th>Cost/item</th>
<th>Amount requested</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Stationery</td>
<td></td>
<td></td>
<td>3,257</td>
</tr>
<tr>
<td>Office Consumables</td>
<td></td>
<td></td>
<td>3,257</td>
</tr>
<tr>
<td>Photocopy, fax, printing</td>
<td></td>
<td></td>
<td>1,902</td>
</tr>
</tbody>
</table>

TOTAL SUPPLY COSTS: $8,416
EQUIPMENT

<table>
<thead>
<tr>
<th>Items</th>
<th>#</th>
<th>Cost/item</th>
<th>Amount requested</th>
</tr>
</thead>
<tbody>
<tr>
<td>-70° Freezer</td>
<td>1</td>
<td>18,000</td>
<td>18,000</td>
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</tbody>
</table>

**TOTAL EQUIPMENT COSTS:** $18,000

OTHER

<table>
<thead>
<tr>
<th>Services</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing Services</td>
<td>130,020</td>
</tr>
<tr>
<td>Counseling Services</td>
<td>30,408</td>
</tr>
<tr>
<td>Rental</td>
<td>20,160</td>
</tr>
<tr>
<td>Training</td>
<td>8,780</td>
</tr>
<tr>
<td>Telecommunication</td>
<td>2,572</td>
</tr>
<tr>
<td>Laboratory costs</td>
<td>170,653</td>
</tr>
<tr>
<td>F &amp; A Costs</td>
<td>46,037</td>
</tr>
</tbody>
</table>

**TOTAL OTHER COSTS:** $408,630

**TOTAL BUDGET FOR FY 2009:** $639,501

Budget Justification

**PERSONNEL**

Salaries reflected in this budget are for total salary packages. Fringe benefits are already included in the total salary package. Fringe benefits are calculated at approximately 27% of the total salary package. Fringe benefits include a pension allowance, housing allowance and an overtime allowance. In addition, medical insurance is available to all staff.

**K Naidoo**, Principal Investigator at 50% effort will be responsible for the overall co-ordination of clinical activities.

**S Gengiah**, Project Coordinator at 50% effort will be responsible for writing reports, managing patient documentation and record collation, and managing the logistics of program implementation.

**S Bamber** and **G Nair**, Clinicians at 50% effort and 100% effort respectively, will be responsible for the treatment and clinical care of the participants.

**F Burton**, Data Manager at 50% effort will be responsible for the management of the data collected.

**SP Ngcobo**, Data Encoder at 100% effort will be responsible for the checking and cleaning of data sent via the data fax system to the central server in Durban.

**Z Mchunu**, Laboratory Technician at 100% effort will be responsible for performing the laboratory assays required.
N Yende, Statistician at 25% effort will be responsible for providing data analysis support.

SD Sing, IT Consultant at 25% effort will be responsible for troubleshooting and user support at both treatment clinics.

E Gumede, Research Assistant at 100% effort will be responsible for providing administrative support to all aspects of the program.

AB Ntsele, Fieldworker at 100% effort will be responsible for follow up and documentation of missed appointments, keeping a log of these and tracking participants.

S Panday, Finance Officer at 25% effort will be responsible for budgeting and financial reporting as well as ensuring that financial regulatory requirements are met.

TRAVEL

International Travel:
The Principal Investigator will travel to the US to participate in the international scientific meeting. The costs is estimated as follows:

- Air ticket: $3,961
- Accommodation: $185 per day x 5 days = $925
- Stipend: $60 per day x 5 days = $300

**TOTAL INTERNATIONAL TRAVEL = $5,186**

Local Travel:
The Principal Investigator and Project Coordinator will attend the local PEPFAR meetings to be held in Gauteng and Western Cape. Costs are estimated as follows:

- **Gauteng**
  - Air ticket: $385 x 2 people = $770
  - Accommodation: $146 per day x 5 days x 2 people = $1,460
  - Stipend: $10 x 5 days x 2 people = $100

- **Western Cape**
  - Air ticket: $385 x 2 people = $770
  - Accommodation: $146 per day x 5 days x 2 people = $1,460
  - Stipend: $10 x 5 days x 2 people = $100

**TOTAL LOCAL TRAVEL = $4,660**

**TOTAL TRAVEL : $9,846**

SUPPLIES
Funds are requested for the purchase of general office supplies as listed below:

General office stationery such as pens, pencils, and files estimated at $271.43 per month x 12 month = $3,257

Office consumables such as paper and ink cartridges estimated at $271.43 per month x 12 month =
$3,257
Photocopying, printing and fax charges estimated at $158.50 per month x 12 months = $1,902
TOTAL SUPPLIES = $8,416

EQUIPMENT
Funds are requested for the purchase of a -70° Freezer for the storage of sputa samples estimated at $18,000.

OTHER EXPENSES
Nursing Services: Nursing Services of South Africa is an employment agency that supplies nurses for various purposes to hospitals, clinics and private patient care in South Africa. Two professional and three staff nurses will be employed. The cost is estimated as follows:
Professional nurses: $2,620 per nurse per month x 2 nurses x 12 months = $62,880  
Staff nurses: $1,865 per nurse per month x 3 nurses x 12 months = $67,140  
TOTAL NURSES COST = $130,020

Counseling Services: Two counselors will be provided by Open Door, which is an NGO providing counselors to various health service institutions. The counselors will responsible for pre- and post-test counseling of participants. The cost is estimated as follows:
$1,267 per counselor per month x 2 counselors x 12 months = $30,408

Rental: Funds are requested to cover rental of space at the eThekwini clinic. The cost is calculated as follows:
84m² x $20 per m² = $1,680 x 12 months = $20,160

Training: Funds are requested for training of staff on Advanced HIV management, TB management, Infection Control and Monitoring and Evaluation estimated as follows:
$219.50 per person per course x 10 staff x 4 courses = $8,780.

Telecommunication: Funds are requested to cover telecommunication costs estimated at $2,572.

Laboratory Test Costs: Funds are requested for laboratory testing as follows:
Sputa: 550 patients x 4 times a year x $76.43 = $168,146
DST: 117 patients x 1 time a year x $21.43 = $2,507
TOTAL LAB COST = $170,653

Facilities & Administration Costs: CAPRISA does not currently have a NICRA but is in the process of applying for one. In the absence of a NICRA, we request a Facilities and Administration cost as per the guideline as set in Notice NOT-OD-01-028 from the National Institutes of Health allows for an F & A cost of eight percent of Total Direct Cost less Equipment.
15. REFERENCES


16. APPENDICES

APPENDIX I: SAPIT STUDY SCHEMA

A Study to compare three existing starting points of ART Initiation in HIV/TB co-infected patients

Schema

**Design:**
This is a randomized, open-label pilot study comparing three existing treatment strategies of ART initiation in HIV/TB co-infected patients:
- **Group 1:** early initiation of ART with TB treatment,
- **Group 2:** initiation of ART upon completion of the intensive phase of TB treatment,
- **Group 3:** initiation of ART upon completion of the continuation phase of TB treatment

**Sample Size:**
Approximately 700 patients will be enrolled.

**Population:**
Men and women ≥ 18 years of age with documented HIV infection and smear-positive pulmonary TB.

**Treatment Programme:**
TB/HIV co-infected patients at the CDC are routinely offered ART in this treatment programme funded by PEPFAR and the Global Fund. The treatment programme includes extensive counselling and adherence support and detailed clinical and laboratory assessment for initiation of ART. At present, the clinicians arbitrarily decide when to start ART – this is the only aspect of the treatment programme which will be changed – patients will now be randomised into one of three ART starting points. All other care and monitoring received by all the patients in the treatment programme is standard.

**STATUS:**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Enrolled</td>
<td>646</td>
</tr>
<tr>
<td>Completed study</td>
<td>190</td>
</tr>
<tr>
<td>Died</td>
<td>57</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>40</td>
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<tr>
<td>Withdrew consent</td>
<td>58</td>
</tr>
<tr>
<td>Active on the study</td>
<td>301</td>
</tr>
<tr>
<td>No. of TB recurrences</td>
<td>33</td>
</tr>
</tbody>
</table>

In September 2008, a safety monitoring committee conducted an interim review of the SAPIT trial data. The committee recommended that the deferred arm in SAPIT (Starting ART after TB therapy) be stopped and all patients in that Arm should initiate ART. The committee’s findings indicated that there was a 55% chance of survival if patients initiated ART with TB treatment. The SAPIT study currently has two arms, the Early Arm (initiating ART within 2 weeks of TB Treatment) and the Post Intensive Arm (initiating ART within 2 months of TB Treatment).
APPENDIX II - START: Starting Tuberculosis and Anti-Retroviral Therapy

Design: This is a two-armed, randomized, open-label clinical trial evaluating whether the integration of HIV care into existing TB care services is feasible and practical in resource-poor settings.

The primary objective is to assess the effectiveness of integrated TB and HIV care provision enhanced with an adherence support program (ASP) versus sequential treatment of TB and HIV, by comparing the progression to AIDS-defining illnesses/mortality in participants with pulmonary TB co-infected with HIV during the first 18 months after enrollment in the study. The study is conducted in two phases. The first phase represents the duration of TB therapy. The second phase represents the period after completion of TB therapy. Study participants will be randomized to one of the following arms stratified by CD4+ cell count, 50-200 cells/µL vs. > 200 cells/µL. Participants randomized into the integrated arm will receive anti-retroviral therapy (ART) consisting of didanosine (ddI)/ didanosine enteric coated (ddI-EC), lamivudine (3TC), and efavirenz (EFV) in conjunction with TB therapy upon randomization. Participants randomized to the sequential arm will complete TB treatment and then start ART consisting of ddI/ddI-EC, 3TC, and EFV. In instances where ddI/ddI-EC, 3TC, and EFV are contraindicated, an alternative regimen will be used.

Duration: Study duration is 24 months after randomization.

Sample Size: 592 participants will be enrolled. Population: Men and women _ 18 years of age with documented HIV infection and smear-positive pulmonary TB.

Regimen: At entry, participants will be randomized (1:1) to one of the following treatment arms:

Integrated arm: (ddI/ddI-EC) + 3TC + EFV once daily concurrently with standard TB treatment upon randomization.

Sequential arm: (ddI/ddI-EC) + 3TC + EFV once daily initiated after completion of TB therapy. ART substitution options will be available for participants who become pregnant, experience toxicities, or have treatment failure.

Current Status of Study:

<table>
<thead>
<tr>
<th></th>
<th>START Study Status</th>
<th>CAT Programme Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Enrolled in START</td>
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<td></td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>3</td>
<td></td>
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<tr>
<td>Died</td>
<td>4</td>
<td></td>
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<tr>
<td>Withdrawal</td>
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<tr>
<td>Transferred to CAT</td>
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<tr>
<td>Active in CAT</td>
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<td>27</td>
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<tr>
<td>Transferred Out</td>
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<tr>
<td>Relocated</td>
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<td>8</td>
</tr>
<tr>
<td>TB recurrence</td>
<td></td>
<td>3</td>
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</table>

Current Status of Study:

START Study Status: 58 participants enrolled. CAT Programme Status: 48 participants transferred to CAT, 27 active in CAT, 10 transferred out, 3 relocated, 8 lost to follow up, 3 TB recurrence.
### APPENDIX III: TUBERCULOSIS (TB) SYMPTOM CHECKLIST AND RISK ASSESSMENT

<table>
<thead>
<tr>
<th>PID</th>
<th>Date</th>
<th>N</th>
<th>Y</th>
<th>Duration</th>
</tr>
</thead>
</table>

Please ask the patient if she/he has experienced the following symptoms. Please mark (X) the appropriate checkbox.

#### 1. TB symptom check

<table>
<thead>
<tr>
<th>Symptom</th>
<th>N</th>
<th>Y</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained persistent cough for more than 2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you coughed up blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained weight loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drenching night sweats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fevers and Chills</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty in breathing</td>
<td></td>
<td></td>
<td></td>
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#### 2. TB Risk Assessment

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
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<tr>
<td>Are you in close contact with someone who has TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had contact with someone who has multidrug resistant TB (MDR TB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you live in a hostel or informal settlement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Refer patient for further TB investigation? YES [ ] NO [ ]
Appendix IV - National Tuberculosis Control Programme Guidelines

South African National Tuberculosis Guidelines

2007

Draft 1, September 2007
PREFACE

The implementation of the DOTS strategy has resulted in substantial global progress in TB control in the past decade, although targets have been reached to varying extents in different regions. The two key global targets, to detect 70% of TB cases and to cure 85% of sputum-positive clients by the year 2000, were first set by the World Health Assembly in 1991. These targets were based on epidemiological modelling which suggested that achieving a 70% case detection rate and 85% cure rate would reduce the prevalence of infectious (sputum smear-positive) TB cases, the number of infected contacts, and the incidence of infectious cases. It was estimated that in the absence of HIV co-infection, the annual incidence of TB would be reduced by 7-12%. The DOTS strategy was launched in 1994 in support of these targets. When it was clear that the targets would not be reached by 2000, the deadline was extended to 2005.

The World Health Organisation Global Tuberculosis Control Report for 2007 estimates however, that global case detection was 60% in 2005 and the treatment success rate for 2004 was 84%. Improvements in TB control globally are reflected in 67 countries having achieved 70% case detection rates, 57 countries having achieved treatment success rates of 85%, with 26 of these achieving both targets, including China, Vietnam and the Philippines. Developing regions however still bear the greatest brunt of TB with 23% of the 8.8 million cases reported in 2005 found in Africa alone. The achievements in TB control in W.H.O. Africa region in particular are poor; case detection was estimated at 51% and smear positive success rates were 74% for new cases and 60% for retreatment cases. Despite efforts at TB control, TB is still a major cause of morbidity and mortality worldwide, with increasing global case numbers being driven largely by poor TB control in sub-Saharan Africa.

The failure to achieve these targets, the impact of HIV in fuelling TB and the problems with TB control in developing countries has led to widespread recognition that TB Control needs to extend beyond the DOTS strategy. The Millennium Development Goals (MDG) set by the United Nations frames TB control within the developmental context of reducing poverty and improving the health of the poor. The Millennium Development Goal 6 (Combat HIV/AIDS, malaria and other diseases) has a target to “have halted by 2015 and begun to reverse the incidence of malaria and other major diseases”. The Stop TB Partnership has endorsed two targets linked to the MDG:

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

The new Stop TB Strategy builds on current achievements of the DOTS strategy, but calls for additional strategies to effectively address constraints and challenges in TB control and efforts to strengthen health systems, alleviate poverty and advance human rights.

TB control in South Africa has met with mixed success. Since the inception of the National TB Control Programme (NTCP) in 1996, TB notification rates have increased due to improved reporting and case detection. TB cure rates have increased slowly, but not at the levels required to meet the targets that have been set. The challenges faced are substantial: growing caseloads in the face of an over-burdened health infrastructure, extremely poor cure rates in some provinces, high mortality and treatment interruption rates, high levels of TB-HIV co-infection, increased levels of multi-drug resistant TB (MDR TB) and the emergence of extensively drug resistant TB (XDR TB).
The key challenges are to strengthen health systems so as to ensure equitable access to services, continuity of care and improved levels of care for TB-HIV co-infected clients. Providing HIV care to co-infected TB clients is important in reducing morbidity and mortality amongst TB clients. Improved TB case-finding and early diagnosis of TB amongst HIV-positive clients will not only reduce their morbidity and mortality, but can play a significant role in reducing TB transmission in communities.

The most cost-effective public health measure to control TB is the identification and cure of the infectious cases, i.e. patients with smear-positive pulmonary TB. Whilst this remains the focus of the NTCP, the aim is to ensure successful treatment of all TB cases, including smear negative PTB and extra-pulmonary TB in both adults and children. Ensuring a regular supply of the TB drugs and good adherence to treatment will prevent the escalation of drug resistance.

This document aims to provide guidance to front-line health care workers and their managers in addressing the challenges in TB control and to successfully manage all TB cases, including those co-infected with HIV.

ACKNOWLEDGEMENTS

The NTCP would like to acknowledge the support provided by:

Prof. N. Beyer (Stellenbosch University)
Prof. R. Gie (Stellenbosch University)
Dr. V. Tihon (National Department of Health)
Ms. C. Idema, (National Department of Health)
Dr Refiloe Matji (URC)
Dr Ruth Cornick (PALSA-Plus, Institute of Lung Health)
Etc…..
And all of those who have made comments on the documents
# List of abbreviations

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

1.1 Global Epidemiology And Burden Of Disease

TB is still a major cause of death and disease worldwide with an estimated 8.8 million new TB cases in 2005 and 1.6 million deaths, including 195,000 in clients also infected with HIV. Even though the global epidemic appears to be on the threshold of decline, with decreasing global TB prevalence and death rates, the total number of new TB cases is still rising because caseloads continues to grow in the African, Eastern Mediterranean and South-East Asia regions. Of the estimated 8.8 million new TB cases in 2005, 7.4 million were in Asia and sub-Saharan Africa.

High burden countries account for 80% of TB cases; these cases are found in only 22 of the total 199 countries that report to the World Health Organisation (W.H.O.). Amongst the 15 countries with the highest TB incidence, 12 are in Africa where high TB incidence correlates with high HIV prevalence rates. The average incidence rate of TB in these 22 high burden countries is 174 cases per 100,000 population.

Factors contributing to the increasing global TB burden include:
- Poverty and rapid urbanisation
- The impact of the HIV-pandemic
- Poor programme management in terms of inadequate case detection, diagnosis and cure
- Poor health infrastructure.

1.2 TB Control In South Africa

According to the W.H.O. Global Tuberculosis Report 2007, South Africa had the 3rd highest TB case notification for 2005 in the world, behind only India and China. The TB incidence in South Africa is reported at over 3 times the average incidence rate found in the 22 high-burden countries. In 2005, South Africa with only 0.7% of the world’s population had 19% of HIV-positive adult TB cases reported globally. Although case detection rates have been increasing, the current rate cannot be accurately calculated due to an underestimation of the true TB incidence (leading to a reported rate of 110%). Correct estimates require new surveillance data.

Over the last five years however, TB case notification has increased by a massive 81%, from 188,695 cases in 2001 to 342,315 in 2006. In 2006, Kwa-Zulu Natal had the highest total TB caseload accounting for 31% of all TB cases nationally.

<table>
<thead>
<tr>
<th>Table 1.1: TB Case Finding 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TB Cases</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Eastern Cape</td>
</tr>
<tr>
<td>Free State</td>
</tr>
<tr>
<td>Gauteng</td>
</tr>
<tr>
<td>Kwa-Zulu Natal</td>
</tr>
<tr>
<td>Mpumalanga</td>
</tr>
<tr>
<td>North West</td>
</tr>
<tr>
<td>Northern Cape</td>
</tr>
<tr>
<td>Limpopo</td>
</tr>
</tbody>
</table>
PTB cases account for 84% of the total TB caseload and EPTB for 16%. Considering the high levels of TB-HIV co-infection, this ratio is low and may reflect missed TB diagnosis, particularly in late stage HIV-infection.

Amongst PTB cases, smear-positive cases account for 60% of the caseload, smear-negative TB for 15% and 25% had no smear taken, 10% of these being children under 8 years of age. The implication is that 15% of PTB cases (children under 8 excluded), had the diagnosis made without laboratory confirmation (no smear or culture). This probably reflects a combination of very ill patients, poor diagnostic practices and poor availability of laboratory culture services in some areas. It should be emphasised however, that the absence of bacteriological confirmation is not an acceptable standard in the diagnosis of pulmonary TB in adults.

Treatment outcomes have improved, with a 57% cure rate and 71% treatment success rate in 2005 compared to 51% and 66% respectively in 2004. The poor documentation of cure (high completion rates), defaulter rates over 10% and large numbers of cases not evaluated are indicative of poor systems at health facilities, and contribute to the failure to reach programme targets.

Table 1.2: New Smear Positive Treatment Outcomes 2005

<table>
<thead>
<tr>
<th>Province</th>
<th>Registered</th>
<th>Cured</th>
<th>Completed</th>
<th>Treatment Success</th>
<th>Died</th>
<th>Failed</th>
<th>Default</th>
<th>Transfer</th>
<th>Not evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cape</td>
<td>20940</td>
<td>53.7%</td>
<td>19.2%</td>
<td>72.9%</td>
<td>7.6%</td>
<td>1.2%</td>
<td>9.0%</td>
<td>3.9%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Free State</td>
<td>9731</td>
<td>67.5%</td>
<td>9.3%</td>
<td>76.9%</td>
<td>10.1%</td>
<td>2.0%</td>
<td>5.9%</td>
<td>4.8%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Gauteng</td>
<td>23921</td>
<td>66.7%</td>
<td>5.0%</td>
<td>71.7%</td>
<td>9.6%</td>
<td>1.5%</td>
<td>6.9%</td>
<td>8.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Kwa-Zulu Natal</td>
<td>36511</td>
<td>45.2%</td>
<td>19.1%</td>
<td>64.2%</td>
<td>6.1%</td>
<td>1.2%</td>
<td>14.7%</td>
<td>5.8%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>7642</td>
<td>51.8%</td>
<td>13.9%</td>
<td>65.7%</td>
<td>9.0%</td>
<td>1.0%</td>
<td>10.8%</td>
<td>4.3%</td>
<td>9.2%</td>
</tr>
<tr>
<td>North West</td>
<td>13771</td>
<td>57.6%</td>
<td>12.3%</td>
<td>70.0%</td>
<td>7.3%</td>
<td>2.9%</td>
<td>9.5%</td>
<td>6.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>3888</td>
<td>50.1%</td>
<td>21.3%</td>
<td>71.4%</td>
<td>6.8%</td>
<td>3.2%</td>
<td>13.1%</td>
<td>2.8%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Limpopo</td>
<td>6007</td>
<td>60.8%</td>
<td>9.2%</td>
<td>70.0%</td>
<td>9.5%</td>
<td>2.0%</td>
<td>7.4%</td>
<td>8.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Western Cape</td>
<td>18838</td>
<td>71.9%</td>
<td>7.8%</td>
<td>79.7%</td>
<td>3.7%</td>
<td>1.9%</td>
<td>11.1%</td>
<td>3.2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>South Africa</td>
<td>142049</td>
<td>57.6%</td>
<td>13.2%</td>
<td>70.8%</td>
<td>7.3%</td>
<td>1.7%</td>
<td>10.4%</td>
<td>5.5%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Source: C. Idema, TB Control Programme, National Department of Health

1.3 Challenges to TB Control

There are many challenges to be addressed in improving TB control:

- Inadequate financial and human resources support for the TB Control Programme
- Poor community participation in TB control, characterised by low levels of awareness of TB, poor health seeking behaviours amongst symptomatic people resulting in late presentation to health facilities and inadequate community support for those on TB treatment
- Inadequate health systems that result in low case detection, poor continuity of care, high levels of treatment interruption (the latter compounded by high levels of client mobility and poor referral systems)
- Poorly trained or supervised health care workers, low levels of accountability of health staff, non-adherence to protocols, poor record keeping and poor relationships with clients
- Low levels of integration of TB and HIV services. According to the W.H.O. Global Tuberculosis Report 2007, only 22% of TB patients had HIV tests in 2005; of these 52% were HIV-positive. The
care provided to those diagnosed HIV-positive does not follow established protocols. The mindset is that TB staff are not responsible for HIV care. Access to HIV care is via referral, which also occurs poorly. Within HIV services likewise, screening for TB to help ensure early diagnosis is not routinely done at every clinical visit and little effort is made to provide TB preventive therapy. The numbers of MDR TB and XDR TB cases have been increasing. The management of drug resistant TB is sub-optimal at facility level, with inadequate early pick-up of possible resistance and follow-up of MDR TB clients discharged from in-patient facilities. Programme management, particularly at the facility level, is often inadequate. Poor quality data is collected and data is not analysed or used to improve current practices.

The new Stop TB Strategy provides an opportunity to reinvigorate the approach to TB control and to focus our collective effort in addressing the challenges presented.

2 The National Tuberculosis Control Programme

2.1 Objectives Of The National Tuberculosis Control Programme

The overall objectives of the NTCP are to:
Achieve equitable access to high-quality diagnosis and patient-centred treatment
Reduce mortality and morbidity attributable to TB
Prevent the development of drug resistance
Ensure appropriate monitoring and evaluation of programme performance.

The targets for TB control in South Africa are:
To cure 85% of newly detected cases of sputum smear-positive TB;
To detect 70% of TB cases
To reduce interruption rates to less than 5%

South Africa subscribes to the Stop TB Strategy to reduce dramatically the global burden of TB by 2015 in line with the Millennium Development Goal (MDG) to “Combat HIV/AIDS, malaria and other diseases”. The target is to have halted by 2015 and begun to reverse the incidence of TB, specifically:
By 2005, to detect at least 70% of new sputum smear-positive TB cases and cure at least 85% of these cases
By 2015, to reduce TB prevalence and death rates by 50% relative to 1990 levels

The specific components of the strategy include:

Pursue high-quality DOTS expansion and enhancement
Political commitment with increased and sustained financing
Case detection through quality-assured bacteriology
Standardized treatment, with supervision and patient support
An effective drug supply and management system
Monitoring and evaluation system, and impact measurement

Address TB/HIV, MDR TB and other challenges
Implement collaborative TB/HIV activities
Prevent and control MDR TB
Address prisoners, refugees and other high-risk groups and situations

Contribute to health system strengthening
Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery, and information systems
Share innovations that strengthen systems, including the Practical Approach to Lung Health (PAL)
Adapt innovations from other fields

Engage all care providers
Public–Public and Public–Private mix (PPM) approaches
International Standards for Tuberculosis Care (ISTC)

Empower people with TB, and communities
Advocacy, communication and social mobilization
Community participation in TB care
Patients’ Charter for Tuberculosis Care

Enable and promote research
Programme-based operational research
Research to develop new diagnostics, drugs and vaccines

2.1.1 DOTS Expansion And Enhancement

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

2.1.2 Address TB/HIV, MDR TB And Other Challenges

Implement collaborative TB/HIV activities – Accelerated HIV prevention efforts will in the long-term play a role in reducing TB. The increasing impact of HIV on TB incidence and mortality however also calls for better integration of TB and HIV services. Fundamental shifts are required within TB services, such as offering HIV testing as the standard of care to all TB clients and TB suspects. With the high levels of co-infection that exist in South Africa, TB services are a natural entry point to HIV care, and the provision of HIV care needs to be integrated into TB services, including cotrimoxazole preventive therapy, the management of other opportunistic infections, provision of antiretroviral therapy and general HIV support services. Equally, routine TB screening should occur in HIV services to ensure early TB diagnosis and access to treatment. The use of isoniazid preventive therapy is promoted as part of the package of care available to HIV+ clients in whom TB has been excluded. One of the challenges to integrating services is to ensure that infection control measures are improved to reduce nosocomial transmission of TB. Where services cannot be fully integrated, improved referral systems need to be established.

Prevent and control MDR TB - The surge in multidrug-resistant TB presents a threat to TB control. The approach first and foremost, requires effective implementation of DOTS Expansion and Enhancement to prevent MDR TB. Measures to improve the management of existing MDR TB cases include earlier detection of MDR TB in clients failing to respond to regimen 1 and 2, standardised treatment regimens, and improved integration of MDR TB care at primary health level.

2.1.3 Contribute To Health System Strengthening

Improving the health system includes addressing policy, human resources, finance, and service delivery and information systems.

TB control and primary health care (PHC) are interdependent. Rapid progress in TB control will not occur unless TB control is integrated into the PHC-system. Similarly, a PHC-programme cannot be truly effective unless it includes TB control. TB is highly prevalent in South Africa and its most frequent clinical manifestation, cough, is one of the most common presenting symptoms among patients attending PHC services. When TB control and PHC are integrated, TB case detection and case holding can be improved and extended to entire populations.

Improving health management and service delivery, including provision of quality, client-centred services that ensure good continuity of care requires motivated, well-trained staff and management being held accountable for the services they deliver.
Innovations in service delivery models such as the syndromic approach to respiratory disease described in W.H.O.’s Practical Approach to Lung Health, can help integrate TB services within primary health care and improve case detection.

Other service delivery innovations adapted from HIV and other programmes should be explored to find ways in which to achieve improved outcomes and use limited resources, including human resources, more effectively.

2.1.4 Engage All Care Providers

Collaboration between public, private and voluntary sectors is essential to ensure accessible and quality-assured TB diagnosis and treatment, including the development of community-based support mechanisms, under the guidance of provincial health authorities.

All services providers, including those within the private sector and other government departments, need to adhere to the standards established or TB diagnosis and treatment.

2.1.5 Empower People With TB And Communities

Advocacy, communication and social mobilization – Advocacy is important in influencing policy and ensuring that commitment to financial and human resources are sustained. High visibility social mobilisation provides and opportunity to engage with communities and to communicate key messages about TB to help improve knowledge levels, modify health seeking behaviour, improve access and utilisation of health services and encourage communities to become active in contributing towards TB control efforts.

Community participation in TB care can be formalised through identifying specific roles and responsibilities for community members and community based organisations in supporting TB diagnosis and treatment. It is essential that expectations, such as the payment of incentives for assisting in providing community-based DOT, is clarified at the outset. Community involvement in TB care is not a matter of devolving the responsibility for TB care; it requires training, supervision, good communication and ensuring lines of accountability between health service sand community organisations.

Respecting the rights of TB clients to free and equitable services, empowering clients with knowledge about their disease, respecting their dignity and fostering partnerships in which these rights are balanced with responsibilities to adhere to treatment can contribute towards TB control.

2.2 The Structure Of The National TB Control Programme

The National TN Control Programme (NTCP) consists of four levels within the general health services:

The National level functions through the National Department of Health to coordinate, facilitate and evaluate tuberculosis services countrywide.

The Provincial level is responsible for implementation and budgeting.

The District level is the key element for the management of primary health care and is the most peripheral unit of the health services administration.

The Health unit level functions within a district to provide primary health care. This level incorporates all the rural hospitals, health centres, dispensaries and clinics within a specific area.
This structure may vary to some extent, for example in some provinces a regional level has been established between the provincial and district levels. In others, districts are further divided into sub-districts.

2.2.1 Core Activities At National Level

The main function of the national unit is to provide support and technical guidance to the provinces on the following key activities:
Countrywide implementation of the expanded framework for TB control
Training of provincial TB co-ordinators on all elements of the expanded framework for TB control
Supervisory visits
Laboratory visits to ensure proper diagnosis and follow-up of TB patients
Ensuring an efficient recording and reporting system for monitoring patients and monitoring and evaluating programme performance
Strengthening the collaboration between TB and HIV/AIDS programmes to ensure better management of co-infected patients
Raising public awareness about the seriousness of TB
Co-ordination of research activities.

2.2.2 Core Activities At Provincial Level

The key functions at provincial level are:
Collaboration with district management teams in planning TB activities so that the provincial work plan is the sum of the district work plans
Organising training and conducting supervisory / support visits, including for laboratory and pharmacy personnel who perform activities related to TB control
Ensuring that a district's needs for TB drugs, forms and laboratory materials are supplied as required
Supervising record keeping of the TB case registers and laboratory registers
Collaborating with staff working in the HIV/AIDS programme to ensure better management of patients
Collaborating with other agencies and NGOs, as well as private doctors, who provide care for TB patients.

2.2.3 Core Activities At District Level

The key functions at district level are to:
Co-ordinate training activities at district level
Develop an efficient patient referral system to ensure continuity of care
Co-ordinate and establish community-based DOTS programmes
Conduct support visits to health facilities including NGOs, laboratories and pharmacies.
Submit quarterly reports on case finding and treatment outcomes
Ensure that diagnostics and drugs are available at all times
Plan and budget for TB activities
Participate in advocacy and social mobilisation activities.

The district TB coordinator, who may be responsible for other programmes in addition to TB, should be part of the district management team.
3 Transmission and Pathogenesis of TB

3.1 Transmission of Tuberculosis

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

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

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

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

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

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

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

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

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

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

3.2 Pathogenesis of tuberculosis

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

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

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

3.3 Primary infection

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

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

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

<table>
<thead>
<tr>
<th>Table 3.1: Possible Outcomes of Primary Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No clinical disease.</strong></td>
</tr>
<tr>
<td>Positive tuberculin skin test</td>
</tr>
<tr>
<td>(usual &quot;outcome&quot; in 90% of cases)</td>
</tr>
<tr>
<td><strong>Hypersensitivity reactions</strong></td>
</tr>
<tr>
<td>e.g. erythema nodosum</td>
</tr>
<tr>
<td>phlyctenular conjunctivitis</td>
</tr>
<tr>
<td>dactylitis</td>
</tr>
<tr>
<td><strong>Pulmonary and pleural complications</strong></td>
</tr>
<tr>
<td>e.g. tuberculous pneumonia</td>
</tr>
<tr>
<td>lobar collapse (bronchial compression)</td>
</tr>
<tr>
<td>pleural effusion</td>
</tr>
<tr>
<td><strong>Disseminated disease</strong></td>
</tr>
<tr>
<td>e.g. lymphadenopathy (usually cervical)</td>
</tr>
<tr>
<td>meningitis</td>
</tr>
<tr>
<td>pericarditis</td>
</tr>
<tr>
<td>miliary disease</td>
</tr>
</tbody>
</table>

3.4 Post-primary TB / Secondary TB

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

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

In a small number of cases it occurs as a progression of primary infection. Following primary infection, rapid progression to intra-thoracic disease is more common in children than in adults. Chest X-rays may show intra-thoracic lymphadenopathy and lung infiltrates.
Post-primary TB usually affects the lungs but can involve any part of the body. The characteristic features of post-primary PTB include upper lobe involvement with extensive lung destruction with cavitation. Sputum smears are usually positive and there is usually no intrathoracic lymphadenopathy.

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

4 Diagnosis Of TB

4.1 Symptoms And Signs Of TB

A productive cough, often accompanied by systemic symptoms, is the commonest presentation of pulmonary tuberculosis. Symptoms of pulmonary TB include:

- Persistent cough for more than 2 weeks
- Sputum production (which may occasionally be blood-stained)
- Fever for more than 2 weeks
- Drenching night sweats
- Loss of appetite
- Unexplained weight loss (more than 1.5 kg in a month)
- A general feeling of illness (malaise) and tiredness
- Shortness of breath, chest pain

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

TB case-finding depends on clients presenting to the health facility with these symptoms and having the appropriate TB tests done (known as passive case finding). In view of the susceptibility of HIV-positive clients to TB, it is essential that active screening of HIV-positive clients take place at every clinical visit. HIV-positive clients should be asked specifically if they have each of the TB symptoms listed; if they have symptoms, the appropriate TB tests should be done.

Symptoms of extra-pulmonary tuberculosis depend on the organ involved. Chest pain from tuberculosis pleurisy, enlarged lymph nodes in the neck and armpit and sharp angular deformity of the spine are frequent signs of extra-pulmonary tuberculosis (see Chapter 6).

4.2 How Is Diagnosis Of Tuberculosis Confirmed?

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

4.2.1 Smear And Culture Evaluation Of A TB Suspect Pre-treatment

**No previous TB or less than 4 weeks previous TB treatment:** Send 2 specimens on consecutive days for TB smear microscopy. The first specimen is a spot specimen and the second an early morning specimen.

**If these are negative:**
And the client is HIV-positive: send a 3rd specimen for smear and culture and commence Amoxicillin.
And the client is HIV-negative or HIV status is unknown: commence 5 days of Amoxicillin. Send a 3rd specimen for smear and culture if there is no response to antibiotics.

**Previous TB treated for more than 4 weeks or MDR contact:** Send a spot specimen for smear microscopy and an early morning specimen for smear microscopy, culture and susceptibility.

**If these are negative:**
And the client is HIV-positive: send a 3rd specimen for smear and commence Amoxicillin.
And the client is HIV-negative or their HIV status is unknown: commence 5 days of Amoxicillin. Send a 3rd specimen for smear if there is no response to antibiotics.

4.2.2 Sputum Smears

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

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

**First specimen:** At the first visit a "spot" (immediate) specimen is collected. This specimen should be collected at the health facility under supervision of a health worker.

**Second specimen:** The client is given a sputum container for the collection of an early morning specimen at home, usually the following day. If the first specimen is collected on a Friday, the second specimen should be collected on the following Monday morning. The jar should be brought back to the clinic on the day that the specimen is collected, as soon after collection as possible.

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

4.2.2.1 Sputum Labelling

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

Name of clinic / hospital.

Name of client.
4.2.2.2 Sputum Collection

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

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

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

4.2.2.3 Completion Of Laboratory Form

Complete the standard National Health Laboratory TB Investigation Form (Annexure 3).
Name of clinic / hospital.
Name of client
Clinic / hospital number.
Date and time of specimen collection
Indicate whether it is a new or re-treatment client
Indicate whether the specimen is pre-treatment (suspect), follow-up (2 or 3 months) or end-of-treatment specimen (5 or 7 months).
Write clear instructions regarding what investigations are required.
Note the appearance of the sputum (e.g. mucoid, lumpy, green, offensive, etc).

4.2.2.4 Sputum Storage

Place the sputum bottle in a plastic bag to prevent contamination.
Send the specimen to the laboratory as soon as possible
Store sputum specimen in a fridge (not a freezer) if transport is not immediately available.

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

4.2.2.6 Completion Of TB Suspect Register

Record the clients’ details and the date on which the specimen was collected in the suspect register (see Annexure 5). The TB Suspect Register should be updated on a daily basis (with clients results and treatment commencement dates)

Each workday, the person responsible should check the sputum register to see which results are outstanding and contact the laboratory to follow-up on these results. Close cooperation with the laboratory will help ensure that sputum positive clients are started on the correct treatment as soon as possible. The target of the NTCP is to have 80% of results back at the health facility within 72 hours.

4.2.2.7 Sputum Results

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

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

<table>
<thead>
<tr>
<th>Number of bacilli seen on a smear</th>
<th>Results reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AFB</td>
<td>Per 100 oil immersion field, 0</td>
</tr>
<tr>
<td>1-9 AFB</td>
<td>Per 100 oil immersion field, Scanty</td>
</tr>
<tr>
<td>10-99 AFB</td>
<td>Per 100 oil immersion field, 1+</td>
</tr>
<tr>
<td>1-10 AFB</td>
<td>Per 1 oil immersion field, 2++</td>
</tr>
</tbody>
</table>

The sputum turn around time (TAT) is the duration of time from taking a smear specimen from the client to receiving the result at the health facility, including weekends and holidays. The standard expected is 48 hours for 80% of smears.

4.2.3 Sputum Culture and Drug Susceptibility Testing

Culture is more sensitive than smear microscopy, detecting a higher proportion of cases among clients with symptoms. The specificity is also higher as each live bacillus forms a colony on culture. However, it is an expensive and slow diagnostic technique, not accessible to some clients and takes at least 4 weeks to provide a definitive result.
Culture is however an important diagnostic tool in clients with paucibacillary tuberculosis, such as HIV-positive clients with smear-negative pulmonary tuberculosis.
Indications for the use of sputum culture include:
Clients with a history of previous TB treatment (interruption, failure, relapse).
In cases where drug susceptibility testing is necessary, including clients who remain positive at the end of the intensive phase of treatment and who fail to improve clinically or bacteriologically or who are positive at the end of treatment
In TB suspects in contact with known MDR TB
To diagnose paucibacillary TB in clients who have two negative smears.

4.2.3.1 Culture Methods

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

These drawbacks have led to the development of faster, more sensitive liquid medium culture techniques:
Semi-automated radiometric systems such as BACTEC 460, which uses radiation technology
Automated non-radiometric systems, such as MGIT, which uses fluorometric technology.

Liquid medium is used in conjunction with solid medium as back up. The detection of bacilli occurs within 7 to 14 days in liquid medium. The major limitation to the use of these methods is the high cost involved.

4.2.3.2 Drug Susceptibility Testing

Susceptibility tests are used to determine the susceptibility or resistance of a client's bacillary strain to the different anti-tuberculosis drugs. There are two types of susceptibility testing:
Direct tests are performed directly on a sample that is rich in bacilli with results available in 4-6 weeks.
Indirect tests are performed on cultures that have to be grown and tested in the exponential phase of growth. Results are only available 2 to 3 months after sampling if grown in solid media or in 1 month if grown on liquid media.

4.2.4 Chest X-rays

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

Chest x-rays are necessary in TB suspects who cannot produce sputum or who have negative smears. They must be interpreted in the light of the client’s history and clinical findings.

4.2.4.1 Indications For The Use Of Chest X-rays

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

4.2.5 Tuberculin Skin Test

The tuberculin test has limited value in clinical work, especially where TB is common. The test shows hypersensitivity to proteins of the TB bacillus, as a result either of infection with M. tuberculosis or induced by Bacille Calmette-Guérin (BCG) vaccination. It does not indicate TB disease.

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

It should also be noted that a negative result does not rule out the diagnosis of TB disease. Various conditions, including HV may suppress the reaction.

4.2.5.1 Performing A Tuberculin Skin Test

The Mantoux tuberculin test uses:
2 units of tuberculin purified protein derivative PPD-RT23 or
5 units of PPD-S
The PPD is injected between layers of skin (intradermally). It is important to ensure that the injection goes into and not under the skin.
The reaction to the test at the site of the injection is measured 48-72 hours later by noting the widest point across the edges of the raised, thickened area.
To help measure accurately, mark the edges of the induration at the widest point with a pen and measure the exact distance between the two points in millimetres.

| Table 4.1: Reading the Tuberculin Skin Test |
|-----------------|-----------------|-----------------|
| Immune Status   | HIV-positive, malnourished, severe | Others (including previous BCG) |

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### 4.2.5.2 Interpreting A Positive Skin Test Result

A positive test indicates infection with TB, but not necessarily TB disease. In a child under 5 years a positive skin test indicates recent (about 6 weeks) infection that is a risk factor for progression to disease. In the presence of other features such as a history of a TB contact, signs and symptoms of TB and chest x-ray changes, a positive tuberculin skin test is suggestive of TB disease in children.

A positive reaction is only one piece of evidence in favour of a TB diagnosis in children. Because of the increased risk of developing active TB, children under the age of 5 years who have a positive skin test and no symptoms or signs of TB should be put on TB prophylaxis for six months (isoniazid 5mg/kg daily).

### 4.2.5.3 Interpreting A Negative Tuberculin Skin Test

A negative tuberculin skin test does not exclude TB; various conditions may cause a negative reaction even if a child has TB, including:

- HIV infection
- Malnutrition
- Severe viral infections (e.g. measles, chicken pox)
- Cancer
- Immuno-suppressive drugs (e.g. steroids)
- Severe disseminated TB.

### 4.3 The Seriously Ill TB-Suspect

An adult TB suspect is classified as seriously ill if they have 1 or more of the following features:

- Unable to walk unaided
- Respiratory rate equal to or more than 30 per minute
- Fever of more than 39°C
- Pulse rate of more than 120 per minute

Treatment of the seriously ill client is as follows:

- Take 2 sputa: 1 for AFB and 1 for AFB and culture as promptly as possible
- Commence parenteral antibiotics: Ceftriaxone 250 mg IM stat
- Refer to secondary level of care

If unable to immediately refer, do:
- Chest-xray
- HIV test
- If HIV+:
Consider treating for PCP
TB treatment can be started on clinical grounds if client does not improve within 3-5 days on antibiotics, AFB are negative and no other diagnosis is confirmed.
TB treatment should be continued unless an alternative diagnosis is confirmed
4.4 Algorithm For Diagnosis of Pulmonary Tuberculosis

**No Previous TB or Less than 4 Weeks TB Treatment**
- Send 2 sputum specimens for smear microscopy for AFBs:
  - 1st spot (immediate) specimen taken at the health facility under supervision
  - 2nd early morning specimen

**HIV-negative or HIV status unknown**
- **AFB+ AFB+**
  - **Treat as TB**
    - Provide full course of treatment
- **AFB+ AFB-**
  - Send 3rd specimen for smear. Request culture if new client.
  - Provide antibiotics.
  - If no improvement send 3rd specimen for sputum smear and culture and do chest x-ray
- **AFB- AFB-**
  - None or Only 1 AFB+ Culture - and TB on C-xray and Medical officer decision to treat on clinical grounds
- **AFB- AFB+**
  - 2 AFB+ or 1 AFB+ and 1 Culture+ or 1 Culture+
    - **Treat as TB**
      - Provide full course of treatment

**Previous TB (More than 4 Weeks TB Treatment) or MDR Contact**
- Send 2 sputum specimens:
  - 1st spot (immediate) specimen taken at the health facility for sputum smear for AFBs
  - 2nd early morning specimen for sputum smear, culture and sensitivity

**HIV-positive**
- **AFB+ AFB+**
  - **Treat as TB**
    - Provide full course of treatment
    - Review drug sensitivity
- **AFB+ AFB-**
  - 1 AFB+ or Culture+
    - AFB- and Culture- TB on C-xray and Medical officer decision to treat on clinical grounds
- **AFB- AFB-**
  - **Treat as TB**
    - Provide full course of treatment
    - Review drug sensitivity
  - None or Only 1 AFB+ Culture - and TB on C-xray and Medical officer decision to treat on clinical grounds

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

5.1 Why Case Definitions?

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

5.2 Why Match Treatment To Standardised Category?

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

5.3 What Determines Case Definitions?

Site of TB disease.  
Bacteriology (sputum smear and culture result).  
Severity of TB disease.  
History of previous treatment of TB.

5.3.1 Site Of TB disease: Pulmonary Or Extra-pulmonary

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

Smear-positive PTB case:
2 sputum smears positive for AFBs or
1 sputum smear positive for AFBs and HIV-positive or
Culture positive or
Chest x-ray abnormalities consistent with active TB and
Clinically ill and considered to be TB by a medical officer.
Even if the first pre-treatment specimen is positive, it is advisable that another specimen be taken.
This will reduce the chance of a false-positive result due to an administrative error.
Identifying smear positive TB is important:
These are the most infectious cases
They have the highest mortality
Reporting on treatment outcomes is most feasible in this group.

Smear-negative PTB case:
Where there is no smear result (children) or
At least 3 sputum smears are negative for AFBs and
Sputum culture is positive for mycobacterium TB or
Chest X-ray abnormalities are consistent with active TB, there has been no response to broad-spectrum antibiotics and a clinician has taken the decision to treat with a full course of TB treatment.

5.3.3 Severity Of Disease

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

<table>
<thead>
<tr>
<th>Table 5.1: Severity of EPTB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe extra-pulmonary disease</strong></td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Military</td>
</tr>
<tr>
<td>Pericarditis</td>
</tr>
<tr>
<td>Peritonitis</td>
</tr>
<tr>
<td>Bilateral or extensive pleural effusions</td>
</tr>
<tr>
<td>Spinal</td>
</tr>
<tr>
<td>Intestinal</td>
</tr>
</tbody>
</table>

5.3.4 History Of Previous Treatment

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

New case: A client who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than four weeks.
Re-treatment case: A client who has taken treatment for TB before for more than 4 weeks and either relapsed, defaulted or had treatment failure.

Relapse: A sputum smear or culture-positive pulmonary TB client who received treatment and was declared cured or treatment completed at the end of the treatment period and has now developed sputum smear or culture positive pulmonary TB again.

Treatment after failure: A pulmonary TB client who is still sputum smear or culture positive at the end of the treatment period and is started on a retreatment regimen.

Treatment after default: A client who completed at least one month of treatment and returns after having interrupted treatment for two months or more, and is still smear or culture positive or has signs of active TB on clinical and radiological assessment.

Transfer out: A client already registered for treatment in one district that has been transferred to another district to continue treatment is recorded as a “transfer out” at the site where treatment was initiated.

Transfer in: A client already registered for treatment in one district that has been transferred to another district to continue treatment is recorded as a “transfer in” at the referral site.

Other: All cases that do not fit the above definitions, including

Chronic case: Client who remains sputum smear positive after completing a supervised re-treatment regimen.

5.4 Recording Treatment Outcomes With Smear-Positive TB

Cure: Client who is smear-negative at, or one-month prior, to the completion of treatment and also on at least one previous occasion at least 30 days prior.

Treatment completed: Client who has completed treatment but who does not meet the criteria to be classified as cure or treatment failure.

Treatment failure: Smear positive client who remains or is again smear-positive at 5 or 7 months after starting treatment.

Died: Client who dies for any reason during the course of TB treatment.

Treatment interrupted: Client whose treatment was interrupted for more than two consecutive months before the end of the treatment period.

Transfer out: Client who has been transferred to another reporting unit (e.g. district) and for whom the treatment outcome is not known.

Moved: Client who moves to another facility within the same district.

Recording, reporting and evaluation of programme performance focuses on smear-positive TB cases. The priority given to this category is appropriate as this is the largest group, containing the most infectious clients and therefore important from a public health perspective. Whilst the goal of the NTCP is to cure 85% of smear-positive TB cases, the intention is to ensure successful treatment in all categories of TB. The outcomes of other categories of clients, such as smear-negative, culture-positive TB and EPTB may also be analysed as separate cohorts.

6 Extra-Pulmonary Tuberculosis

Although most commonly affecting the lungs, tuberculosis can involve any organ in the body. Extra-pulmonary tuberculosis covers all forms of tuberculosis in which the disease process occurs outside the lung parenchyma. It accounts for about 20-25% of tuberculosis cases. Many forms of extra-pulmonary tuberculosis originate from direct, lymphatic or haematogenous spread of mycobacteria from a primary focus in the lung. Disseminated tuberculosis affects many parts of the body simultaneously.
The most common types of extra-pulmonary tuberculosis are:
TB lymphadenitis
Tuberculous pleural effusion (usually single-sided)
TB of the bones and joints
Tuberculous pericardial effusion
TB meningitis
Disseminated / miliary tuberculosis
Tuberculous empyema
TB peritoneal effusion

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

Common signs of extra-pulmonary TB include:
Cough for 2 weeks or more
Unintentional weight loss (more than 1.5 kg in a month), night sweats and fever for more than 2 weeks
Breathlessness (due to pleural or pericardial effusion)
Enlarged glands in the neck or armpits
Chronic headache or altered mental state

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

The basic principles of treatment for pulmonary tuberculosis also apply to extra-pulmonary forms of the disease. Regimens of 6 months are as effective in extra-pulmonary as in pulmonary disease. In some instances of severe disease therapy may need to be extended for 9 months. The use of corticosteroids is also more commonly required in extra-pulmonary tuberculosis, particularly for TB meningitis and pericarditis. Only a specialist may make decisions on extended treatment and the use of steroids.

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

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

6.1 TB Meningitis

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

Clients present with gradual onset of headache, malaise, confusion, decreased consciousness and sometimes vomiting. Examination reveals neck stiffness and a positive Kernig’s sign (flex one of the client's legs at hip and knee with the client lying on back, and then straighten the knee - resistance to straightening the knee and pain in the low back and posterior thigh suggest meningeal inflammation). Diagnosis rests on clinical presentation and a lumbar puncture examination of cerebrospinal fluid (CSF). The following CSF features are highly suggestive of TB meningitis:

- Clear CSF
- Elevated pressure
- High levels of protein (>1g/ l)
- High lymphocyte count (30-300/mm³)
- Low glucose
- Negative Indian ink stain for cryptococcus

Clients with suspected TB meningitis should be referred to hospital without delay as TB meningitis is life threatening, with serious complications if not treated promptly. Those presenting with more severe neurological impairment such as drowsiness or coma have a greater risk of neurological sequelae and a higher mortality.

<table>
<thead>
<tr>
<th>Disease</th>
<th>White Cell count</th>
<th>Protein</th>
<th>Glucose</th>
<th>Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous meningitis</td>
<td>Elevated L &gt; PMN</td>
<td>Increased</td>
<td>Decreased</td>
<td>Presence of AFB (rare)</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>Elevated PMN &gt; L (L increases with partial treatment)</td>
<td>Increased</td>
<td>Decreased</td>
<td>Presence of bacteria after gram staining (rare)</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>Elevated L &gt; PMN</td>
<td>Moderately increased</td>
<td>Normal</td>
<td>Negative</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>Elevated L &gt; PMN</td>
<td>Increased</td>
<td>Decreased</td>
<td>Presence of parasites shown by Indian ink stain</td>
</tr>
</tbody>
</table>

L-lymphocytes  PMN-polymorphonuclear leucocytes

6.2  Disseminated / Miliary TB

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

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

6.2.1  Clinical Features

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

6.2.2 Diagnosis

Chest X-ray shows diffuse, uniformly distributed, small miliary ("like small millet seeds") nodules. Full blood count may show pancytopenia (this may also be seen as a result of HIV) or anaemia. Liver function tests may be abnormal. Bacteriological confirmation is sometimes possible from sputum, C.S.F., or bone marrow. Smear microscopy of sputum from cases with disseminated (miliary) tuberculosis is usually negative, as the disease is paucibacillary.

6.3 Tuberculous Lymphadenopathy

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

6.3.1 Clinical Features

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

6.3.2 Diagnosis

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

6.4 Tuberculous Serous Effusions

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

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

6.4.1 Tuberculous Pleural Effusion

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

6.4.1.1 Clinical Features

Presentation is most often acute with a non-productive cough, chest pain, shortness of breath and high temperature.

The chronic form is found predominantly in the elderly and presents with systemic symptoms such as weakness, anorexia, weight loss, slight fever, cough, and chest pain.

Clinical examination shows:
- Tracheal and mediastinal shift away from the side of the effusion
- Decreased chest movement
- Stony dullness on percussion on the side of the effusion

6.4.1.2 Diagnosis

Suspected pleural effusions should be confirmed by immediate chest x-ray. This will show unilateral, uniform white opacity, often with a concave upper border.

Pleural aspiration should be undertaken wherever possible: the fluid is a straw coloured exudate and has a protein content >30g/l. The white cell count is high (1000-2500 per mm$^3$) with predominantly lymphocytes. The adenosine deaminase (ADA), which is a measure of the lymphocyte count, is raised >30 IU.

Failure of the aspirate to clot does not exclude TB as it may indicate lower protein content in wasted clients; the predominance of lymphocytes (>50%) confirms a TB diagnosis. Since the number of bacilli present is relatively small, AFB are not usually seen on microscopy of centrifuged specimens of pleural fluid, however, culture may be positive.
If aspiration is not possible, commence TB treatment unless the chest x-ray suggests a different diagnosis.
Differential diagnosis of a pleural exudate includes malignancy, a post-pneumonia effusion and pulmonary embolism.
Bilateral effusions or those with cloudy or bloody aspirates should be investigated further.
Pleural biopsy is not recommended, as it is unnecessarily invasive.

6.4.2  Tuberculous Pericardial Effusion

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

6.4.2.1  Clinical features

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

6.4.2.2  Diagnosis

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

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

6.4.3  Peritoneal Tuberculosis

Peritoneal TB is the commonest type of abdominal TB.

6.4.3.1  Clinical features

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

Always do a diagnostic ascitic tap - the aspirated fluid is usually straw coloured, but is occasionally turbid or blood stained. The fluid is an exudate, usually with more than 300 white cells per mm$^3$ with lymphocytes predominating (polymorphonuclear leucocytes predominate in spontaneous bacterial peritonitis which is a common complication of cirrhosis).

Investigate for pulmonary TB
Abdominal ultrasound may show retroperitoneal or mesenteric lymph node enlargement · Diagnosis is usually presumptive - in doubtful cases, a macroscopic examination and bacteriological or histological examination of the samples may be considered in a hospital where exploratory surgery or laparoscopy can be performed.

6.5 Tuberculous Empyema

This usually arises when a tuberculous cavity in the lung ruptures into the pleural space. The physical signs are similar to a pleural effusion, but aspiration reveals thick pus. Send the pus to the laboratory for examination for TB, gram stain and bacterial culture. The main differential diagnosis is bacterial empyema.

A succussion splash is a splashing sound heard with the stethoscope while shaking the client's chest. It indicates a pyopneumothorax (pus and air in the pleural space). After chest x-ray confirmation of a pyopneumothorax, insert a chest drain with underwater seal to remove fluid and air.

6.6 Tuberculosis of the Spine

TB can affect any bone but most commonly affects the vertebral column. It is seen both in children and adults and can be severe when there are neurological sequelae.

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

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

6.6.1 Clinical features

Features include back pain, stiff back, reluctance to bend the back
There may be referred pain radiating out from the site of origin
Localised swelling, sometimes with an obvious lump or abnormal curvature of the spine
A child that refuses to walk or has weakness or paralysis of the lower limbs.
Involvement of cervical vertebrae may cause pain in the neck and shoulders and rigidity of the neck. A cold abscess can develop behind the sternocleidomastoid muscle. More rarely, neurological involvement leads to progressive tetraplegia.
Involvement of the thoracic vertebrae causes localized back pain, deformity of the spine, and in extreme cases an angulated kyphosis (gibbus). The chief risk is spinal cord compression and paraplegia.
Involvement of the lumbar vertebrae results in lower back pain. A “cold abscess” from here can drain along the psoas muscle towards the inguinal area.
In the early stages physical examination can be non-specific.
Client with weakness or paraplegia should be referred to a specialist urgently.

6.6.2 Diagnosis

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

The principles of treatment for clients with EPTB are the same as for PTB:
Regimen 1 for new cases
Regimen 2 for retreatment cases
A specialist may decide to extend the treatment of severe forms of extra-pulmonary TB from 6 to 9 months and to provide corticosteroids.
The response to treatment is assessed clinically. Weight loss may occur as large effusions / ascites resolves and does not necessarily indicate failure to respond.

7 Principles Of TB Treatment

The aims of TB treatment are to:
Cure the client of TB
Decrease transmission of TB to others
Prevent the development of acquired drug resistance
Prevent relapse
Prevent death from TB or its complications

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

7.1 The Essential TB Drugs

There are three main properties of TB drugs: bactericidal, bacteriostatic (sterilising) and the ability to prevent resistance. The TB drugs possess these properties to different extents.

In a tuberculosis lesion there are various populations of bacilli:
Metabolically active
Intermediately active
Semi-dormant bacilli (persisters), which undergo occasional spurts of metabolism.
Dormant bacilli that may become active.

Different TB drugs act against different populations of bacilli. Bacilli may occur in extracellular or intracellular spaces. The pH in the extracellular space is usually neutral or alkaline, whereas it is acid intracellularly. Some TB drugs act best in an acid environment; others better at a more alkaline pH.

<table>
<thead>
<tr>
<th>Table 7.1: Properties of TB Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Isoniazid (H)</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
</tr>
</tbody>
</table>

7.2 Fixed Dose Combination Tablets

The use of fixed dose combinations (FDCs) has several advantages over individual drugs: Prescription errors are less likely as dosage recommendations are more straightforward and adjustment of doses according to client weight is easier. The number of tablets to be ingested is fewer and this may encourage client adherence. If treatment is not observed, clients cannot be selective in the choice of drugs ingested.

7.3 Standard Treatment Regimens for Adults (8 years and older)

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

A standard code is used to describe treatment regimens. It describes the duration of both the intensive and continuation phases, the fixed drug combinations used in each of the phases and the number of doses of the drugs per week. Each antituberculosis drug has an abbreviation: R (Rifampicin), H (Isoniazid), Z (Pyrazinamide), E (Ethambutol) and S (Streptomycin).

The number before a phase is the duration of that phase in months: 2 months for the intensive phase and 4 months for the continuation phase.

Letters in brackets indicate fixed dose combinations of drugs in that phase.

A subscript after the letters in brackets indicates the number of doses of that drug per week. If there is no subscript treatment
2 (HRZE) / 4 (HR)

New recommendations are that treatment is given daily. The exception is where Streptomycin injections may be given a minimum of 5 times per week.

7.3.1 New Cases

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

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

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

7.3.2 Retreatment Cases

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

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

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

The standard regimen for retreatment cases is regimen 2: 2(HRZE)7(S)5 / 1(HRZE) / 5(HRE)
The intensive phase is 2(HRZE)7(S)5 / 1(HRZE). It lasts 3 months in total. For the first two months treatment is with isoniazid, rifampicin, pyrazinamide and ethambutol in fixed dose combinations given 7 days a week and streptomycin given five times a week. In the third month only isoniazid, rifampicin, pyrazinamide and ethambutol in fixed dose combinations are given 7
days a week.
The continuation phase is 5(HRE). It lasts 5 months. Treatment is with isoniazid, rifampicin and ethambutol in fixed dose combinations given 7 days a week.

7.4 Standard Treatment Regimen Dosages

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

Daily doses of TB drugs are given in Table 7.2. To further facilitate standardisation, the daily dosage is standardised for 3 weight bands. The following fixed-dose combination tablets are available for adults:

<table>
<thead>
<tr>
<th>Table 7.3: Fixed dose combination tablets available for adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHZE (150,75,400,275mg)</td>
</tr>
<tr>
<td>RH(150,75mg)</td>
</tr>
<tr>
<td>RH(150,150mg)</td>
</tr>
<tr>
<td>RH(300,150mg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 7.4: Regimen 1 (New Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment body weight</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>30-37 kg</td>
</tr>
<tr>
<td>38-54 kg</td>
</tr>
<tr>
<td>55-70 kg</td>
</tr>
<tr>
<td>30-37 kg</td>
</tr>
<tr>
<td>38-54 kg</td>
</tr>
<tr>
<td>55-70 kg</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>R-Rifampicin, H-Isoniazid, Z-Pyrazinamide, E-Ethambutol</td>
</tr>
</tbody>
</table>

R- Rifampicin, H- Isoniazid, Z- Pyrazinamide, E- Ethambutol
Table 7.5: Regimen 2 (Retreatment Cases)

<table>
<thead>
<tr>
<th>Pre-treatment body weight</th>
<th>Intensive Phase</th>
<th>Intensive Phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZE 7 days a week &amp; streptomycin 5 days a week for 2 months.</td>
<td>RHZE 7 days a week for 1 month</td>
<td>RHZE 7 days a week for 5 months</td>
</tr>
<tr>
<td></td>
<td>RHZE (150,75, 400,275)</td>
<td>Streptomycin (g) *</td>
<td>RHZE (150,75,400,275)</td>
</tr>
<tr>
<td>30-37 kg</td>
<td>2 tabs 0.5</td>
<td>2 tabs 0.5</td>
<td>2 tabs 2 tabs</td>
</tr>
<tr>
<td>38-54 kg</td>
<td>3 tabs 0.75</td>
<td>3 tabs 0.75</td>
<td>3 tabs 2 tabs</td>
</tr>
<tr>
<td>55-70 kg</td>
<td>4 tabs 1.0</td>
<td>4 tabs 1.0</td>
<td>2 tabs 3 tabs</td>
</tr>
<tr>
<td>&gt;71 kg</td>
<td>5 tabs 1.0</td>
<td>5 tabs 1.0</td>
<td>2 tabs 3 tabs</td>
</tr>
</tbody>
</table>

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

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

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

7.5 Side-Effects Of TB Drugs And Their Management

7.5.1 Isoniazid (H)

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

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

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

Adverse effects:
Gastro-intestinal: nausea, anorexia and mild abdominal pain; diarrhoea occurs less frequently. Cutaneous reactions: mild flushing and itchiness of the skin.
Hepatitis: This is uncommon unless the client has a history of liver disease or alcoholism. Serious side effects like influenza syndrome and shock may occur in clients who take the medicine intermittently instead of daily. Stop the treatment and refer the client. The client should be warned that rifampicin colours the urine, sweat and tears pink (urine looks orange-pink).

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

7.5.3 Streptomycin (S)

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

Contra-indications:
Do not give streptomycin to client above 65 years, to pregnant women or to young children. Older people (>65 years) have reduced renal function and should not be given streptomycin. Do not give to clients with existing renal disease, as it will further impair renal function.

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

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

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

Contra-indication:
Ethambutol should not be given to children under the age of 8 years who are unable to tell you that they are losing their sight. The client should be warned about the possible changes in vision and informed to report any changes in the eyesight.

7.5.5 Pyrazinamide (Z)

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

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

7.5.6 Pyridoxine

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

7.6 Symptom-Based Approach To The Management Of Side-Effects

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

8 Monitoring The Response To Treatment

All clients with bacteriological confirmation of pulmonary tuberculosis should have bacteriological as well clinical monitoring to assess their response to treatment:

- Clients with smear positive PTB are monitored by sputum smear examination
- Clients with smear negative, culture positive PTB are monitored by sputum smear and culture examination
- Clients with EPTB and those in whom there has been no confirmed bacteriological diagnosis, response to treatment are assessed through clinical monitoring.

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

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

8.1 New Cases

8.1.1 New Smear-Positive Cases

Response to treatment should be monitored by sputum smear examination. Two sputum specimens should be collected for smear examination at each time point:
- One week before the end of the 2 month intensive phase of treatment (i.e. at 7 weeks), to evaluate smear conversion
- At the end of 5 months of treatment, to evaluate treatment outcome.
There should be no interruption to treatment whilst smears are evaluated. Negative sputum smears indicate good treatment progress. At the end of the second month of treatment, most clients will have negative sputum smears and be able to start the continuation phase of treatment. If a client has a positive smear at this time, it indicates one of the following:
Most frequently, that the initial phase of therapy was poorly supervised and that client’s adherence to treatment was poor.
Sometimes, that there is a slow rate of progress with smear conversion. For example, when a client has extensive cavitations and a heavy initial bacillary load.
Rarely, that the client may have drug resistant TB that does not respond to first line drugs.

Whatever the reason, if either of the sputum smears are positive at the end of the second month, the intensive phase with four drugs is prolonged for one month, after which the smears are repeated and the continuation phase of treatment with two drugs is started.
If smears are positive at 2 months and there is no bacteriological improvement (e.g. 2+ smears becoming 1+) or no clinical improvement, a sputum culture and susceptibility should also be done. In clients in whom the continuation phase has been extended for a 3rd month, two sputum smears are repeated at the end of 3 months.
If the client is still positive at the end of the third month, a sputum culture should be done for susceptibility testing.

**If 2 or 3-month susceptibility test shows MDR TB, the client should be recorded as a treatment failure and referred immediately for MDR treatment.**

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

8.1.2 New Smear-Negative, Culture-Positive Cases

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

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

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

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

8.2 Retreatment Cases

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

8.2.1 Retreatment Smear-Positive Cases

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

There should be no interruption to treatment whilst smears are evaluated. Negative sputum smears indicate good treatment progress. If the smears are negative at the end of the intensive phase, the client is started on the continuation phase of treatment.

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

**Treatment outcome:**
If the client has negative smears at 7 months and had negative smears on at least one previous occasion, the client is discharged as cured after 8 months of treatment
If the client has shown susceptibility to the first line drugs and the sputum smear is still or becomes positive at 7 months, the client is categorised as a treatment failure and referred for management of chronic TB.
8.2.2 Retreatment Smear-Negative, Culture-Positive Cases

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

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

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

8.3 EPTB And Smear-Negative, Culture-Negative Cases

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

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

New Smear-Positive PTB

At 7 weeks: Take 2 sputum smears

- Both Negative
  - Commence continuation phase of treatment with daily RH after 2-month intensive phase complete

- One / Both Positive
  - Continue daily RHZE for 3rd month:
    - If no clinical or bacteriological improvement check culture and sensitivity
  - Repeat smears at 3 months and commence continuation phase of daily RH

- Negative
  - Resist
  - Refer MDR

- Positive
  - Sensitive

At 5 months: Take 2 sputum smears

- Negative: Discharge as cure when 6 months treatment completed
- Positive: Register as treatment failure and commence Regimen 2

New Smear-Negative, Culture-Positive PTB

At 7 weeks: Take 2 sputum smears

- Two Negative Smears
- One Positive Smear
- Two Positive Smears

- Two Negative Smears
  - Commence continuation phase of treatment with daily RH after 2-month intensive phase complete

- One Positive Smear
  - Check culture and sensitivity
  - Positive smear / culture:
    - Register as treatment failure and commence Regimen 2
  - Negative:
    - Discharge as cure when 6 months treatment completed

- Two Positive Smears
  - Register as a treatment failure.
  - Start client on the intensive phase of Regimen 2 with daily RHZES
    - Streptomycin 5 days per week

At 5 months take 2 sputa: 1 for smear and 1 for smear and culture
8.5 Monitoring Algorithm For Retreatment PTB Adults

- **Retreatment Smear Positive PTB**
  - At 11 weeks: Take 2 sputum smears
    - **Negative**: Commence continuation phase of treatment with daily RHE
    - **Positive**: Repeat smears at 4 months and commence continuation phase with RHE
      - **Negative**: Continue daily RHZE for 4th month: If no clinical or bacteriological improvement repeat culture and sensitivity
      - **Positive**: Refer MDR
    - **Resistant**: Check culture and sensitivity
    - **Sensitive**: Discharge as cure when 8 months treatment completed
  - At 7 months: Take 2 sputum smears
    - **Negative**: Discharge as cure when 8 months treatment completed
    - **Positive**: Register as treatment failure and refer to specialist

- **Retreatment Smear-Negative, Culture Positive PTB**
  - At 11 weeks: Take 2 sputum smears
    - Two Negative Smears
    - One Positive Smear
    - Two Positive Smears
      - **Repeat 3rd smear**: Commence continuation phase of treatment with RHE
        - **Negative**: Discharge as cure when 8 months treatment completed
        - **Positive**: Register as a treatment failure. Refer to specialist
    - **Negative**: Discharge as cure when 8 months treatment completed
    - **Positive**: Register as treatment failure and refer to specialist

At 7 months take 2 sputa: 1 for smear and 1 for smear and culture
9  Adherence To Treatment

The public health priority of the NTCP is to cure smear-positive cases, while preventing the emergence of drug resistance. Ensuring good adherence to treatment is necessary to achieve this priority. TB is curable if clients take a complete and uninterrupted course of the appropriate drug therapy. However, poor adherence to TB medication is a common problem. Treatment interruption presents a problem for clients, for their family and community and for the health care workers caring for them. The consequences of inadequate and incomplete treatment are serious:
- Prolonged illness and disability for the client
- Infectiousness of the client causing continued TB transmission in the community
- Development of drug resistant TB
- The possibility of death.

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

- **Social and economic factors** such as extreme poverty, poor support networks, unstable living circumstances, substance abuse and beliefs about TB and its treatment
- **Health system factors** such as poor health infrastructure, poorly trained or supervised health care workers, low levels of accountability of health staff, poor relationships with clients and inadequate development of community based support for clients
- **Client related factors** such as stigma, depression, disempowerment, and poor knowledge about TB and the efficacy of treatment
- **Therapy related factors** such as the complex treatment regimens, large pill burden, adverse effects of medication and long treatment duration.

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

9.1  Adherence

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

Promoting good adherence is more effective than spending time and resources on defaulter tracing. The basic approach to supporting adherence is to facilitate access to treatment, to simplify treatment and to ensure that services are client-centred and as convenient for the client as possible by:
- Providing laboratory tests for diagnosis and TB drugs free of charge.
- Reducing the time and cost to the client to obtain treatment
- The use of fixed dose combination tablets and blister packs to simplify treatment
- Being attentive to the client’s needs and providing other social and medical services as required
- Providing quality, efficient attention
- Choosing with the client the most convenient time and place for direct observation of treatment
Convenience to the client must be balanced with the assurance of regular drug intake. Close monitoring of adherence gives the client the best chances of cure.

9.2 What Is Directly Observed Treatment (DOT)?

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

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

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

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

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

9.3 Applying DOT To Fit Clients' Needs

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

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

9.3.1 Clinic DOT

Clients who live close to a clinic should be encouraged to take treatment at the clinic if this is convenient for the client. During the first two months of Regimen 2, all clients require intra-muscular streptomycin and should therefore receive DOT at the clinic.
The following measures are required to ensure effective clinic DOT:
Daily medication collected through fast-tracks that reduce waiting times
Recording of daily doses taken on client-held green cards
Regular updating of blue clinic folders
Systems to identify clients who did not present for DOT on that day and to trace and recall them rapidly
Pill containers with tablets or blister pack cut-outs provided on Fridays for medication required on the weekend
Responsibility allocated to a family member to observe and sign the green card for doses taken on weekends
A system to identify clients presenting for DOT who are also due for sputum collection

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

9.3.2 Workplace DOT

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

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

The treatment supporter in the workplace could be an occupational health nurse, manager, supervisor, shop steward or other employee. Establishing workplace DOT requires:
Training of workplace treatment supporters
Establishing systems that allow treatment to be taken and monitored in privacy
Confidentiality to be ensured
Good communication with the clinic where the client is registered
Allocating time for clinic visits so that medication can be collected, sputa provided for monitoring the response to treatment and clinical evaluation undertaken.

9.3.3 Community DOT

Community DOT can contribute substantially to local TB Control Programmes. It has the advantage of being more accessible and convenient to clients. A TB client who has far to travel for treatment is less likely to adhere to treatment and community based DOT can be a viable alternative. In some areas, limited resources and high TB caseloads overwhelm clinics; using community-based DOT may be a more rational way to use these limited resources.
The treatment supporter can be an existing community health worker or a community member trained to provide DOT. Collaboration with other programmes (e.g. home-based care) allows the identification of staff that, with suitable training and supervision, can support TB clients.

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

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

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

9.3.4 The Role Of Family / Friends

Members of the client's family should be encouraged to provide support and encouragement to the client to complete treatment. Where possible, a family member or friend should be counselled about TB with the client at initiation of treatment, so that they have all the information necessary to help the client complete treatment.
In situations where a child or an elderly or infirm person is receiving TB treatment, family members have a far greater role to play and may be required to provide DOT. It is essential that these family members are adequately equipped through counselling and that they agree to monitor and record daily treatment and to contact the clinic if difficulties are experienced. Having a community health worker visit the family at regular intervals provides an opportunity to reinforce key messages and to review the record of treatment taken.

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

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

### 9.4 Strategies For Good Adherence

Achieving good adherence to TB treatment is an objective that has to be specifically planned for, including the following aspects:
- Education and counselling of clients
- Adherence planning
- Developing and monitoring a treatment plan that is client specific
- Ensuring treatment availability at points most accessible to clients
- Adopting a caring, client-centred approach to treatment
- Involvement of family members / friends / community based organisations as part of the team supporting clients

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

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

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

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

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

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

9.4.1 Education And Adherence Counselling

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

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

It is important that the information provided to clients and their families on TB and its treatment is appropriately structured and emphasises the key messages:
Do not overload the client with too much information at one time.
Always check the clients understanding of information given.
Be clear about the length of the treatment regimen. Emphasise key milestones (such as sputa checks) during treatment and the importance of completing treatment.
Use educational materials that are culturally and linguistically appropriate for the client.
Assess the client's beliefs about TB and if possible integrate the beliefs into the treatment plan. Clarify client's questions and respond to these clearly.

Appropriately trained nurses, lay counsellors or community health workers can do adherence counselling.

9.4.2 The TB Support Team
Completing treatment and documenting a cure wherever possible is the joint responsibility of health workers, TB clients and communities. In sharing responsibility for treatment outcomes, the roles and responsibilities of the TB support team need to be clarified (see Table 9.1).

Building a good relationship between members of the team and the client can help improve adherence. This can be achieved through:
- Creating a sense of partnership between the TB support team, the client and their family
- Emphasising the importance of the client (and family) taking responsibility for treatment, supported by health care workers
- Giving the client adequate time at each visit
- Treating clients with respect and consideration
- Being positive; not intimidating or frightening the client
- Addressing any anxieties the client may have
- Understanding the client’s cultural beliefs and values.

<table>
<thead>
<tr>
<th>Table 9.1: Roles and Responsibilities of the TB Support Team</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB Client</strong></td>
</tr>
<tr>
<td>Take their tablets as prescribed</td>
</tr>
<tr>
<td>Report side-effects to the treatment supporter or clinic nurse</td>
</tr>
<tr>
<td>Return to the clinic for scheduled visits</td>
</tr>
<tr>
<td>Bring sputum specimens to the clinic for testing at the required times</td>
</tr>
<tr>
<td>Provide feedback to the team of any problems that they experience</td>
</tr>
<tr>
<td>Inform treatment supporter and clinic staff if they are going away and make plans for taking medication whilst away</td>
</tr>
<tr>
<td>Take responsibility for completing their treatment</td>
</tr>
<tr>
<td><strong>Family / Friend:</strong></td>
</tr>
<tr>
<td>Provide emotional support to the client</td>
</tr>
<tr>
<td>Encourage/remind client to take their tablets daily</td>
</tr>
<tr>
<td>Supervise treatment on the weekends, or daily if required, and record doses in the client-held green card</td>
</tr>
<tr>
<td>Remind client to bring sputum specimens to the clinic for testing at the required times</td>
</tr>
<tr>
<td>Motivate client to complete the full course of treatment</td>
</tr>
<tr>
<td>Report problems to the clinic</td>
</tr>
<tr>
<td><strong>Nurse:</strong></td>
</tr>
<tr>
<td>Provide basic information on TB</td>
</tr>
<tr>
<td>Initiate TB treatment and explain how to take the tablets</td>
</tr>
<tr>
<td>In consultation with client, allocate to DOT that is most suitable for them</td>
</tr>
<tr>
<td>Provide daily treatment at the clinic for all clients for a minimum of 2-3 weeks and for those clients receiving Clinic DOT thereafter</td>
</tr>
<tr>
<td>Keep a record of where all clients registered at the facility are receiving DOT</td>
</tr>
<tr>
<td>Complete clinical records: clearly indicate when sputa are due; maintain daily records in blue clinic and green client-held cards</td>
</tr>
<tr>
<td>Update the TB register</td>
</tr>
<tr>
<td>Assess clients on a scheduled basis, monitor response to treatment, encourage treatment completion</td>
</tr>
<tr>
<td>Provide monthly treatment to the client or treatment supporter</td>
</tr>
<tr>
<td>Get feedback from treatment supporters on clients receiving community DOT</td>
</tr>
<tr>
<td>Arrange transfer of clients moving to another area</td>
</tr>
<tr>
<td>Arrange tracing of clients who have defaulted treatment</td>
</tr>
</tbody>
</table>
Treatment supporter
If possible, visit clients commencing treatment at their homes: assess and refer other suspects and contacts to the clinic; identify problems in the household that might affect adherence and report these to the clinic; confirm the clients address
Keep clients’ TB tablets in a safe place
Meet with clients on a daily basis (including over weekends if possible) and supervise their treatment
Complete the client-held green card to record doses taken
Ensure that clients have collected their monthly medication
Provide support to TB clients and their families
Motivate TB clients to complete their treatment
Remind TB clients to bring their sputa to the clinic for testing at the appropriate times
Provide regular feedback to the clinic on their clients
Trace clients who have interrupted treatment
Create awareness in the community around TB and HIV

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

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

9.5.1 Minimise The Duration Of Treatment Interruption

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

9.5.2 Managing Treatment Interruption

The management of clients who have interrupted treatment is complex and takes into consideration multiple variables including their immune status, degree of remission of the disease with the previous treatment and drug susceptibility. A simplified decision tree is suggested in table 9.2.
### Table 9.2: Management of Treatment Interruption

#### Interruption for less than one month
- Trace client
- Address the cause of interruption
- Continue treatment and prolong it to compensate for missed doses

#### Interruption for one to two months

<table>
<thead>
<tr>
<th>Smears negative or EPTB</th>
<th>One or more smears positive: Send sputum for culture and sensitivity</th>
<th>Continue treatment and prolong it to compensate for missed doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trace client</td>
<td>Address the cause of interruption</td>
<td>Continue treatment while waiting for</td>
</tr>
<tr>
<td></td>
<td>Do 3 sputum smears</td>
<td>Treatment received:</td>
</tr>
<tr>
<td></td>
<td>Continue treatment while waiting for</td>
<td>More than 5 months</td>
</tr>
</tbody>
</table>

#### Treatment received: Less than 5 months
- Regimen 1: Start Regimen 2
- Regimen 2: Treat until culture & sensitivity available & refer appropriately

#### Treatment received: More than 5 months
- Regimen 1: Start Regimen 2
- Regimen 2: Refer (may evolve to chronic TB)

#### Interruption for two months or more (defaulter)

<table>
<thead>
<tr>
<th>Smears negative or EPTB</th>
<th>One or more smears positive: Send sputum for culture and sensitivity</th>
<th>Clinical decision on whether to: continue or restart or have no further</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trace client</td>
<td>Address the cause of interruption</td>
<td>Regimen 1</td>
</tr>
<tr>
<td></td>
<td>Do 3 sputum smears</td>
<td>Start Regimen 2</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Regimen 2</td>
</tr>
</tbody>
</table>

- Regimen 2: Refer (may evolve to chronic TB)
10 Treatment Regimens In Special Circumstances

10.1 Pregnant Women

Untreated tuberculosis represents a far greater hazard to a pregnant woman and the foetus than does treatment of the disease. It is important before starting TB treatment to ask a woman if she is pregnant. Most TB drugs are safe for use in pregnant women. The exception is streptomycin, which is ototoxic to the foetus and should not be used in pregnancy.

10.2 Breastfeeding Women

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

If the mother is infectious (both smear-positive and smear-negative PTB) the child should be given prophylactic isoniazid (5mg/ kg/ daily) for six months and continue breastfeeding. BCG vaccination should be postponed until the end of isoniazid prophylaxis.

10.3 Women Using Contraceptives

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

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

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

10.4 Liver Disorders

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

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

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

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

10.6 Acute Hepatitis

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

10.7 Renal Failure

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

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

10.8 HIV / AIDS

Co-administration of rifampicin with any of the protease inhibitors (ritonavir, indinavir, and nelfinavir) or non-nucleoside reverse transcriptase inhibitor (nevirapine) is contraindicated. These drugs may inhibit or induce cytochrome P-450 isoenzymes, thus altering the serum concentration of rifampicin.

Rifampicin induces the cytochrome P-450 and may substantially decrease blood levels of the antiretroviral drugs resulting in the potential development of resistance. If a protease inhibitor or non-nucleoside reverse transcriptase inhibitor is to be started after giving rifampicin, then at least two weeks should elapse after the last dose of rifampicin. This time gap is necessary for reduction of the enzyme inducing activity of rifampicin prior to commencement of antiretroviral drugs.

Refer to Chapter 12 for additional issues relating to TB-HIV co-infection.
11 TB In Children

There are 2 stages of tuberculosis to be differentiated in children:
TB Infection - About 30% of children in contact with an infectious case of TB (smear or culture positive PTB) will become infected with TB, but will not necessarily develop symptoms and disease.
TB Disease – About 10% of children who have been infected with TB will develop symptoms and progress to TB disease.

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

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

BCG provides children with a certain degree of protection against serious forms of tuberculosis especially TB meningitis and disseminated TB. In most Expanded Programmes of Immunization, BCG is given soon after birth. There is no value in revaccinating with BCG and this should be discouraged. Asymptomatic HIV infected babies should all receive BCG. However, BCG should be withheld in a child with symptomatic HIV infection as it can lead to disseminated BCG disease.

11.1 Tuberculous Infection

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

The risk of infection is increased with:
Long duration of exposure to an infectious case.
High intensity of exposure – smear-positive cases are the most infectious, smear-negative, culture-positive cases are less infectious and extrapulmonary TB cases are least infectious.
Close exposure – where the mother or caregiver has active TB.
Young children – those under the age of 5 and particularly those under 2 years of age.
HIV positive children

Drug resistant TB is as infectious as drug sensitive TB. Children exposed to drug resistant TB are therefore have the same risk of being infected as children exposed to drug sensitive TB.
11.1.1 Diagnosis Of Tuberculous Infection

A child that has been infected by TB develops a positive tuberculin skin test (TST). It takes between 6 weeks and 3 months for a positive TST to develop after exposure. The TST measures the hypersensitivity to tuberculin purified protein derivative (PPD). A positive tuberculin test, measured after 48-72 hours, does not indicate the presence or extent of tuberculosis disease; it only indicates TB infection.

There are different types of TSTs but the Mantoux is regarded as the best. See section 4.2.5.1 for information on how to do the Mantoux test. The Mantoux skin test is positive when the diameter of skin induration is 10mm or greater. In HIV infected children the TST is less likely to be positive and a Mantoux result of 5 mm or greater is regarded as positive.

Any child, under 5 years of age or HIV infected, with a positive Mantoux skin test, has been infected with TB. If active disease has been excluded, the child should receive a course of INH prophylaxis to prevent the development of TB disease (whether there is known contact with an index case or not), unless the child has had previous TB.

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

Children with tuberculous infection are asymptomatic. Most children have immunity that is strong enough to prevent the infection from developing further, but a few will progress to TB disease.

11.1.2 Contact Screening

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

All children under 5 years of age in close contact with an infectious case of TB, who are asymptomatic for TB, should receive a course of INH prophylaxis to prevent the development of TB disease. The likelihood of TB disease in these children is high and a Mantoux skin test is not required prior to commencing INH prophylaxis.

11.1.3 Management Of Children With Tuberculous Infection

After exclusion of TB disease, INH prophylaxis should be given to:
All children in under 5 years of age in contact with an infectious case of TB
All children under 5 years of age with a positive Mantoux (10 mm in diameter or greater)
All HIV-positive children, irrespective of their age, with a positive Mantoux (5 mm in diameter or greater)
The recommended regimen is isoniazid (INH) 5 mg/kg/day for 6 months.

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

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

INH prophylaxis is not recommended in asymptomatic child contacts of infectious MDR TB cases. The only chemoprophylaxis regimens to have been studied are based on isoniazid and, to a lesser extent, rifampicin. Since by definition MDR TB is resistant to both of these drugs, it is unlikely that use of these drugs will prevent active disease in those with latent infection caused by MDR TB. Close contacts of MDR TB clients should receive careful clinical follow-up for a period of at least two years. These children should ideally be referred to the expert MDR centre in the Province. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR TB is recommended. On the basis of the currently available evidence, WHO does not recommend second-line drugs for chemoprophylaxis in MDR TB contacts.

11.1.4 The Baby Born To A Mother With Tuberculosis

A baby born to a mother diagnosed with TB in the last two month of pregnancy needs to be carefully managed as the infant is at risk for developing severe disease.

The baby should not receive BCG at birth. The baby requires either full TB treatment if TB is diagnosed or prophylaxis with INH if asymptomatic.

If the baby is symptomatic:

The baby needs to be referred to a central hospital for evaluation to exclude TB

If the baby has TB, the baby should receive a full course of TB treatment with regimen 3. TB treatment should be started in a referral centre to ensure correct dosages.

If the baby is asymptomatic:

The baby needs preventive therapy (isoniazid 5 mg/kg/day) for 6 months.

The baby should not initially receive a BCG vaccination.

If the baby continues to be asymptomatic the BCG is administered after completion of the preventive treatment (unless the child is symptomatic for HIV)

If tuberculin is available, the child can be tested after 3 months of INH treatment and, if non-reactive and the mother has become sputum smear-negative, the INH can be stopped and the child given BCG vaccination.

The mother can continue to breastfeed. Although anti-tuberculosis drugs are secreted in breast milk, the concentrations are very low and do not affect the baby. The low concentrations however, are not effective preventive treatment.

11.2 TB Disease

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

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

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

Young children (under 5 years of age), HIV-infected children and malnourished children not only have an increased risk of infection but also an increased risk of developing serious forms of TB like TB meningitis and disseminated or military TB.

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

11.3 Clinical Presentation Of TB

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

History and symptoms of TB disease:
Contact with a smear and/or culture positive pulmonary TB case, especially if there is close contact (family member, person living in the same household or care-giver). Other information about the source case that is important is their response to treatment, as failure to respond might indicate exposure to a drug resistant source case.
The commonest symptoms are chronic unremitting cough, fever and weight loss.
Chronic cough is a cough that has been present for more than 14 days and that is not improving, especially if the child fails to respond to a course of antibiotics (amoxycillin)
Fever of greater than 38°C for 14 days after common causes like malaria or pneumonia have been excluded.
Children with weight loss, especially when documented on the “Road to Health” chart should be investigated for TB. A child in a nutrition programme who fails to gain weight should also be investigated for TB.

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

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

11.4 Diagnosis Of TB

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

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

Many children who present with chronic symptoms suggestive of TB may not have been tested for HIV infection. An HIV test is important in the diagnosis of childhood TB. As with adults, the standard of care is to provide HIV counselling to all child TB suspects and their parents/caregivers. Families should be given the necessary information about HIV to help make an informed choice about an HIV test. The HIV test should be strongly recommended and consent for testing sought from parents or the legal guardian of children younger than 14 years of age.

In children younger than 12 months, a PCR test should be used to diagnose HIV infection. In children 12-18 months of age, rapid tests can be used for screening. A negative rapid test excludes HIV. A positive rapid test could be due to maternal antibodies, sometimes present until 18 months of age. PCR tests should be done to diagnose HIV in those with positive rapid tests. In children over 18 months of age, rapid tests can be used to diagnose HIV.

The diagnosis of TB disease in HIV-positive children is exactly the same as for HIV-negative children except that:
- The symptoms of TB can be confused with the symptoms of HIV disease
- The chest x-ray is more difficult to interpret

**Any child presenting with a history of exposure to an infectious TB case or with confirmed infection (positive Mantoux) is regarded as a TB case if:**
- There are symptoms of TB
  - and
- An abnormal chest x-ray suggestive of TB

**Any child presenting with symptoms of TB is regarded as a case of TB if there is:**
- History of exposure to an infectious TB case or confirmed infection (positive Mantoux)
  - and
- An abnormal chest x-ray suggestive of TB
The diagnosis can be confirmed by collecting a gastric aspirate or sputum for smear and culture. In areas where a chest x-ray is not available a case of TB can be diagnosed in children presenting with symptoms of TB and a history of exposure to an infectious TB case or a positive Mantoux skin test.

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

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

11.4.1 Chest X-rays

Chest x-rays need to be of good quality and the results depend on the expertise of the person reading them. The most common radiological signs of TB in children are:
An enlarged hilar region of the lung or a widened mediastinum due to enlarged hilar or mediastinal glands. Compression of the airways due to the enlarged lymph glands may be observed. The enlarged lymph glands can occlude the airway resulting in collapse of a lobe.
The parenchymal lesion can enlarge causing widespread opacification in a segment or lobe of the lung.
Acute dissemination causes widespread fine millet-sized (1-2 mm) lesions (miliary TB). Pleural effusions may occur in children older than six years.

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

11.4.2 Smear And Culture

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

However, older children (6 years or older) should be able to produce sputum and sputum samples should be sent for smear and/or culture as per adult diagnostic algorithms (See Chapter 4).

11.4.3 Diagnosis Of Extra-pulmonary TB

The commonest forms of extra-pulmonary TB are
Lymph node involvement
Pleural effusion
TB meningitis
Disseminated TB (military TB).
11.4.4 Diagnosis Of Lymph Node TB

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

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

11.4.5 Diagnosis Of TB Meningitis

TB meningitis is a very serious form of TB in children. Complications include obstruction of cerebrospinal fluid (CSF) flow, hydrocephalus, inappropriate anti-diuretic hormone secretion, hemi-

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

or quadriplegia, convulsions, deafness, blindness and mental retardation.

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

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

Investigations:
Lumbar puncture - CSF has raised protein, low glucose, low chloride, predominantly lymphocytes; the gram stain is negative and acid fast bacilli are seldom found
The Mantoux test can be positive or negative and chest x-ray may be normal or abnormal.

TB meningitis is a very serious form of TB and should not be treated at a primary health care facility but should be urgently referred to a higher health care level where such children can be managed.

11.5 Management Of A Child With TB

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

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

All children on treatment for TB must be recorded in the TB registers and should be reported to the NTCP as part of the routine quarterly cohort reports. The same case definitions apply to both adults and children (See Chapter 5). It is particularly important to document the age of the child in the register, because children are reported to the NTCP in two age groups:
Children 0-4 years (up to 4 years and 11 months)
Children 5-14 years

As with adults, the standard of care is to provide HIV counselling to all children with TB and their parents/caregivers. Families should be given the necessary information about HIV to help make an informed choice about an HIV test. The HIV test should be strongly recommended and consent for testing sought from parents or the legal guardian of children younger than 14 years of age (see section 11.4).

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

11.5.1 Directly Observed Treatment Short Course

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

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

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

All children with severe forms of tuberculosis (meningitis, spine, peritonitis, miliary, skeletal) and
those suspected of having MDR TB (in contact with MDR case or not responding to first line
therapy) should be referred for opinion on the management. In these children the drug therapy may
be given for a longer time but still through directly observed therapy (DOT). Children with severe
disease are also treated with 4 drug regimens. Ethambutol may be replaced by streptomycin.
Streptomycin should always be used when the child has disseminated tuberculosis or TB
meningitis.

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

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

Table 11.1: Regimen 3 Dosages

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Intensive Phase (2 months) Treatment given 7 days a week</th>
<th>Continuation phase (4 months) Treatment given 7 days a week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZ 60,30,150</td>
<td>RH</td>
</tr>
<tr>
<td>3-4 kg</td>
<td>½ tab</td>
<td>½ tab</td>
</tr>
<tr>
<td>5-7 kg</td>
<td>1 tab</td>
<td>1 tab</td>
</tr>
<tr>
<td>8-9 kg</td>
<td>1½ tabs</td>
<td>1½ tab</td>
</tr>
<tr>
<td>10-14 kg</td>
<td>2 tabs</td>
<td>2 tabs</td>
</tr>
<tr>
<td>15-19 kg</td>
<td>3 tabs</td>
<td>3 tabs</td>
</tr>
<tr>
<td>20-24 kg</td>
<td>4 tabs</td>
<td>4 tabs</td>
</tr>
<tr>
<td>25-29 kg</td>
<td>5 tabs</td>
<td>5 tabs</td>
</tr>
<tr>
<td>30-35 kg</td>
<td>6 tabs</td>
<td>6 tabs</td>
</tr>
</tbody>
</table>

11.5.3 Regimens 1 And 2

Children with smear positive or cavitatory TB (usually about 5% of cases) should be treated with
Regimen 1, with 4 drugs (RHZE) in the intensive phase and 2 drugs (RH) in the continuation phase,
as with adults. The dosage of ethambutol used in children is 20 mg/kg daily (range 15-
25mg/kg/day).

Children under 8-years of age, who require retreatment and who are smear negative, are treated
with Regimen 1.
Children above 8 years of age and adolescents should be treated like adult clients with Regimen I for newly diagnosed and Regimen 2 for retreatment cases and treatment failures. Dosages for these regimens are calculated on the child’s weight.

11.5.4 The Use Of Steroids In Children With TB

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

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

11.5.5 Response To Therapy

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

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

The chest x-ray is a poor indicator of response as the hilar and mediastinal lymph glands can enlarge as a result of the improvement in the immunity of the child. Therefore follow-up chest x-rays are not routinely required in children, particularly as many children will have a slow radiological response to treatment. After 6 months only approximately 66% of children who had abnormal chest x-rays at the beginning of treatment, will have normal chest x-rays. In an asymptomatic child a routine chest x-ray is not indicated during or at the end of therapy.

A child who is not responding to TB treatment should be referred for further assessment and management. These children may have drug-resistant TB, an unusual complication of pulmonary TB, other causes of lung disease, or problems with treatment adherence.

Adolescents and younger children with smear-positive PTB should be followed through the same routine as adult clients. Repeat sputum examinations should be done at 2 and at 5 months treatment for new cases of TB and at 3 and 7 months for retreatment cases to evaluate the response to treatment (See Chapter 8).

11.5.6 Immune Reconstitution Syndrome (IRS)

Temporary exacerbations of symptoms, signs or x-ray manifestations sometimes occur after beginning anti-TB therapy. This can simulate worsening disease, with fever, increased size of lymph nodes or tuberculomas. It is usually the result of immune reconstitution brought about by improved nutritional status, anti-TB treatment itself, or antiretroviral therapy in HIV-infected children.
Anti-TB treatment should be continued, though in some cases the addition of corticosteroids might be useful. If in doubt, refer the child to the next level of care for evaluation.

11.5.7 Adverse Events

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

However, the occurrence of liver tenderness, hepatomegaly, or jaundice should lead to investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs. Clients should be referred and screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver functions have normalized. An expert should be involved in the further management of such cases. If treatment for TB needs to be continued for severe forms of TB, non-hepatotoxic anti-TB drugs should be introduced (e.g. ethambutol, an aminoglycoside, and a fluoroquinolone).

Isoniazid may cause symptomatic pyridoxine deficiency, particularly in severely malnourished children and HIV-infected children on antiretroviral therapy (ART). Supplemental pyridoxine (5-10 mg/day) is recommended in:
- Malnourished children
- HIV-infected children
- Breastfeeding infants
- Pregnant adolescents.

11.6 MDR TB In Children

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

**Features in the index case suggestive of MDR TB**
- Index case remaining smear-positive after 3 months of treatment
- History of previously treated TB, treatment interruption or recurrence after treatment

**Features in a child suspected of having drug resistant TB**
- Contact with a known case of MDR TB
- Child not responding to the TB treatment regime
- Child with recurrence of TB after completing TB treatment

The diagnosis and treatment of drug resistant TB in children is complex and should be done at provincial expert centres.

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

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

11.7.1 TB Diagnosis In HIV-Positive Children

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

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

There is a risk both that TB will be over-diagnosed in children and they will be treated unnecessarily; alternately that TB may be missed, and therefore an opportunity to treat an HIV-infected child for a curable disease will also be missed. LIP is the most difficult condition to distinguish from TB, due to radiological similarities. Bacteriologically confirmed TB can occur in children with an underlying diagnosis of LIP, bronchiectasis, or any other lung infection.

In spite of the difficulties TB (if present) can be diagnosed in the great majority of HIV infected children. Due to the overlap of symptoms and radiological changes tuberculosis will be more likely to be over-diagnosed in HIV infected children especially in those with AIDS.

The approach to diagnosing TB in HIV-positive children is essentially the same as for HIV-negative children:

Any child presenting with a history of exposure to an infectious TB case or with confirmed infection (positive Mantoux) is regarded as a TB case if:
There are symptoms of TB
and
An abnormal chest x-ray suggestive of TB
Any child presenting with symptoms of TB is regarded as a case of TB if there is:

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

The diagnosis can be confirmed by collecting a gastric aspirate or sputum for smear and culture. In areas where a chest x-ray is not available a case of TB can be diagnosed in children presenting with symptoms of TB and a history of exposure to an infectious TB case or a positive Mantoux skin test.

Table 11.2: World Health Organisation Staging Of Children With Confirmed HIV Infection

<table>
<thead>
<tr>
<th>Stage One</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Persistent Generalised Lymphadenopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Two</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatosplenomegaly</td>
<td>Papular pruritic eruptions</td>
</tr>
<tr>
<td></td>
<td>Seborrhoeic dermatitis</td>
</tr>
<tr>
<td></td>
<td>Extensive human papilloma virus infection</td>
</tr>
<tr>
<td></td>
<td>Extensive molluscum contagiosum</td>
</tr>
<tr>
<td></td>
<td>Fungal nail infections</td>
</tr>
<tr>
<td></td>
<td>Recurrent oral ulcerations</td>
</tr>
<tr>
<td></td>
<td>Lineal gingival erythema (LGE)</td>
</tr>
<tr>
<td></td>
<td>Angular cheilitis</td>
</tr>
<tr>
<td></td>
<td>Parotid enlargement</td>
</tr>
<tr>
<td></td>
<td>Herpes zoster</td>
</tr>
<tr>
<td></td>
<td>Recurrent or chronic RTIs (otitis media, otorrhoea, sinusitis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Three</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate unexplained malnutrition not adequately responding to standard therapy</td>
<td></td>
</tr>
<tr>
<td>Unexplained persistent diarrhoea (14 days or more)</td>
<td></td>
</tr>
<tr>
<td>Unexplained persistent fever (intermittent or constant, for longer than one month)</td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis (outside neonatal period)</td>
<td></td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td></td>
</tr>
<tr>
<td>Acute necrotizing ulcerative gingivitis/periodontitis</td>
<td></td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td></td>
</tr>
<tr>
<td>Severe recurrent presumed bacterial pneumonia</td>
<td></td>
</tr>
<tr>
<td>Unexplained anaemia (&lt;8g/dl), and or neutropenia (&lt;1000/mm3) and or thrombocytopenia (&lt;50 000/mm3) for more than one month</td>
<td></td>
</tr>
<tr>
<td>Chronic HIV-associated lung disease including brochiectasis</td>
<td></td>
</tr>
<tr>
<td>Symptomatic lymphoid interstitial pneumonitis (LIP)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Four</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td></td>
</tr>
<tr>
<td>Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)</td>
<td></td>
</tr>
<tr>
<td>Chronic herpes simplex infection; (orolabial or cutaneous of more than one month’s duration)</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td></td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td></td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td></td>
</tr>
<tr>
<td>CNS toxoplasmosis (outside the neonatal period)</td>
<td></td>
</tr>
<tr>
<td>HIV encephalopathy</td>
<td></td>
</tr>
</tbody>
</table>
CMV infection (CMV retinitis or infection of organs other than liver, spleen or lymph nodes; onset after 1 month of age)
Extrapulmonary cryptococcosis including meningitis
Cryptosporidiosis
Isosporiasis
Disseminated non-tuberculous mycobacterial infection
Candidiasis of trachea, bronchi or lungs
Visceral herpes simplex infection
Acquired HIV-associated rectal fistula
Cerebral or B-cell non-Hodgkins lymphoma
Progressive multifocal leucoencephalopathy (PML)
HIV-associated cardiomyopathy or nephropathy

11.7.2 TB Treatment

TB in HIV-infected children should be treated with a six-month regimen as in HIV-uninfected children. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance, and alternative diagnoses should be investigated in children who are not improving on TB treatment.

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

11.7.3 General HIV Care for Co-infected Children

Once a child with TB has been diagnosed HIV-positive, it is the responsibility of TB staff to ensure that the child and family receives appropriate HIV-related care, including:
Counselling and social services support (eg. access to child support grants)
Clinical staging of disease, CD4%
Treatment of other concurrent opportunistic infections
Prophylaxis against other opportunistic infections (Cotrimoxazole)
Regular monitoring of growth and development
Nutritional supplements (including micronutrients)
Appropriate completion of the immunisation schedule
Evaluation for antiretroviral therapy
Referral for palliative care if required

11.7.4 Cotrimoxazole Prophylaxis

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

The recommended dosage for children is trimethoprim 6-8 mg/kg, sulphamethoxazole 20 mg/kg. Cotrimoxazole syrup contains trimethoprim/sulphamethoxazole 40/200mg and the recommended dosage is therefore 0.625 ml/kg (see table 12.3).
### Table 11.3: Cotrimoxazole Prophylaxis Dosing Schedule For Children

<table>
<thead>
<tr>
<th>Weight</th>
<th>Cotrimoxazole (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 kg</td>
<td>2.5 ml</td>
</tr>
<tr>
<td>5-9.9. kg</td>
<td>5 ml</td>
</tr>
<tr>
<td>10-14.9 kg</td>
<td>7.5 ml</td>
</tr>
<tr>
<td>15-21.9 kg</td>
<td>10 ml or 1 single (480mg) strength tablet</td>
</tr>
<tr>
<td>&gt;22 kg</td>
<td>15 ml or 1.5-2 single (480mg) strength tablets</td>
</tr>
</tbody>
</table>

#### 11.7.5 Antiretroviral Therapy

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

- Recurrent hospitalisations (>2 per year) or prolonged hospitalisation (> 4 weeks)
- WHO Clinical Stage 3 or 4 disease (See Table 11.2)
- CD% <20% for children under 18 months and <15% if over 18 months

Children with Pulmonary TB are classified as WHO Stage 3 and those with Extrapulmonary TB as WHO Stage 4.

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

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

**If a child presents with TB before starting ART:**

- A child who is Stage 3 can complete the TB treatment if the CD4 is >20% for children under 18 months and >15% if over 18 months
- In others, it is preferable to complete 2 months of TB treatment before starting ART
- The regimen used is stavudine, lamivudine and either ritonavir (if failed PMTCT, <3 years-old or <10kg in weight) or efavirenz.
- Monitor ALT monthly

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

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

- If child is on lopinavir/ritonavir or nelfinavir, switch to ritonavir
- If child is on nevirapine and is <3 years old or <10kg in weight switch to ritonavir
- If child is on nevirapine and is >3 years old and >10kg in weight switch to efavirenz
- If the child is unable to tolerate all drugs, in consultation with a specialist, ART may be interrupted
The development of TB in a child on ART could be due to immune reconstitution syndrome, a new TB infection, or failure of the ART regimen. TB treatment should be started without delay in these children.

Clinically significant drug interactions occur between the rifamycins, especially rifampicin, and some of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). The adverse events of the anti-TB drugs and the antiretroviral drugs are similar and can cause confusion as to which drugs need to be stopped. Rifampicin reduces the serum concentrations of most PIs by 20-80% and NNRTIs by between 20-60%.

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

12 TB And HIV/AIDS

12.1 Introduction

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

In the absence of HIV infection, only about 10% of people infected with M. tuberculosis get sick with TB during their lifetime. In people with HIV, about 50% will develop active TB disease at some stage, which translates to a ten fold increase in risk. Currently, about 55% of TB clients are co-infected with HIV in South Africa. The increased TB in persons living with HIV/AIDS poses an increased risk of TB transmission to the general community.

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

Three approaches can help to minimise the impact of TB on those with HIV:
- TB preventive therapy to reduce an individual client’s risk of developing TB
- Early, prompt diagnosis of TB through intensified case-finding
- Appropriate case management of TB including the provision of comprehensive HIV care to the co-infected

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

12.2 TB Preventive Therapy

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

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

To exclude TB, specifically ask about signs and symptoms of tuberculosis:
Cough for more than 2 weeks
Fever for more than 2 weeks
Drenching night sweats
Weight loss of greater than 1.5 kg in the past 4 weeks: weight should be measured at each clinic visit to document weight loss. A weight loss of more than 1.5 kg is an indicator to screen for TB.
Pleuritic chest pains or haemoptysis

All clients with 1 or more of the symptoms and signs must be investigated further for TB and are not eligible for TB preventive therapy, until TB is excluded. To screen for TB, follow the screening algorithm in section 4.4.

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

12.2.1 Eligibility For TB Preventive Therapy

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

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

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

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

12.2.2 When And How To Start TB Preventive Therapy

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

At the first visit:
The client is screened for TB symptoms. This is essential to exclude active tuberculosis. Specifically enquire about all of the signs and symptoms of TB. If symptomatic, the client should be investigated for TB.
If the client has no symptoms of TB, has not had TB in the last 2 years, does not have liver disease or alcoholism and is not eligible for ART, do a tuberculin (Mantoux) skin test:
Inject 2 units of tuberculin purified protein derivative PPD-RT23 or 5 units of PPD-S intradermally (between the layers of skin). It is important to ensure that the injection goes into and not under the skin.
Ask the client to return to the clinic in 48 – 72 hours to read the Mantoux skin test

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

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

12.3 Diagnosis Of TB In HIV-Positive Clients

Tuberculosis can occur at any point in the course of HIV infection. Pulmonary tuberculosis is the most common manifestation of tuberculosis in adults infected with HIV. The clinical pattern of tuberculosis correlates with the client's immune status:
If TB occurs in the early stages of HIV infection when immunity is only partially compromised, the features are more typical of post-primary TB.
As immune deficiency worsens, HIV-infected clients present with atypical pulmonary disease resembling primary TB, extra-pulmonary TB or disseminated disease.

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

<table>
<thead>
<tr>
<th>Features of PTB</th>
<th>Early HIV Infection</th>
<th>Late HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical picture</td>
<td>Often resembles post-primary TB</td>
<td>Often resembles primary TB</td>
</tr>
<tr>
<td>Sputum smear results</td>
<td>Often positive</td>
<td>Often negative</td>
</tr>
<tr>
<td>Chest X-ray appearance</td>
<td>Often cavities</td>
<td>Hilar lymphadenopathy, infiltrates,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no cavities. Can be normal.</td>
</tr>
</tbody>
</table>

Compared to other infections that develop when the CD4 counts falls below 250/mm³, TB develops when the CD4 count falls below 400/ mm³. This means that TB is one of the earlier infections to occur in an HIV-positive client; it may therefore happen that TB is diagnosed before HIV in co-infected clients.

12.3.1 Diagnosis Of Pulmonary Tuberculosis

Clinical features:
Generally there is no difference in clinical presentation of TB between HIV-positive and HIV-negative clients. However, among HIV-positive clients cough is reported less frequently, probably because there is less cavitation, inflammation and endobronchial irritation as a result of decreased cell-mediated immunity. Similarly, haemoptysis, which results from caseous necrosis of the bronchial arteries, is less common.

Sputum Microscopy and Culture:
Sputum microscopy is the cornerstone to diagnosis of TB even in high HIV-prevalence areas. All clients suspected of having TB should have two initial sputum specimens examined for acid-fast bacilli (AFB) as per diagnostic algorithm (section 4.4). HIV infected, smear-positive clients tend to excrete significantly fewer organisms per ml of sputum than HIV-negative clients, which can lead to AFB being missed if the appropriate number of sputum samples as well as high power fields are not examined by microscopy. In both new and retreatment clients in whom the first 2 smears are negative, a 3rd smear should be taken.
Sputum culture is the gold standard for TB diagnosis. Amongst those with previous TB, a sputum culture is done routinely. In an HIV-positive client with no previous TB and 2 initial negative smears, the 3rd specimen should be sent for both smear and culture. The diagnosis of smear-negative, culture-positive TB requires at least 3 sputum smears that are negative for AFBs and a positive sputum culture. The use of culture as part of the diagnostic algorithm substantially improves the diagnosis of TB in HIV-positive clients.

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

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

12.3.2 Extra-Pulmonary Tuberculosis

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

Presentation of extra-pulmonary TB is generally no different between HIV-positive and HIV-negative clients, however:
- HIV-related TB lymphadenopathy can occasionally be acute and resemble an acute pyogenic bacterial infection. Diagnosis can be made using simple techniques such as needle aspiration and examination of direct smears.
- In TB meningitis, the CSF may be completely normal in HIV-infected persons.
- Pericardial TB is not rare and may be diagnosed presumptively based on the characteristic balloon-shaped appearance of cardiac shadow on chest X-ray.
- Disseminated TB may be difficult to diagnose.

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

12.3.3 TB Recurrence

There are 2 possibilities for TB recurring after a previous cure:
- True relapse: relapse of Mycobacterium tuberculosis persisters not killed by anti-TB drugs.
- Re-infection: due to re-exposure to another source of infection.

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

Outbreaks of multi-drug resistant TB have been reported in clients with HIV infection in various countries. HIV itself does not cause multi-drug resistant TB, but it fuels the spread of this dangerous condition by increasing susceptibility to infection and accelerating the progression from infection to disease.

12.4 Treatment Of TB In HIV-Positive Clients

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

12.4.1 Response To Treatment

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

12.4.2 Side Effects To TB Drugs

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

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

12.4.3 Case Fatality

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

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

Common HIV-related infections (pneumonia, diarrhoea, fungal infections) cause considerable morbidity during treatment of HIV-infected TB clients and contribute to the increased case fatality rate. Clients should be provided with appropriate HIV care during TB treatment, to prevent and identify and treat these infections early.
12.5 Diagnosis Of HIV In TB Clients

The definitive diagnosis of HIV infection rests on a positive HIV test. The standard of care required in TB services is to provide HIV counselling to all TB clients. Clients should be given the necessary information about HIV to help make an informed choice about an HIV test. All clients should be strongly advised to have an HIV test and consent sought for testing. In children under 14 years of age with TB, parents or the legal guardian of the child should be counselled and asked to provide consent for the test. Ideally, the offer of an HIV test should take place soon after the initiation of TB treatment, as the morbidity and mortality of co-infected clients is highest in the first 2 months of treatment.

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

12.6 HIV Care For Co-infected Adult TB Clients

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

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

Components of HIV care to be provided to TB-HIV co-infected clients include:
WHO Clinical Staging (see Table 12.2)
HIV-positive clients with PTB are classified as at least WHO Stage 3. If the client has any other Stage 4 defining illness at present or in the past, they are classified as WHO Stage 4.
Clients with EPTB or MDR TB are classified as WHO Stage 4.
All WHO Stage 4 clients require antiretroviral therapy
WHO staging should be repeated when the client presents with any major new illness or on a regular basis
CD4 counts:
The CD4 count assesses the number of T-helper immune cells in the blood and is an indication of the level of immunosuppression
If the CD4 count is less than 200 cells/mm$^3$, refer the client for ART.
If the CD4 count is less than 50 cells/mm$^3$ the client urgently requires ART.
Repeat the CD4 count annually if it is greater than 350 cells/mm$^3$ and 6-monthly if between 200-350 cells/mm$^3$
As ART is commenced relatively late (CD4 count below 200 rather than below 350 as used in some countries) and the early morbidity and mortality in those with low CD4 counts is high, it is beneficial for the client to have an early CD4 count despite the fact that the CD4 count will recover during TB treatment
If the client has no history of or current WHO Stage 4 illness, and a CD4 count of more than 200 cells/mm$^3$, ART is not yet needed. Treat the client's TB; the need for ART should be reassessed on completion of TB treatment.
An RPR test
PAP smears for all HIV-positive women
Symptomatic screening for STI’s at every visit and syndromic management of STI’s
Reproductive health care with an emphasis both on effective contraception whilst on TB treatment and the use of condoms to prevent transmission of HIV and re-infection
Diagnosis and management of other opportunistic infections
Cotrimoxazole prophylaxis against opportunistic infections
Nutritional assessment and the provision of nutritional supplements
Social assessment:
Family circumstances and status of caregivers
Identification of orphans or vulnerable children
Applications for disability grants, child support grants or care dependency grants.
On-going counselling support
To assess how the client is dealing with their HIV status
To discuss disclosure and support available to the client
To emphasise messages about reducing re-infection and transmission through safer sexual practices
To reinforce good adherence to treatment

All HIV+ clients TB clients should be provided with holistic clinical care for both TB and HIV at clinical visits. This will help reduce morbidity and mortality of co-infected clients and help improve treatment outcomes. It is important to ensure that the clients discharged from the TB programme access on-going HIV care.
Table 12.2: World Health Organisation Clinical Staging For Adults

<table>
<thead>
<tr>
<th>Stage One</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute retroviral infection (seroconversion illness)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
</tr>
<tr>
<td>Persistent generalised lymphadenopathy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Two</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unintentional weight loss &lt; 10% of body weight</td>
<td></td>
</tr>
<tr>
<td>Minor mucocutaneous (e.g. seborrhoea, prurigo, fungal-nail infections, oral ulcers, angular cheilitis)</td>
<td></td>
</tr>
<tr>
<td>Herpes zoster within the last five years</td>
<td></td>
</tr>
<tr>
<td>Recurrent upper respiratory tract infection (e.g. bacterial sinusitis)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Three</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unintentional weight loss &gt; 10% of body weight</td>
<td></td>
</tr>
<tr>
<td>Chronic diarrhoea &gt; one month</td>
<td></td>
</tr>
<tr>
<td>Prolonged fever &gt; one month</td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td></td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td></td>
</tr>
<tr>
<td>Pulmonary TB within the last year</td>
<td></td>
</tr>
<tr>
<td>Severe bacterial infections (pneumonia, pyomyositis)</td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal candidiasis &gt; one month / poor response to therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Four</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV wasting (weight loss &gt; 10% and diarrhoea or fever for &gt; 1 month)</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td></td>
</tr>
<tr>
<td>CNS toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td>Cryptosporidiosis diarrhoea &gt; one month</td>
<td></td>
</tr>
<tr>
<td>Isosporiasis diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus infection other than liver, spleen or lymph node</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex infection (visceral or &gt; one month mucocutaneous)</td>
<td></td>
</tr>
<tr>
<td>Progressive multifocal leucoencephalopathy</td>
<td></td>
</tr>
<tr>
<td>Disseminated mycosis</td>
<td></td>
</tr>
<tr>
<td>Candidiasis of the oesophagus, trachea or lungs</td>
<td></td>
</tr>
<tr>
<td>Atypical mycobacteriosis disseminated</td>
<td></td>
</tr>
<tr>
<td>Non-typhoidal Salmonella septicaemia</td>
<td></td>
</tr>
<tr>
<td>Extra-pulmonary tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td></td>
</tr>
<tr>
<td>HIV encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Recurrent pneumonia</td>
<td></td>
</tr>
</tbody>
</table>

12.7 Cotrimoxazole Prophylaxis

Prophylaxis against inter-current infections decreases morbidity and mortality in HIV-positive TB clients. Cotrimoxazole is highly effective in preventing pneumocystis carinii pneumonia and toxoplasmosis. It also has activity against pneumococcus, Salmonella and Nocardia. Cotrimoxazole has been shown to decrease hospitalisations and mortality in HIV infected TB clients and has been recommended as part of a minimum package of care for HIV-positive adults and children.
The national HIV/AIDS Policy Guideline recommends trimethoprim/ sulphamethoxazole (cotrimoxazole) 160/800mg (960mg) daily for all HIV positive adults (whether they have TB or not) who:
Have symptomatic HIV disease (WHO Clinical stage 2,3 or 4), or
Have a CD4 count less than 200 cells/mm³, or
Have already had pneumocystis carinii pneumonia.

HIV positive people with TB are all in WHO clinical stage 3 (PTB) or 4 (EPTB/MDR). It is therefore recommended that all HIV positive TB clients be provided with cotrimoxazole prophylaxis:
Wait until the client has completed one month of TB treatment. This helps differentiate between side effects from anti-TB drugs and from cotrimoxazole.
Counsel clients on the effectiveness and side effects of cotrimoxazole:
That cotrimoxazole can help prevent pneumonia and other infections
That it is only effective while the client takes it so that it should be taken for the rest of their lives (unless on ARVs with CD4 count recovery to above 200)
That it can cause a rash and other side effects.
Provide cotrimoxazole 960mg (2 single strength or 1 double strength tablet) daily to adults.
The recommended dosage for children is trimethoprim 5mg/kg, sulphamethoxazole 25mg/kg (see section 11.7.4).

12.8 Antiretroviral Therapy And TB

Co-infected clients with a CD4 count below 200/mm³ or EPTB or MDR TB or other Stage 4 defining illness require ART. Those with a CD4+ count > 200/mm³ (and no stage 4 defining illness) do not require ART and should be reassessed for ART after completing TB treatment.

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

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

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

12.8.1 Drug Interactions

Nucleoside reverse transcriptase like zidovudine, didanosine, zalcitabine, stavudine, lamivudine and abacavir can be safely co-administered with anti-tuberculosis drugs.
Isoniazid, ethambutol, pyrazinamide and streptomycin can be concurrently used with protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

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

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

### Table 12.4: Shared Side Effects of TB and Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Antiretroviral treatment</th>
<th>Tuberculosis treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Didanosine, zidovudine, ritonavir, saquinavir</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Nevirapine, efavirenz</td>
<td>Rifampicin, isoniazid, pyrazinamide</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Stavudine, didanosine</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Rash</td>
<td>Nevirapine, efavirenz</td>
<td>Rifampicin, isoniazid, pyrazinamide</td>
</tr>
</tbody>
</table>

#### 12.8.2 Client Develops Tuberculosis While On Antiretroviral Therapy

Antiretroviral therapy should be continued throughout TB treatment, with changes to the regimen and monitoring as follows:

**Regimen 1:** A change to efavirenz is recommended for clients on nevirapine wherever possible. If this is not possible (e.g. intolerant of efavirenz or significant risk of falling pregnant), nevirapine may be continued in selected cases, with monthly ALT monitoring. Discuss these cases with an antiretroviral expert.

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

#### 12.8.3 Client Presents With TB Before Commencing Antiretroviral Therapy

The optimal time to commence ARVs in a co-infected client is unknown. Mortality in the first 2 months of TB treatment is high, especially if HIV disease is advanced, and early ARVs can be life saving.

If the client has a history of WHO Stage 4 illness or a CD4 count of less than 200 cells/mm³, start TB treatment and add ARVs after completion of 2 months of TB treatment.

However, if the client has a CD4 count of less than 50 cells/mm³ or other serious HIV-related illness, complete at least two weeks of TB treatment and initiate ARVs. Make sure that the client is...
tolerating TB treatment before initiating ARVs. Clients in this group should be started on first-line therapy consisting of stavudine, lamivudine and efavirenz. Nevirapine should generally be avoided because drug levels might decrease with TB medication and there is a danger of shared hepatotoxicity.

<table>
<thead>
<tr>
<th>Table 12.5: Antiretroviral Treatment For Adults With Concomitant TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB develops while on ARVs</strong></td>
</tr>
<tr>
<td><strong>Continue ARV therapy throughout TB treatment.</strong></td>
</tr>
<tr>
<td><strong>First-line regimen</strong> containing nevirapine should generally be swapped to efavirenz. Regimen is as follows:**</td>
</tr>
<tr>
<td>Stavudine 40mg 12 hourly (or 30mg if weight &lt;60kg)</td>
</tr>
<tr>
<td>Lamivudine 150mg every 12 hours</td>
</tr>
<tr>
<td>Efavirenz 600mg at night</td>
</tr>
<tr>
<td><strong>Second-line regimen</strong> should be changed to the following:**</td>
</tr>
<tr>
<td>Zidovudine (AZT) 300mg 12 hourly</td>
</tr>
<tr>
<td>Didanosine (ddI) 400mg daily on an empty stomach (250mg daily if weight &lt;60kg)</td>
</tr>
<tr>
<td>Lopinavir/ritonavir 400/400mg 12 hourly</td>
</tr>
<tr>
<td><strong>CD4+ count 50 - 200/mm³:</strong> Delay ARVs for two months (until intensive phase of TB therapy complete). Then start first line therapy as below. First-line therapy:**</td>
</tr>
<tr>
<td>Stavudine 40mg 12 hourly (or 30mg if weight &lt;60kg)</td>
</tr>
<tr>
<td>Lamivudine 150mg 12 hourly</td>
</tr>
<tr>
<td>Efavirenz 600mg at night</td>
</tr>
<tr>
<td><strong>CD4+ count of &lt;50/mm³ or other serious HIV illness:</strong></td>
</tr>
<tr>
<td>Introduce ART regimen above as soon as the client is stabilized on TB therapy (at least 2 weeks between starting TB therapy and starting ART).</td>
</tr>
</tbody>
</table>

Clients with advanced HIV disease, particularly those with a CD4 count of less than 50 cells/mm³ may become ill with an immune reconstitution illness during the first few weeks of antiretroviral therapy.

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

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

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

12.8.5 Counselling Of Co-infected Clients

Clients on TB medication and ARVs should be counselled about specific problems they are likely to encounter:
They will be taking a large number of tablets and may struggle with adherence.
When antiretroviral treatment is commenced, the client's TB symptoms may transiently worsen as part of immune reconstitution.
High rates of drug intolerance and drug interactions may occur between TB and ARV drugs.

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

13 Multi-Drug Resistant Tuberculosis

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

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

Since the mid-eighties, clients with MDR tuberculosis have been diagnosed in each of the nine provinces in South Africa. A 2001 national survey by the Medical Research Council indicated an MDR rate of 1.6% in new TB cases and 6.6% in previously treated cases. This translates into at least 6 000 new cases of MDR TB in South Africa each year.

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

There is ample reason to believe that the full brunt of MDR TB is still to be faced in the country. Several epidemiological and genetic studies have confirmed ongoing transmission of drug-resistant tuberculosis. Nosocomial outbreaks of MDR TB associated with HIV infection haves been documented and HIV-positive clients being treated in hospitals for drug susceptible tuberculosis have been re-infected with MDR strains.

Experience in other countries has shown that clients with active, untreated MDR TB can infect large numbers of HIV-positive individuals, leading to significant outbreaks of MDR TB with high case-fatality rates. It is therefore of utmost importance that MDR TB be prevented by rigorous adherence to the principles of the National Tuberculosis Control Programme (DOTS Expansion and Enhancement Strategy) and by building partnerships with clients, their families and communities to cure cases of tuberculosis at the first attempt.

Whilst the implementation of sound tuberculosis control based on the DOTS Expansion and Enhancement Strategy is the top priority, it is recognised that MDR tuberculosis poses a considerable risk to the effectiveness of this strategy. The National Tuberculosis Control Programme (NTCP) developed a policy in 2000 to treat clients with MDR tuberculosis in South Africa. This policy recommended that MDR tuberculosis treatment be provided as part of the NTCP in areas where the DOTS Expansion and Enhancement Strategy has been implemented successfully. Each of the nine provinces currently provides MDR TB treatment through NTCP structures.
13.1 Factors Contributing To MDR

As with other forms of drug resistance, MDR tuberculosis is a man-made problem, being largely the consequence of human error in any, or all of the following:
Management of drug supply
Client management, including prescription errors
Client adherence.

13.1.1 Poor Management Of Drug Supply

The most common errors observed in the management of drug supply are:
Frequent or prolonged shortages of first line anti-tuberculosis drugs due to poor stock management and/or procurement problems
Use of tuberculosis drugs (or drug combinations) of unproven bioavailability
The use of single first line drugs rather than fixed-dose combination tablets

13.1.2 Poor Client Management

Health system failures that lead to poor client management, inadequate or inappropriate treatment and poor adherence all contribute to MDR TB, including:
Uncaring staff attitudes, showing little empathy for clients, being paternalistic, failing to adopt a problem solving approach to help resolve issues all contribute to poor relationships between clients and health care workers
Inadequate counselling of client's leading to low knowledge levels and poor understanding of what is expected of the client
Ineffective systems, including lack of support for directly observed therapy, unsupervised clients, poor record keeping and follow-up of clients, poor referral
Insufficient contact tracing and follow-up of MDR cases
Frequent staff changes, poor staff morale, lack of regular support and supervision and low accountability of staff for programme outcomes.
Prescription errors including:
The use of 2 or 3 drugs when 4 or 5 first line drugs should be used
Adding one extra drug to a failing regimen.

13.1.3 Client-Related Factors

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

13.2 The PHC Role in MDR TB Management

Although the specialist MDR units in each of the provinces have a key responsibility for MDR TB, primary health facilities have an essential role to play by:
Implementing effective TB control and reducing the likelihood of resistance developing
Ensuring early diagnosis of potential MDR in clients who fail to respond to regimen 1 and 2
Initiating treatment under the guidance of the MDR unit when in-patient care is not possible
Providing on-going care post discharge from the MDR unit
Providing counselling and support to MDR clients, their families and contacts

13.3 Preventing MDR TB

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

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

13.4 Early Diagnosis Of MDR TB

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

Early, prompt diagnosis of MDR TB through sputum culture and susceptibility testing should be sought in the following circumstances:
MDR TB contacts who are symptomatic for TB
TB suspects who give a history of close contact with an MDR TB case
Any client on TB treatment in whom there is clinical deterioration despite good adherence
**New TB clients**, if despite good adherence:
Sputum smears or culture are positive at 2 months and there is no bacteriological improvement (e.g. 2+ smears becoming 1+) or no clinical improvement
When the continuation phase has been extended for a 3rd month and the sputum smear or culture is still positive at the end of the third month
If sputum smears were negative at 2-months but positive at 5-months
**Retreatment TB clients**, if despite good adherence:
Sputum smear or culture remains positive after three months of intensive therapy  
Sputum smear or culture was negative at 3 months but becomes positive at 7 months  
In new or retreatment clients with smear-negative TB that becomes smear-positive after 2 months of treatment

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

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

13.5 Management Of MDR TB

MDR TB is the responsibility of the TB Control Programme at all levels: national, provincial, regional, district, sub-district and facility.  
All MDR TB clients should be referred to an MDR TB unit where experienced clinicians can treat the client according to the "DOTS-Plus Standardised Management of MDR TB in South Africa, Policy Guidelines, January 2004".  
Management of MDR TB at all levels should include:
Drug susceptibility testing of specimens from MDR TB clients  
Provision of a social worker for counselling and support  
Provision of key nursing staff to provide continuity during the treatment period  
Providing the appropriate treatment regimen  
Direct observation of treatment throughout the course of treatment  
Good clinical records and keeping updated registers  
Monitoring compliance  
Developing measures for rapid recall if clients interrupt their treatment  
Increasing education and motivation of clients  
Rapid tracing and evaluation of contacts.

The Role of PHC facilities:  
Under ideal circumstances, all MDR TB clients should be referred to an in-patient unit for the intensive phase of MDR treatment  
However, the non-availability of beds at the MDR unit should not prevent the initiation of MDR treatment. It is recommended that the MDR unit evaluate all MDR cases that cannot be admitted, with a view to commencing treatment at home. Appropriate support for infection control should be provided and close monitoring of daily treatment through DOT through the PHC facility. These measures serve to reduce the spread of MDR TB in communities.  
Although standardised treatment regimens are used in MDR TB, the decision to commence treatment should still be taken by a specialist at the MDR unit and not at the PHC facility level.  
On discharge from MDR units, clients will continue treatment under the direct supervision of the PHC facility and be evaluated on a regular basis (at 4, 7 and 11 months) by the MDR unit.  
Adequate records of individual client progress as well as district / sub-district based registers are required to monitor overall response to treatment and track treatment outcomes.
All of the issues relating to support and clinical care of clients with susceptible TB disease apply to MDR TB including HIV testing and general HIV care. All HIV-positive MDR TB clients are eligible and would benefit from antiretroviral therapy.

13.6 MDR TB Contact Management

Prompt contact tracing should take place for all MDR TB clients.
If symptomatic: clients should be appropriately investigated, including the use of sputum culture and susceptibility to identify whether they have MDR TB or not
If asymptomatic: clients should be counselled about the signs and symptoms of TB and be asked to present at a health facility immediately if these develop. Early diagnosis, before lung damage occurs, and correct treatment is the best way to improve outcomes of those infected with MDR TB.

**Prophylaxis for contacts of MDR clients:**
Routine INH prophylaxis is not recommended in asymptomatic child contacts of infectious MDR TB cases. The only chemoprophylaxis regimens to have been studied are based on isoniazid and, to a lesser extent, rifampicin. Since by definition MDR TB is resistant to both of these drugs, it is unlikely that use of these drugs will prevent active disease in those with latent infection caused by an MDR TB.
Close contacts of MDR TB clients should receive careful clinical follow-up for a period of at least two years. These children should ideally be referred to the expert MDR centre in the Province. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR TB is recommended.
On the basis of the current evidence, WHO does not recommend second-line drugs for chemoprophylaxis in MDR TB contacts.

13.8 Treating Mono-Resistance

If susceptibility tests show mono-resistance to isoniazid, streptomycin or ethambutol but susceptibility to rifampicin after completion of regimen 1, the standard retreatment regimen is effective.

Mono-resistance to rifampicin is rare. If it occurs and the client clinically deteriorates on the retreatment regimen, repeat culture and susceptibility tests and consider MDR treatment.

13.9 XDR TB

XDR- TB refers to extensively drug-resistant TB. It refers to a situation in which there is:
Resistance to INH and RIF and
Any fluoroquinolone and
At least 1 of 3 injectable second line drugs (capreomycin, kanamycin, amikacin).

There is probably no difference in the spread of XDR TB to any other form of TB. XDR TB is curable in up to 30% of cases, depending on the extent of drug resistance, the severity of disease and the immune status of the client.

The most important approach to XDR TB is to prevent it through appropriate management of new and retreatment TB cases.
14 Non-Tuberculosis Mycobacteria

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

14.1 Epidemiology And Pathogenesis

Synonyms for non-tuberculous mycobacteria (NTM): Mycobacteria other than tuberculosis
(MOTTS); Atypical mycobacteria.

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

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

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

14.2 Clinical Manifestations

NTM are generally less virulent than MTB, but may cause a variety of diseases including
pulmonary disease, lymphadenitis, skin and soft tissue abscesses, wound infections, osteomyelitis
and disseminated disease particularly in clients with advanced HIV disease. Clinical manifestations
are often similar to MTB. Clients commenced on TB treatment, however, will not respond.

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

Peripheral lymphadenitis is most frequently found in children between 1- 5 years of age and occurs
typically in the head and neck. The disease is localised and requires surgical excision.

The species most frequently causing infections of the skin, soft tissue, and bones are M. fortuitum,
M. abscessus, M. marinum, and M. ulcerans. These normally occur after open trauma injuries and
the insertion of catheters and prostheses.

Disseminated disease presents in two different ways:
Clients who are immunosuppressed, not due HIV, may present with fever of unknown origin
(commonly due to M. avium) or with subcutaneous nodules and abscesses that drain spontaneously
(due to M. kansasii).
Severely immunosuppressed AIDS clients (CD4 count < 50 cells/mm\(^3\)) present with a high temperature, night sweats, weight loss, abdominal pain, and diarrhoea. This is most commonly due to M. avium but can also be due to M. kansasii. The diagnosis can frequently be made with a blood haemoculture.

14.3 Bacteriology

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

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

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

The importance of differentiating NTM from TB bacilli is that they require a different approach to management.

14.4 Management of NTM

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

The clinical and radiological details, type of specimen, the number of isolates, and the specific NTM identified are all taken into consideration in treatment decisions. There are standard treatment regimens for each specific NTM.

Most NTM are resistant to standard TB drugs. NTM can therefore be misdiagnosed as MDR TB. NTM should never be treated as MDR TB. A client has been diagnosed with symptomatic NTM should be referred to a specialized centre for further management.

15 Admission and Discharge Criteria for TB Clients

15.1 Introduction

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

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

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

15.2 Admission Criteria To TB Hospitals

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

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

Admission to TB hospitals should only take place when the TB diagnosis has been confirmed and the clients other medical conditions have been stabilised:
Clients with negative smears require a culture to confirm PTB. Other conditions such as bacterial or viral pneumonias, congestive cardiac failure, asthma, chronic obstructive lung disease, bronchiectasis and bronchial carcinoma need to be excluded in the differential diagnosis.
TB clients with medical conditions such as diabetes mellitus, epilepsy and severe hypertension should be stabilized before referral.
Severely ill extra-pulmonary TB clients (TB meningitis, TB spine, TB pericarditis) need to be stabilised in general hospitals before transfer to TB hospitals.
Treating MDR TB clients requires experience and special expertise. MDR TB clients must be referred for evaluation, treatment and follow-up to a specialised MDR unit.

15.3 Essential Elements Of In-patient Care In TB Hospitals

15.3.1 Clinical Management

TB diagnosis, treatment and monitoring:
Ensure proper diagnosis for pulmonary TB sputum e.g. sputum smears and culture for AFB and / or chest X-rays and extra-pulmonary cases diagnosed by histology or chemical pathology. Ensure proper classification of the case i.e. new or re-treatment case and site of disease. Ensure correct TB regimen is prescribed. Ensure proper registration of the client.

A health education plan should be implemented within 2 weeks of admission to ensure that client is counselled about TB and an adherence plan is developed to ensure treatment completion. All clients should be offered HIV counselling and testing by appropriately trained counsellors during the course of their hospitalisation. It is the responsibility of the TB hospital to offer all dually infected clients the full package of HIV care defined in section 12.6-12.8. Once they are clinically ready for discharge, TB clients with HIV infection can be referred to home-based care services or "step-down" facilities if palliative care required.

A social evaluation should be undertaken to assess eligibility for support grants. Within one week of hospitalisation, a plan for DOT management on discharge should be developed: confirm the client’s correct address and contact the clinic and organisation providing community DOT to identify a potential DOT supporter. Meet with family members to discuss the treatment plan and to ensure DOT when client is discharged.

15.4 Criteria For Referral From TB hospitals To District / Regional Hospitals

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

15.5 Discharge Criteria From TB Hospitals To PHC Clinics

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

15.6 Discharge Process

Within 2 weeks of admission a discharge plan must be completed which ensures:
Continuation of care (recruitment of DOT supporters, contact with the most accessible clinic).
Client education on TB management (e.g. infection control measures to be taken, duration of treatment and importance of compliance with the treatment and attendance at the nearest clinic for clinical evaluation and provision of sputa to monitor response to treatment).
Client and DOT supporter to meet before discharge from the hospital where possible.
Nutritional support should be arranged for clients with an inadequate access to food at home. A social worker needs to be involved to arrange support for such needy clients.
Referral to a local clinic or another hospital should always be done by:
Completing the pink referral form in detail with all the relevant information. One copy is for the client to take to the clinic, one copy to be sent to the referral clinic and one is kept at the hospital. The green client card should be updated before the client leaves the TB hospital and the clinic or DOT supporter should keep it updated until the treatment is completed. If possible the client should physically be delivered to the clinic, or be accompanied by a DOT supporter or Social worker on discharge, or the clinic should collect the client. Where this is not possible, follow up with the clinic, should be made to confirm that client arrived.

16 Infection Control

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

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

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

There are three types of infection control measures:
- Administrative (managerial) control
- Environmental control
- Personal respiratory protection

16.1 Administrative Control

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

Administrative measures aim to reduce the generation of droplet nuclei containing Mycobacterium tuberculosis in health facilities and to thus reduce the exposure of staff and clients. A comprehensive, written infection control plan underpins administrative control:
Early recognition of TB suspects or confirmed TB cases through screening all clients entering facility with a cough for 2 weeks or more, and fast-tracking their process through reception to access appropriate services (service that client presented for as well as TB screening)
Advice on respiratory hygiene to those with cough:
Covering nose and moth with tissue when coughing
Spitting / coughing into a tissue and discarding it into a designated bin
Use of disposable surgical masks by clients/staff who are coughing to reduce spread of droplets when coughing
Separation of TB suspects from the general waiting area to a designated, well-ventilated sub-waiting area
Prompt investigation for TB in symptomatic clients
Symptomatic screening of clients
Collection of sputum samples according to protocols
Follow-up of sputum results and promptly commencing or referring client for treatment if diagnosed with TB
Appropriate collection of sputum samples
Away from other people
In area with good circulation but where privacy is ensured
Not in a closed space such as a toilet
Hand-washing after handling of sputum samples
Fast tracking clients (TB suspects and newly diagnosed TB cases) through services so that they spend as little time as possible in the facility
Educating clients and communities to seek health care early with signs or symptoms of TB and protecting themselves and others e.g. through appropriate cough hygiene and good ventilation in the household.
Improved TB/HIV integration in the health facility, particularly symptomatic screening of HIV-positive clients at every clinical visit and appropriate tests for those who are symptomatic, will also help with early diagnosis.

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

All staff need to be trained to ensure that they understand the importance of infection control and how best to protect themselves and their clients. All staff also needs to be trained on screening of TB suspects, to reduce delays in screening.

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

16.2 Environmental Control Measures

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

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

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

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

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

16.3 Personal Respiratory Protection

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

The recommended respirator is the type that covers the mouth and nose and is fitted with a special particulate filter to filter out very small particles. US certified N95 or greater or EU specified FFP2 or greater are recommended for use in health care settings.

Surgical masks are meant to prevent the spread of infectious particles from the person wearing the mask to others. They do not protect the person wearing it from inhaling the particles as they are not sealed and have a limited filtration capacity. These are recommended for infectious clients/staff on a short-term basis. The concern is that they could perpetuate stigma.

16.4 Protection of Health Care Workers
In addition to reducing exposure, specific measures that target health care workers who are at increased risk include:
Informing staff of the signs and symptoms of TB and encouraging early recognition of symptoms and sputum tests
Providing VCT and encouraging HCW to know their status
Advocating / providing precautionary measures for HIV-positive staff, such as TB preventive therapy and antiretroviral therapy.
Appropriate placement of HIV-positive staff in low risk areas of the facility

17 Monitoring And Evaluation

A key element of the DOTS Strategy is the establishment and maintenance of a system to monitor case detection and treatment outcomes. A monitoring and evaluation (M&E) system is essential to programme management since it provides the basis for assessing progress made towards achieving programme goals. In addition, it allows the size of the tuberculosis problem and its evolution over time to be evaluated. Staff and managers need to have a thorough understanding of the content and process of NTCP monitoring and evaluation to enable them plan adequately and to use information to drive service improvements.

M&E is an important management tool at every level in programme management. It plays an important role in the day-to-day management of health programmes and provides programme managers with the information and insight needed for strategic planning, programme design and implementation, and decision-making about human and financial resources, especially in resource-limited settings.

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

A good M&E system is required at every level in the health system, characterized by the following:
Clear goals, objectives and targets (that are cumulative, with sub-district targets leading to district targets leading to provincial targets leading to national targets)
The selection of indicators which are valid, reliable, specific, operationally feasible and comparable over time and in different districts, provinces and countries
Quality assurance procedures to ensure that quality data is collected
The timely submissions and processing of data
The ability to process and analyse data
Data dissemination in both directions

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

17.1 Monitoring

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

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

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

17.2 Evaluation

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

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

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

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

Programme indicators to be evaluated include:
Case detection - this compares the notified and expected annual rates (per 100,000 population) of smear-positive pulmonary TB cases. The notified rates are determined from the quarterly report on case finding. The expected rates can be estimated from TB prevalence studies. W.H.O. have set case detection targets at 70% and this is the target used for national purposes. However, calculation of the case detection rate is problematic at present because it is difficult to establish the denominator of real incidence, due to high levels of HIV and the absence of reliable data on the Annual Risk of Infection.

Evaluation of coverage - in general it is expected that at least 2% of adult outpatients will have respiratory symptoms and that 5-15% of these will be sputum positive. Diagnostic practises can be evaluated by determining the proportion of smear positive cases among all pulmonary cases diagnosed. If the proportion who are smear positive is <50%, either smear examinations are being done poorly, or there is over-diagnosis of smear negative TB or both.

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

17.4 Standard Tools Used In The National TB Control Programme

The standardised tools utilised by the NTCP are included in the Annexures:

**TB Suspect Register (GW):** Used at facility level to record symptomatic clients reporting to that facility, to assist the follow-up of results and initiation of treatment. (Annexure 3)

**Laboratory request form for Sputum Examination:** A specific TB laboratory request form, available from the National Health Laboratory should be used by all facilities. Correct completion can help assess case-finding. (Annexure 4)

**Clinic/Hospital card (GW 20/12):** The blue clinic/hospital card is used in all facilities to collect all the information about the client, treatment and outcomes (demographic, disease classification, treatment regimen, monitoring and outcomes). This is the source document used to complete the register. (Annexure 5)

**Client treatment card (GW 20/15):** The green client-held card is used to record details of treatment including daily doses taken for all TB clients on treatment. (Annexure 6)

**Tuberculosis Register (GW 20/11):** Used in all facilities to summarise key information from the clinic / hospital card on each registered client (demographic, disease classification, treatment regimen, monitoring and outcomes). Information from the register is collated electronically and forms the basis for monitoring and evaluation of the NTCP. The register needs to be updated on a daily basis. It provides an overview of all registered clients and should be used as a clinical and programme management tool at facility level. (Annexure 7)

**Transfer form (GW20/14):** Used in all facilities to report on the key client information from the register when the client is transferred from one district to another. (Annexure 8)

17.4.1 The Electronic TB Register

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

The following reports can be generated by the system:
- Report on Case Finding
- Report on Sputum Conversion
- Report on Treatment Outcome
- Facility Profile Reports

Aggregated data is exported to the district health information system (DHIS) at sub/district level. Data is then transmitted electronically from the sub/district level to provincial level where it is aggregated and analysed before it is passed on to the national level. Client based data is exported to the Notification system.

17.5 Standard Reports

The following reports should be analysed on a quarterly basis:
**Quarterly report on case finding:** Completed at sub/district level and reports on the completed quarters cohort.

**Quarterly report on smear conversion:** Completed at sub/district level and reports on the previous quarter's cohort.

**Quarterly report on treatment outcomes for smear positive cases of pulmonary TB:** Completed at sub/district for the cohort registered 12 months earlier.

**Quarterly report on programme management:** Compiled at sub/district level, and is mainly a narrative report.

### 17.6 Information flow

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

**Recommended timelines for data collation:**

- In the 1st week after a quarter, the TB Coordinator and sub-district data capturer / health information officer need to ensure that all TB Register sheets due but still outstanding are collected.
- In the 2nd week after a quarter, the data capturer / health information officer needs to ensure that all outstanding data (new cases and updates) is captured.
- During the 3rd week after a quarter, the TB Coordinator and data capturer / health information need to run data checks and ensure that all the data that has been captured is correct and complete.
- At the end of the 3rd week, dispatch files need to be sent to the next level.

**Due dates for reporting:**

- Case finding data is due at the end of the quarter
- Smear conversion data is due 3 months after the end of the quarter
- Treatment outcome data is due 9 months after the end of the quarter

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

<table>
<thead>
<tr>
<th>Table 17.1: Information Processing and Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Client records:</strong></td>
</tr>
<tr>
<td>Update on a daily and weekly basis</td>
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<tr>
<td><strong>Facility TB Register (Paper-based):</strong></td>
</tr>
<tr>
<td>Update on a daily to weekly basis</td>
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<tr>
<td>Submit TB Register sheets to the sub-district office weekly:</td>
</tr>
<tr>
<td>Pink sheets – as soon as all client identification information, disease information and pre-treatment sputum results have been entered.</td>
</tr>
<tr>
<td>Yellow sheets – as soon as all the smear conversion sputum results at the end of the intensive phase (2 or 3 months) have been captured</td>
</tr>
<tr>
<td>Green sheets – as soon as all outcomes have been recorded (the correct outcome as well as the outcome date).</td>
</tr>
</tbody>
</table>
Sub-district register (Electronic):
Update on a weekly basis
Run checks to validate data
Submit reports to district level within 3 weeks of:
End of quarter for case finding
3 months after end of quarter for smear conversion
9 months after end of quarter for treatment outcomes
Provide facility reports

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

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

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

Table 17.2: Timelines for Reporting

<table>
<thead>
<tr>
<th>Start of Treatment</th>
<th>Report</th>
<th>Level</th>
<th>Date of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 January – 31 March</td>
<td>CASE FINDING</td>
<td>Facility level</td>
<td>Monthly</td>
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<tr>
<td></td>
<td></td>
<td>Sub-district level</td>
<td>1st till 3rd Week of April</td>
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<td></td>
<td></td>
<td>District level</td>
<td>4th Week of April</td>
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<tr>
<td></td>
<td></td>
<td>Provincial level</td>
<td>1st Week of May</td>
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<tr>
<td></td>
<td></td>
<td>National</td>
<td>2nd Week of May</td>
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<tr>
<td>01 April – 30 June</td>
<td>SMEAR CONVERSION</td>
<td>Facility level</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sub-district level</td>
<td>1st till 3rd Week of July</td>
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<tr>
<td></td>
<td></td>
<td>District level</td>
<td>4th Week of July</td>
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<tr>
<td></td>
<td></td>
<td>Provincial level</td>
<td>1st Week of August</td>
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<tr>
<td></td>
<td></td>
<td>National</td>
<td>2nd Week of August</td>
</tr>
<tr>
<td></td>
<td>TREATMENT OUTCOME</td>
<td>Facility level</td>
<td>Monthly</td>
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<tr>
<td></td>
<td></td>
<td>Sub-district level</td>
<td>1st till 3rd Week of January</td>
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<td></td>
<td></td>
<td>District level</td>
<td>4th Week of January</td>
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<td></td>
<td></td>
<td>Provincial level</td>
<td>1st Week of February</td>
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<td></td>
<td></td>
<td>National</td>
<td>2nd Week of February</td>
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<tr>
<td>01 April – 30 June</td>
<td>CASE FINDING</td>
<td>Facility level</td>
<td>Monthly</td>
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<td></td>
<td>Sub-district level</td>
<td>1st till 3rd Week of July</td>
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<td></td>
<td></td>
<td>District level</td>
<td>4th Week of July</td>
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<tr>
<td>Event</td>
<td>Level</td>
<td>Frequency</td>
<td>Date Range</td>
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</tr>
<tr>
<td>Case Finding</td>
<td>National</td>
<td>Monthly</td>
<td>2nd Week of August</td>
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<tr>
<td>SMEAR Conversion</td>
<td>Provincial</td>
<td>Monthly</td>
<td>1st Week of August</td>
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<tr>
<td>Treatment Outcome</td>
<td>District</td>
<td>4th Week of August</td>
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<td></td>
<td>Provincial</td>
<td>1st Week of November</td>
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<td></td>
<td>National</td>
<td>2nd Week of November</td>
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<tr>
<td>SMEAR Conversion</td>
<td>Facility level</td>
<td>Monthly</td>
<td>1st till 3rd Week of October</td>
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<tr>
<td></td>
<td>Sub-district</td>
<td>3rd Week of October</td>
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<td>District</td>
<td>4th Week of October</td>
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<td>1st Week of November</td>
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<td></td>
<td>National</td>
<td>2nd Week of November</td>
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17.7 Using Monitoring And Evaluation As A Management Tool

Substantial effort is made to collect information in the NTCP, but the quality of information and the way in which it is used at all levels in the health system limit the benefits that can be realised from M&E. Common problems in M&E include:

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

An M&E system is only as good as the data that is collected. The data should be appropriate, complete, consistent, and provided in a timely manner. Many current efforts at routine data collection result in poor-quality data because of a lack of proper training and supervision. If the individuals recording the data are not using the data and do not fully appreciate data needs for programme management beyond the facility level, the quality will most likely remain poor. This in turn leads to declining use of the data. One of the key functions of an M&E system is to oversee all data collection, ensure that data is appropriately used and the results are disseminated throughout the system, but especially to the facility level.
Changes in health programmes that are directly based on evidence from the field reinforce the efforts at the peripheral level to complete routine reporting. When health workers understand the importance of the data they are collecting, quality is likely to improve, building more confidence in the data being collected and increasing the likelihood that the data will be used. The key challenge is to use data to drive quality improvements in the TB Control Programme.

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

**Case finding indicators:**
- Total TB
- New cases and Retreatment cases
- Smear positive - New and Retreatment
- No smear provided
- EPTB

**Case holding indicators:**
- New and retreatment smear conversion rates

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

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

**TB-HIV Indicators**
- % TB clients tested for HIV
- % TB clients tested positive for HIV

An analysis of the facility data should answer the following questions:
- What does the data show?
- How is the facility performing in comparison to previous quarters?
- Relative to the targets that have been set, in which areas is the facility performing well and which are areas of concern?
- What are the most important problems that should be addressed?
- What factors at different points in the TB service contribute to these problems?
- What activities will be undertaken to remedy the problems at each point in the service?
- What resources will be required to undertake the activities?
- Who will undertake each of the activities?
- What is the target set for each of the indicators where quality improvement is sought?
- How will the facility manager monitor whether these activities are undertaken?

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

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

17.8.1 Case Finding Indicators

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Source</th>
<th>Collection</th>
<th>Level</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. TB case notification rate</td>
<td><strong>Numerator:</strong> Total TB cases reported in the past year (× 100,000) &lt;br&gt;<strong>Denominator:</strong> Total population in the specified area</td>
<td>ETR.net</td>
<td>Quarterly</td>
<td>All</td>
<td>-</td>
</tr>
<tr>
<td>2. PTB case notification rate</td>
<td><strong>Numerator:</strong> Total PTB cases reported in the past year (× 100,000) &lt;br&gt;<strong>Denominator:</strong> Total population in the specified area</td>
<td>ETR.net</td>
<td>Quarterly</td>
<td>All</td>
<td>-</td>
</tr>
<tr>
<td>3. TB suspect smear positivity rate</td>
<td><strong>Numerator:</strong> Number of sputa found to be smear-positive amongst TB suspects &lt;br&gt;<strong>Denominator:</strong> Total number of sputum smear samples sent for TB suspects</td>
<td>Suspect register</td>
<td>Quarterly</td>
<td>All</td>
<td>5-20% (check)</td>
</tr>
<tr>
<td>4. Case detection rate (Smear positive)</td>
<td><strong>Numerator:</strong> Annual number of new smear-positive TB cases notified &lt;br&gt;<strong>Denominator:</strong> Annual number of new smear-positive TB cases estimated (incidence)</td>
<td>ETR.net</td>
<td>Annual</td>
<td>National</td>
<td>70%</td>
</tr>
<tr>
<td>5. Proportion smear-positive pulmonary cases</td>
<td><strong>Numerator:</strong> Number of smear positive pulmonary cases &lt;br&gt;<strong>Denominator:</strong> Total number of pulmonary cases</td>
<td>ETR.net</td>
<td>Quarterly</td>
<td>All</td>
<td>50-70%</td>
</tr>
<tr>
<td>6. Smear-positive Retreatment ratio</td>
<td><strong>Numerator:</strong> Number of retreatment smear positive pulmonary cases &lt;br&gt;<strong>Denominator:</strong> Total number of smear positive pulmonary cases (new and retreatment).</td>
<td>ETR.net</td>
<td>Quarterly</td>
<td>All</td>
<td>6-8%</td>
</tr>
<tr>
<td>7. Smear-positive sputum turnaround time</td>
<td><strong>Numerator:</strong> Number of days elapsed between receiving a sputum specimen from the client and receiving a smear positive result from the laboratory, including weekends and public holidays.</td>
<td>Suspect register</td>
<td>Quarterly</td>
<td>All</td>
<td>80% within 48 hours</td>
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</tbody>
</table>

17.8.2 Case Holding

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Source</th>
<th>Collection</th>
<th>Level</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Smear-positive treatment commencement ratio</td>
<td><strong>Numerator:</strong> Number of smear positive pulmonary clients in TB register &lt;br&gt;<strong>Denominator:</strong> Number of smear positive clients diagnosed (from TB suspect register)</td>
<td>TB register</td>
<td>Quarterly</td>
<td>All</td>
<td>95-100%</td>
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<tr>
<td></td>
<td></td>
<td>and Suspect</td>
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<td>register</td>
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</tr>
<tr>
<td>2. New smear-positive conversion rates</td>
<td><strong>Numerator:</strong> Number of new smear positive cases that convert from smear positive to smear negative at 2 months &lt;br&gt;<strong>Denominator:</strong> Total number of new smear-positive cases</td>
<td>ETR.net</td>
<td>Quarterly</td>
<td>All</td>
<td>&gt; 85%</td>
</tr>
<tr>
<td>3. Retreatment smear-positive conversion rates</td>
<td><strong>Numerator:</strong> Number of retreatment smear positive cases that convert from smear positive to smear negative at 3 months &lt;br&gt;<strong>Denominator:</strong> Total number of retreatment smear-positive cases</td>
<td>ETR.net</td>
<td>Quarterly</td>
<td>All</td>
<td>&gt; 85%</td>
</tr>
</tbody>
</table>

17.8.3 TB-HIV Indicators
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Source</th>
<th>Collection</th>
<th>Level</th>
<th>Target</th>
</tr>
</thead>
</table>
| 1. HIV testing rates | **Numerator:** Number of TB cases (adults and children) with known HIV status  
**Denominator:** Total number of TB cases registered | ETR.net | Quarterly | All | 90% |
| 2. HIV seroprevalence amongst TB cases | **Numerator:** Number of registered TB clients known to be HIV positive  
**Denominator:** Total number of registered TB clients tested for HIV | ETR.net | Quarterly | All | - |
| 3. Proportion of HIV+ TB cases on ART pre-TB treatment | **Numerator:** Total number of registered TB clients on ART prior to commencing TB treatment  
**Denominator:** Total number of registered TB clients known to be HIV-positive | ETR.net | Quarterly | All | |
| 4. Proportion of HIV+ TB not on ART pre-TB and requiring ART | **Numerator:** Total number of registered HIV+ TB clients not on ART pre-TB treatment who require ART (Child: WHO Stage 3 or 4 or CD4<20% in child <18 months or <15% in child >18months or recurrent hospitalisation. Adult with CD4<200 or WHO Stage 4.)  
**Denominator:** Total number of registered TB clients who are known to be HIV positive | ETR.net | Quarterly report | All | |
| 5. Cotrimoxazole coverage rates amongst TB clients | **Numerator:** Total number of registered HIV+ TB clients commencing CPT  
**Denominator:** Total number of registered HIV+ TB clients requiring CPT (all TB clients except child over 6 years or adult on ARV with CD4>200 or child over 18 months with CD4%>15% for at least 6 months) | ETR.net | Quarterly | All | |
| 6. Proportion HIV+ TB cases commenced on ART whilst on TB treatment | **Numerator:** Total number of registered HIV+ TB clients not on ART who commence ART whilst on TB treatment  
**Denominator:** Total number of registered HIV+ TB clients not on ART pre-TB treatment who require ART ((Child: WHO Stage 3 or 4 or CD4<20% in child <18 months or <15% in child >18months or recurrent hospitalisation. Adult with CD4<200 or WHO Stage 4.) | ETR.net | Quarterly report | All | |
## 17.8.4 TB Treatment Outcome Indicators

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Source</th>
<th>Collection</th>
<th>Level</th>
<th>Target</th>
</tr>
</thead>
</table>
| 1. New smear-positive cure rates | **Numerator:** Number of new smear-positive cases that are smear negative in the last month of treatment and on at least one other occasion at least 30 days prior  
**Denominator:** Total number of new smear-positive cases registered | ETR.net | Quarterly | All | 85% |
| 2. New smear-positive completion rates | **Numerator:** Number of new smear-positive cases that complete the full course of treatment who did not meet the criteria for cure or failure  
**Denominator:** Total number of new smear-positive cases registered | ETR.net | Quarterly | All | Less than 5% |
| 3. New smear-positive interrupter rate | **Numerator:** Number of new smear-positive cases that interrupted treatment for more than 2 consecutive months  
**Denominator:** Total number of new smear-positive cases registered | ETR.net | Quarterly | All | Less than 5% |
| 4. New smear-positive death rate | **Numerator:** Number of new smear-positive cases that died during treatment, irrespective of cause  
**Denominator:** Total number of new smear-positive cases registered | ETR.net | Quarterly | All | Less than 5% |
| 5. New smear-positive treatment failure | **Numerator:** Number of new smear-positive cases that are smear positive 5 months or later after initiating treatment  
**Denominator:** Total number of new smear-positive cases registered | ETR.net | Quarterly | All | Less than 5% |
| 6. Retreatment smear-positive cure rates | **Numerator:** Number of retreatment smear-positive cases that are smear negative in the last month of treatment and on at least one other occasion at least 30 days prior  
**Denominator:** Total number of retreatment smear-positive cases registered | ETR.net | Quarterly | All | 75% |
| 7. Retreatment smear-positive completion rates | **Numerator:** Number of retreatment smear-positive cases that complete the full course of treatment who did not meet the criteria for cure or failure  
**Denominator:** Total number of retreatment smear-positive cases registered | ETR.net | Quarterly | All | Less than 5% |
| 8. Retreatment smear-positive interrupter rate | **Numerator:** Number of retreatment smear-positive cases that interrupted treatment for more than 2 consecutive months  
**Denominator:** Total number of retreatment smear-positive cases registered | ETR.net | Quarterly | All | Less than 5% |
| 9. Retreatment smear-positive death rate | **Numerator:** Number of retreatment smear-positive cases that died during treatment, irrespective of cause  
**Denominator:** Total number of retreatment smear-positive cases registered | ETR.net | Quarterly | All | Less than 5% |
| 10. Retreatment smear-positive treatment failure | **Numerator:** Number of retreatment smear-positive cases that are smear positive 5 months or later after initiating treatment  
**Denominator:** Total number of retreatment smear-positive cases registered | ETR.net | Quarterly | All | Less than 7% |
### 17.8.5 Programme Management

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Source</th>
<th>Collection</th>
<th>Level</th>
<th>Target</th>
</tr>
</thead>
</table>
| 1. DOTS Coverage | **Numerator**: Number of primary health care facilities clinics offering DOTS services (diagnostics and daily observed therapy)  
**Denominator**: Total number of primary health care facilities | Progress report | Annual | Province National | 100% |
| 2. Timely Reporting Rates (Province/District) | **Numerator**: Number of provinces / districts submitting correctly validated quarterly reports by the due dates to national / provincial level  
**Denominator**: Total number of provinces / districts | Progress report | Quarterly report | Province National | 100% |
| 3. Supervisory visit rates | **Numerator**: Number of supervisory visits undertaken at district level  
**Denominator**: Number of supervisory visits planned at district level | Progress report | Quarterly report | Province National | 100% |
| 4. Drug stocks out rates* | **Numerator**: Number of TB facilities with a drug stock-out of any regimen 1 or regimen 2 drug in a 6-month period  
**Denominator**: Total number of TB facilities | Progress report | Quarterly | District, Province | 0% |
| 5. Sputum smear quality control | **Numerator**: Proportion of false positive or false negative slides in QA sample  
**Denominator**: Number of slides evaluated | QA report | Supervision | Province National | FP: 0-2%  
FN: 0-5% |
| 6. Accessibility of laboratory culture services | **Numerator**: Number of NHLS laboratories with sputum culture services  
**Denominator**: Number of NHLS laboratories providing smear microscopy. | Progress reports | Half-yearly evaluation meetings | Province National | Area specific |
| 7. MDR rate | **Initial resistance rates**: Prevalence and trends of drug resistance, MDR TB | Project report | Survey every 3 years | Province National | IR: 0-1%  
AR: 2-4% |
| 8. MDR rate ** | **Initial resistance rates**: Prevalence and trends of drug resistance, MDR TB  
**Acquired resistance rates**: Prevalence and trends of drug resistance, MDR TB | Project report | Survey every 3 years | Province National | IR: 0-1%  
AR: 2-4% |

*To avoid drug stockouts each province should have 12 month reserve stock of drugs  
**Initial resistance: Convention is that this should ideally be 0% and not more than 1%. Acquired resistance should be low as well, but will be somewhat higher than IR.
### TB SERVICES STAFF AND SYSTEMS AUDIT

**Section 1**

<table>
<thead>
<tr>
<th>Description</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total TB caseload (4 most recent quarters; source - ETR.net)</td>
<td></td>
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</tr>
<tr>
<td>Number of clients treated in the community and workplace at a specified time (last DOTS report)</td>
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</tr>
<tr>
<td>Total number of TB clients on treatment at same specified time (last DOTS report)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of New Smear Positive clients (4 most recent quarters; source - ETR.net)</td>
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<tr>
<td>Number of NSP treatment interrupters (4 most recent quarters; source - ETR.net)</td>
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<td></td>
</tr>
<tr>
<td>Number of NSP clients cured (4 most recent quarters; source - ETR.net)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of NSP clients completed treatment (4 most recent quarters; source - ETR.net)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Section 2**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there a specific nurse allocated to manage the TB programme in the facility?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of clinical staff (nurses and doctors) present today:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of clinical staff (nurses and doctors), present today, who have attended a TB clinical training programme:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of community health workers involved in the TB programme:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of community health workers involved in the TB programme who have undergone DOTS training:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is daily screening for TB and daily DOTS for TB available?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there a mechanism in place to recall clients to the clinic?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes: a) Which clients are recalled?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Who does the recall?</td>
<td></td>
<td></td>
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<tr>
<td>c) How often is recall done?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) How do staff members know who to recall?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coding: Positive TB suspects:</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>b) Who does the recall?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) How often is recall done?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) How do staff members know who to recall?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coding: Responsibility allocated:</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Coding: Done at a minimum on a weekly basis:</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Coding: Check that process exists for keeping track / getting feedback about those recalled:</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Have you had stockouts of any of the following items in the last 6 months? (If &quot;Yes&quot; provide details)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Details:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole (Bactrim)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB Drugs (Regimen 1 or 2)</td>
<td></td>
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</tbody>
</table>

Ask and observe whether there is a mechanism in place to monitor stock levels of these items (Bin cards, electronic system etc)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Mechanism:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole (Bactrim)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB Drugs</td>
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</tbody>
</table>
### TB FOLDER AUDIT

Sampling procedure: From the TB register, starting on a date 4 months ago and working backwards to 6 months ago, sequentially select TB clients until 10 folders are found. The evaluation aims to assess clients currently on TB treatment. Note any folders.

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

Number of folders found in the folder system _________________

Number of folders requested for review but not found in the folder system _________________

158
References

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Guidelines for National Tuberculosis Programmes on the Management of Tuberculosis in Children, World Health Organisation, 2006
Tuberculosis Treatment Support and Adherence Guidelines, 2006, National Department of Health South Africa
Interventions for Tuberculosis Control and Elimination, International Union Against Tuberculosis and Lung Disease, 2002
Guidelines for the Prevention of Tuberculosis in Health Care Facilities in Resources Limited Settings, World Health Organisation, 1999
Compendium of Indicators for Monitoring and Evaluating National Tuberculosis Programs, WHO/HTM/TB/2004.344, August 2004
Appendix IV – CLINICAL TRIAL PATIENT TRANSFER FORM

New CAT PID 0 5 3 1 2

CAPRISA TRIAL PATIENT TRANSFER TO CAT

CLINICAL SUMMARY

Date of Birth: [ ] [ ] [ ] [ ] [ ]

Sex: [ ] Male
[ ] Female

From: [ ] SAPIT
[ ] START

SCREENING VISIT DETAILS:
1. Date: [ ] [ ] [ ] [ ] [ ]

ENROLLMENT:
1. Date: [ ] [ ] [ ] [ ] [ ]

2. ARM: ________________________

3. CD4: ________________________

4. V/L: ________________________

5. WHO stage [ ]

6. Summary of clinical condition:

___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

Clinical Summary Form
Version 1.0
Principal Investigator: Dr Kogieleum Naidoo

1 23 January 2009

Protocol version 2.1, 22 July 2009
TB HISTORY:

1. Date TB Treatment Started:

2. Date TB Treatment completed:

3. Outcome:
   - Cure: ☐
   - Failure: ☐
   - Recurrence: ☐
   - Other: ☐
   - Specify: _______________________________
   - Defaulted: ☐

4. Comments: (Relevant regimen changes, drug resistance etc.):

   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________

ART INITIATION:

1. Date: [ ] [ ] [ ] [ ]

2. CD4: ________________

3. V/L: ________________

4. Comments:
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________
   ___________________________________________________________________________________

5. Regimen Changes (where relevant), and reasons:
   ___________________________________________________________________________________
   ___________________________________________________________________________________

6. ART interruptions (where relevant) and reasons:
   ___________________________________________________________________________________
CLINICAL HISTORY:

1. Months on ART to date: [ ]

2. Latest CD4: _______________ taken at Date: [ ]

3. Latest V/L: _______________ taken at Date: [ ]

4. History of AE’s and SAEs:

___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

Comments:

___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

Clinical Summary Form
Version 1.0
Principal Investigator: Dr Kogieleum Naidoo
Protocol version 2.1, 22 July 2009
ART SUMMARY:

1. Date of 1st dose: __ __ __ __
2. Date of last study dose dispensed: __ __ __ __
3. Regimen codes of last study dose dispensed: __ __ __
4. Dosage of last study dose dispensed (mg): __ __ __

Visit Code of Last Study Visit: __ __ __
Date of Last Study Visit: __ __ __

Clinician: __ __ __ Sign: __________ Date: __ __ __ __ __ __

Pgs 1-3 completed by __ __ __ Sign: __________ Date: __ __ __ __ __ __ (if not clinician)
Appendix V: Transition of SAPIT patients into the TRuTH study

Baseline sputum on SAPIT enrolment

Exit from SAPIT study at 18 months of follow-up, consent and enrolment into TRuTH study

Clinical assessment of TB recurrence
- 3 monthly TB symptom screen
- TB sputum microscopy and culture
- Radiological assessment

Sputum Microscopy TB+ve

RFLP to determine relapse or re-infection

Serum Immunological assessment:
- CD4
- Viral Load
- CMI
- Cytokines
- Host genetics

Negative TB

Ongoing follow-up
APPENDIX VI – Informed Consent form

STUDY INFORMED CONSENT FORM

TITLE OF PROGRAMME:  CAPRISA AIDS TREATMENT PROGRAMME (ENGLISH)

TITLE OF STUDY:

Is TB Recurrence in Treated TB-HIV Co-infected?

Patients Relapse or Re-infection?

Principal Investigator (s): Dr Kogieleum Naidoo, MBChB
Prof. Salim S Abdool Karim, MBChB, PhD

INTRODUCTION
You are being asked to take part in this research study because you are eligible for the CAPRISA AIDS Treatment Programme (CAT). The doctor in charge of this study at this site (CAPRISA) is Dr Kogieleum Naidoo, MBChB. Before you decide if you want to be a part of this study, we want you to know about the study.

This consent form gives you information about this study, which will be done at Prince Cyril Zulu Communicable Disease Centre (PCZCDC). Ask questions and discuss any concerns you may have with the research staff. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this consent form to keep.

Please note that:

- Your participation in this study is entirely voluntary. You may decide not to participate in the study, but you are still eligible for anti-retroviral therapy. You may decide to obtain your HIV care through your own medical care provider.
- You may stop taking part in the study at any time and this will not affect the care you receive through the CAT Programme.
- You will be informed of any new information that may arise, which could affect your decision to remain apart of the study.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to learn why some HIV –infected patients on Highly Active Antiretroviral Therapy (HAART) acquire Tuberculosis (TB), even after being cured of the TB previously. Very little is known about why HIV patients on HAART can acquire several episodes of TB and the main purpose of this study is to monitor patients whom we know have had TB in the past for new episodes of TB.

WHAT IS THE DURATION OF THE STUDY?
The study will be conducted over 3 years (36 months).

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**
About 550 people will take part in this study.

**WHAT DO I HAVE TO DO IF I PARTICIPATE IN THIS STUDY?**
If you join this study, you will need to come into the clinic for examinations, interviews, and laboratory tests frequently. **For your first 3 visits on the study, you will be required to come to the clinic for: an Entry visit, Month 1 and Month 3. Thereafter you will be required to come to the clinic once every 3 months for approximately three years.** If you miss appointments, the persons you named will be contacted or field workers will be sent to your home. Please inform a study staff member, should you wish not to be visited at home.

Any time that results of exams and laboratory tests such as viral load (which measures how much HIV virus is in your blood), CD4+ T cell counts (immune cells that help fight infection such as HIV), sputum, chest x-rays and safety tests are known, they will be given to you. There may be times that you must come for additional visits if these exams or tests show abnormal results. Some of the blood drawn and sputum taken throughout the study can be stored. You will be asked for your permission to store the blood and sputum for future research and asked to sign a separate consent form if you agree to do this. You may still participate in the study if you do not agree to have blood stored.

**Screening and Study Visits**
You will be asked questions about your medical history and any medicines that you have taken. You will be asked how to be contacted in case you miss a visit or there are ever problems with your lab results. You will be given a physical exam and have about 60 mL (about 4 tablespoons) of blood drawn for routine tests, CD4 + cell counts, and viral load assessments. **You will have a Chest X-Ray at Entry and then every 6 months thereafter. You will have bloods drawn at the Entry visit and then every 3 months thereafter.** You will be told your test results throughout the study. Some of your blood will be stored for future HIV-related testing including a test for HIV resistance (to see if the HIV is able to respond to the ART). Sputum samples will also be taken from you once every 3 months to test for the presence of TB. Your blood and sputum samples will be identified by a number and not your name. If you are a woman and able to become pregnant, you will be asked to provide some urine for a routine pregnancy test. If you are admitted to hospital, you will be asked questions about the reasons for your stay there.

**USE OF STORED SAMPLES**
The stored samples may be used for future research, to confirm test results, or to do additional testing. Your samples will not be sold or used in products that make money for the researchers. You will be asked to sign a separate form asking for your consent to have your samples stored. Should you decide not to have your samples stored; this will not affect your ability to take part in the study.

**WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT?**
You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
• The study staff feels that staying in the study may be harmful to you.
• You are not able or willing to attend study visits or to complete the study procedures.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
Instead of being in this study you have the choice of:
• Participation in the CAT programme.
• Treatment with ART through the South African national rollout programme.
• No treatment

Antiretroviral medications, laboratory tests to monitor the effectiveness of these medications, and quality medical care for HIV/AIDS may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices.

WHAT ABOUT CONFIDENTIALITY?
Your medical records, personal information, and the results of your HIV tests and other medical and laboratory evaluations will be kept strictly confidential within the extent of South African law. Only your doctor and/or nurse will know the results of your tests. Your records will be identified by a study code. Any publication of this study will not use your name or identify you personally.

Every effort will be made to protect your confidentiality but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, namely the Biomedical Research Ethics Committee, Centres for Disease Control (CDC), Medicines Control Council and study staff.

WHAT ARE THE RISKS AND DISCOMFORTS ASSOCIATED WITH THE STUDY?
Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection. Many people do not understand the facts about infection with the AIDS virus. Being HIV positive can be a very stressful experience. You may be treated badly by friends and family if you are HIV positive and your HIV status becomes known to others. If you have a Chest X-ray and you are pregnant, then there is a risk to your unborn baby.

WHAT HAPPENS IF I BECOME PREGNANT?
If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices and refer you to a provider of prenatal care if you do not have one. You may still continue to be part of the study, however, you will not have the chest x-rays done during the duration of your pregnancy due to the risk this poses to your unborn baby. All female patients who participate in this study will be offered a pregnancy test at every study visit.

WHAT ARE THE BENEFITS ASSOCIATED WITH THE STUDY?
If you participate in this study, there may be a direct benefit to you, but no guarantee can be made. Your health will be followed more closely than usual while you are on the study, which may help you to feel better.

WILL I RECEIVE ANY PAYMENT?
Participants will be reimbursed R50 on enrollment in the study and for every scheduled study visit thereafter.
WHAT ARE THE COSTS TO ME?
The HIV treatment will be provided free of charge while you are on study. If you require HIV treatment that does not include these drugs, you will receive this care from a local authority and/or provincial health facility. Provincial hospitals may ask you to pay a fee, depending on your income.

If you acquire TB, then TB treatment is provided free of charge to you by the Tuberculosis Control Study at the CDC.

WHAT HAPPENS IF I AM INJURED?
It is very unlikely that you will become injured as a result of involvement in this study. However, in the case of a research related injury, you will be referred to the King Edward hospital for treatment. The cost of this treatment will be borne by the research team. There is, however, no compensation provided for research related injuries. You do not give up any legal rights by signing this consent form.

For questions about this study or a research-related injury, contact any of the following persons:

Clinic Manager at Prince Cyril Zulu Communicable Disease Clinic:
Dr. Nesri Padayatchi
CAPRISA Deputy Director
Tel: (031) 260-4574

Principal Investigator:
Dr. Kogieleum Naidoo
Tel: (031) 260-4687/1922

For questions about your rights as a research participant, you may contact:
BREC Administrator or Chair – for reporting of complaints/problems-
Biomedical Research Ethics Committee
Private Bag X54001
Durban
4000
Telephone: +27 (0) 31 260 4769
Fax: +27 (0) 31 260 4609
E-mail: ramnaraind@ukzn.ac.za
I have read this form, or had it read to me, and voluntarily agree to take part in the study. The purpose of the study, the procedures, and the risks and benefits has been explained to my satisfaction. My signature, thumbprint or mark indicates that I consent to take part in the study, have received a copy of this consent form, and that I understand what is required from me and the consequences of taking part in the study.

__________________________________________  Date:__________
Participant Name and Signature

__________________________________________  Date:__________
Witness Name and Signature

__________________________________________  Date:__________
Translator’s Name and Signature

Withdrawal of Consent

I hereby withdraw my consent to participate in this study. I am aware that I may withdraw my consent at any time without prejudice to further care.

__________________________________________  Date:__________
Participant Name and Signature

__________________________________________  Date:__________
Witness Name and Signature

__________________________________________  Date:__________
Translator’s Name and Signature
APPENDIX VII – Specimen Storage

STORAGE INFORMED CONSENT

INFORMED CONSENT FORM FOR SPECIMEN STORAGE
(ENGLISH)

Is TB recurrence in treated TB-HIV co-infected patients relapse or re-infection?

Sponsored by: Centre for the AIDS Programme of Research in South Africa
University of KwaZulu-Natal

Principal Investigator: Dr Kogieleum Naidoo, MBChB
Prof. Salim S Abdool Karim, MBChB, PhD

INTRODUCTION:
We are inviting you to participate in a research study. If you decide to participate in the TRuTH study, blood, sputum and other biological samples will be taken from you for testing. Some of these samples may be kept for future research relating to the study of HIV. This consent form gives you information about this storage and the use of samples. You are being asked to consent to the storage of your blood and other samples. The study staff will discuss this with you. Please ask if you have any questions. If you agree to the storage of your blood and other samples, you will be asked to sign this consent form. You will be given a copy of this form to keep.

Please note that:

- Your participation in this study is entirely voluntary. You may decide not to participate in the study, but you are still eligible for anti-retroviral therapy. You may decide to obtain your HIV care through your own medical care provider.
- You may stop taking part in the study at any time and this will not affect the care you receive through the CAT Programme.

BLOOD AND BIOLOGICAL SAMPLES
Blood samples will be taken from you every 3 months, approximately 60 ml (4 Tablespoons). Sputum (saliva) samples will be taken from you every 3 months. As with your other samples, only a number, not your name, will be used to identify these samples. These samples may provide valuable information in the future when different immune system and HIV tests become available.

USE OF STORED SAMPLES
The stored samples may be used for future research, to confirm test results, or to do additional testing. Your samples will not be sold or used in products that make money for the researchers. Any studies that use your samples will be reviewed by the Biomedical Research Ethics Committee of the Nelson R. Mandela School of Medicine.
The researchers do not plan to contact you or your regular doctor with any results that are done on the stored samples after the study has been completed. This is because research tests are often done with experimental procedures so the results from one study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that a specific test result would provide important information for your health, the researchers will notify the study doctor who will try to contact you or your regular doctor. If you wish to be notified of this type of test result, you need to make sure that you contact the study nurse or doctor with any changes to your phone number or address. If you want your regular doctor to be told about this kind of test result, you need to provide the study team with the contact details of your regular doctor.

**STORAGE OF SAMPLES**
Your samples will be stored at laboratories that are specially designed to keep stored samples safely. Only approved researchers working on this project and related projects will be able to access your samples. The people who work at these laboratories will have access to your samples when they store them and keep track of them, but they will not know who you are as your samples will be stored by number. There is no time limit on how long your samples may be stored. Should you decide during the study that you do not want the samples to be stored, you do have the right to request that your samples be destroyed. A study staff member will ask you to sign a form documenting your decision. Deciding to withdraw consent to have your samples stored will not affect the quality of care and attention that you receive within the study.

**BENEFITS TO HAVING SAMPLES STORED**
There is no direct benefit to you through having your samples stored and tested later. Information learned from stored samples may help others who have HIV/AIDS as well as for publication in a scientific medical journal.

**RISKS**
There is very little risk to you when you have your samples stored. There is a small risk that others may find out information about your HIV status from stored samples. This risk is reduced as your sample is stored under a study number, and not your name. You are entitled to the same protections of confidentiality and privacy for stored samples as you are for the samples that are drawn and used during the study. It is possible that tests that have yet to be developed may tell us things about your health we cannot currently test for. Results from these tests may cause distress to you.

**PREGNANCY**
All female patients who participate in this study will be offered a pregnancy test at every study visit. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices and refer you to a provider of prenatal care if you do not have one. You may still continue to be part of the study, however, you will not have the chest x-rays done during the duration of your pregnancy due to the risk this poses to your unborn baby.

**WHAT ARE THE BENEFITS ASSOCIATED WITH THE STUDY?**
If you participate in this study, there may be a direct benefit to you, but no guarantee can be made. Your health will be followed more closely than usual while you are on the study, which may help you to feel better.
CONFIDENTIALITY
The results of future tests of your samples will not go into your medical record. Although every effort is made to make sure that your samples are stored confidentially (by number and not name), we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, such as the Medicines Control Council (MCC), the University of KwaZulu Natal Biomedical Research Ethics Committee, Centres for Disease Control (CDC), study staff and study monitors.

PARTICIPANT RIGHTS
The decision to allow your samples to be stored is completely voluntary. If you do not allow your samples to be stored, you may still participate in the main study. You may decide not to allow your samples to be stored after the tests that are needed for this study have been done or you decide to stop participating in the study. If you do decide to allow your samples to be stored, you can change your mind at any time and still participate in the main study. You must contact the study doctor or nurse and let them know that you do not want your samples to be stored any more. If you decide to do this, your samples will no longer be stored. You will then be asked if you want all stored samples to be destroyed. In this case, any samples that have been stored will be destroyed. You will then be asked to sign this form again under the section, “Withdrawal of Consent” so that there is a record of your decision. At the end of the study you will also be given the opportunity to review your consent for the storage of your samples.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about your rights as a research participant, you may contact:
Principal Investigator:
Dr. Kogieleum Naidoo
University of KwaZulu-Natal
Tel: (031) 260-4687

Clinic Manager at Prince Cyril Zulu Communicable Disease Clinic:
Dr. Nesri Padayatchi
CAPRISA Deputy Director
Tel: (031) 260-4574

For questions about your rights as a research participant, you may contact:
BREC Administrator or Chair – for reporting of complaints/problems-
Biomedical Research Ethics Committee
Private Bag X54001
Durban
4000
Telephone: +27 (0) 31 260 4769
Fax : +27 (0) 31 260 4609
E-mail: ramnaraind@ukzn.ac.za

Protocol Version 2.1
Principal Investigator: Dr Kogieleum Naidoo
22 July 2009
SPECIMEN STORAGE CONSENT FORM SIGNATURES PAGE

Please read the statement below and think about your choice. No matter what you decide, it will not affect your care.
I agree to allow some of my biological samples to be stored and used for testing and future research in HIV studies (please tick only one).

Yes_______  No _______

I am aware that I may withdraw my consent at any time without prejudice to further care.

__________________________________________  Date:______________
Participant Name and Signature

__________________________________________  Date:______________
Witness Name and Signature

__________________________________________  Date:______________
Translator’s Name and Signature

Withdrawal of Consent

I hereby withdraw my consent for the storage of my biological samples. It is my wish that (please tick only one):

_____ Samples that have already been stored may continue to be stored and used

_____ All samples that have already been stored must be destroyed.

__________________________________________  Date:______________
Participant Name and Signature

__________________________________________  Date:______________
Witness Name and Signature

__________________________________________  Date:______________
Translator’s Name and Signature
Appendix VIII – Patient Information leaflet

Patient Information Leaflet

Study Title: Is TB Recurrence in treated TB-HIV co-infected patients relapse or reinfection?

Principal Investigator: Dr Kogielem Naidoo, MBChB

The purpose of this document is to give you information on a study that we would like to conduct at this clinic. We are doing research on HIV-infected patients and want to understand why some patients may develop Tuberculosis (TB) more than once while on highly active antiretroviral therapy (HAART).

What will be expected of me in this study?

Should you be agreeable to participate in this study, you will first be asked to read or have someone read to you the “Informed Consent Document” and you will need to sign on the document. Participating in this study will involve giving some blood and sputum (saliva) samples and these will be stored. You will be asked by the study staff member for your consent to have your blood and sputum samples stored. You will be asked to sign the “Storage Informed Consent” indicating whether you wish to have your samples stored or not.

Please note that:

• Your participation in this study is entirely voluntary. You may decide not to participate in the study, but you are still eligible for anti-retroviral therapy. You may decide to obtain your HIV care through your own medical care provider.

• You may stop taking part in the study at any time and this will not affect the care you receive through the CAT Programme.

Once you have agreed to participate in the study you will be required to make regular visits to the clinic. **You will be required to come to the clinic for the Entry visit, Month 1 and Month 3 and thereafter you will be required to come once every 3 months.** During your clinic visits you will be seen by a doctor for a physical exam. Once every 6 months you will be required to have a Chest X-ray, and once every 3 months you will be required to have blood draws (about 60mL of blood will be drawn which is equal to approximately 4 tablespoons). Sputum (saliva) samples will be taken every 3 months. The purpose of the Chest X-rays and sputum tests is to determine if you may have TB and the blood draws are important for obtaining your CD4+ T cell count (immune cells that help fight infection such as HIV) and viral load (which measures how much of the HIV is in your body). There will be approximately 550 people who will participate in this study. The study will be conducted over 3 years.

**STORAGE OF SAMPLES**

Your samples will be stored at laboratories that are specially designed to keep stored samples safely. Only approved researchers working on this project and related projects will be able to access your samples. The people who work at these laboratories will have access to your samples when they store
them and keep track of them, but they will not know who you are as your samples will be stored by number. There is no time limit on how long your samples may be stored.

Should you decide during the study that you do not want the samples to be stored, you do have the right to request that your samples be destroyed. A study staff member will ask you to sign a form documenting your decision. Deciding to withdraw consent to have your samples stored will not affect the quality of care and attention that you receive within the study.

WHAT ARE THE RISKS AND DISCOMFORTS ASSOCIATED WITH THE STUDY?

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection. Many people do not understand the facts about infection with the AIDS virus. Being HIV positive can be a very stressful experience. You may be treated badly by friends and family if you are HIV positive and your HIV status becomes known to others. If you have a Chest X-ray and you are pregnant, then there is a risk to your unborn baby.

What are the benefits of being in this study?
The benefit of being in this study is that a clinician will actively search for TB disease at every 6 month visit that you make to the clinic. Your health will be followed more closely and this may make you feel better though no guarantee can be made. However, should you wish to not to participate in the study, this will not affect the quality of care and treatment within the CAPRISA AIDS Treatment (CAT) programme.

Will there be reimbursement?
Patients who agree to participate in this study will be reimbursed R50 for every scheduled study visit.

What about confidentiality?
Your medical records, personal information, and the results of your HIV tests and other medical and laboratory evaluations will be kept strictly confidential within the extent of South African law. Only your doctor and/or nurse will know the results of your tests. Your records will be identified by a study code. Any publication of this study will not use your name or identify you personally.

Every effort will be made to protect your confidentiality but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by regulatory authorities, such as the Medicines Control Council (MCC), the University of KwaZulu Natal Biomedical Research Ethics Committee, Centres for Disease Control (CDC), study staff and study monitors.

Why You May Be Withdrawn From The Study Without Your Consent?
You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- The study staff feels that staying in the study may be harmful to you.
- You are not able or willing to attend study visits or to complete the study procedures.
What other choices do I have beside this study?

Should you decide not to participate, you will be offered treatment and care in the CAPRISA AIDS Treatment (CAT) programme.

Signing of the patient informed consent form and specimen storage consent form

If you are agreeable to taking part in this study, a staff member will read or will explain to you the information in the Informed Consent Form. This form will provide you with further information about the study and what is expected of you while you are in the study. Please tell or ask the study staff any concerns or queries that you may have.

You will also be asked for your permission to have blood and sputum samples stored for the study and for future research purposes. The study staff member will read and have explained to you the information on the Informed Consent Form for Specimen Storage. Please tell or ask the study staff any concerns or queries that you may have.

You will be given a copy of both these forms. You may also keep this document with you.

For questions about this study or a research-related injury, contact any of the following persons:

Clinic Manager at Prince Cyril Zulu Communicable Disease Clinic:
Dr. Nesri Padayatchi
CAPRISA Deputy Director
Tel: (031) 260-4574

Principal Investigator:
Dr. Kogieleum Naidoo
Tel: (031) 260-4687

Co-Principal Investigator:
Prof. Salim Abdool Karim
Tel: (031) 260-4550

For questions about your rights as a research participant, you may contact:
BREC Administrator or Chair – for reporting of complaints/problems-
Biomedical Research Ethics Committee
Private Bag X54001
Durban
4000
Telephone: +27 (0) 31 260 4769
Fax: +27 (0) 31 260 4609
E-mail: ramnaraind@ukzn.ac.za
Appendix IX – Draft Patient Demographics and Household Form

<table>
<thead>
<tr>
<th>PID</th>
<th>1</th>
<th>2</th>
<th>Visit Code</th>
</tr>
</thead>
</table>

Patient demographics

1. Date of birth [D D] [M M M] [Y Y] OR Age [ ]

2. Sex: Male [ ] Female [ ]

3. Race: Black [ ] White [ ]
Indian [ ] Coloured [ ]
Other [ ] specify______________________

4. Marital Status: Single [ ] Married [ ] Divorced/Separated [ ]
Widowed/death of partner [ ] [D D] [M M M] [Y Y]

5. Duration with current/last partner [ ] [ ] years [ ] [ ] months

6. Education: No schooling [ ] Primary school not complete [ ]
Primary school complete [ ] Secondary school not complete [ ]
Secondary school complete [ ] Attended college/university [ ]

7. Occupation: Unemployed [ ] Employed part-time [ ]
Employed full time [ ] Student/Scholar [ ]
Running household [ ] Other [ ]
specify: ____________________

Form Version 1.0 - 1 - 23 January 2009
Principal Investigator: Dr Kogieleum Naidoo
Protocol version 2.1, 22 July 2009
**Household Information**

8. **Head of household:**
   - Self
   - Parent
   - Partner
   - Grandparent
   - Other: please specify________________________

9. **Source of income:**
   - Self
   - Grandparent
   - Parent
   - Partner
   - Social Grant/Pension
   - Single Care grant
   - How many children
   - Other: please specify________________________

10. **Does your home have:**
    - Yes
    - No
    - Tap water
    - Electricity
    - Telephone

11. **How many adults live in your home?**

11. **How many children (<18 years) live in your home?**

Staff Initials ___________________ Date: ___________________
### Appendix X – DRAFT PHYSICAL EXAMINATION FORM

<table>
<thead>
<tr>
<th>PID</th>
<th>Visit Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date of visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulse</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>bpm</td>
<td>cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BP</th>
<th>mmHg</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pregnancy test:</th>
<th>Negative</th>
<th>Positive</th>
<th>Not done</th>
<th>Not applicable</th>
</tr>
</thead>
</table>

### Medical Exam Findings:

<table>
<thead>
<tr>
<th>Medical Exam Findings</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karnofsky Score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Karnofsky Score: 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ]

Principal Investigator: Dr. Kogieleum Naidoo

Protocol version 2.1, 22 July 2009
## Appendix XI – DRAFT Safety Blood Results Form

<table>
<thead>
<tr>
<th>PID</th>
<th>Visit Code</th>
<th>Date of visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb</strong></td>
<td>g/dl</td>
</tr>
<tr>
<td><strong>Haematocrit</strong></td>
<td>l/l</td>
</tr>
<tr>
<td><strong>Platelet count</strong></td>
<td>$X10^9/l$</td>
</tr>
<tr>
<td><strong>Leucocyte count</strong></td>
<td>$X10^9/l$</td>
</tr>
<tr>
<td><strong>Lymphocytes</strong></td>
<td>$X10^9/l$</td>
</tr>
<tr>
<td><strong>Neutrophils</strong></td>
<td>$X10^9/l$</td>
</tr>
<tr>
<td><strong>Monocytes</strong></td>
<td>$X10^9/l$</td>
</tr>
<tr>
<td><strong>Eosinophils</strong></td>
<td>$X10^9/l$</td>
</tr>
<tr>
<td><strong>Basophils</strong></td>
<td>$X10^9/l$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Staff initials</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Form Version 1.0

Principal Investigator: Dr Kogieleum Naidoo
### Appendix XII – Draft ART Efficacy Monitoring Form

<table>
<thead>
<tr>
<th>PID</th>
<th>Visit Code</th>
<th>Date of visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4</th>
<th>cells/µL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD8</th>
<th>cells/µL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4:CD8 ratio</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD3</th>
<th>cells/µL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Viral load</th>
<th>Copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td></td>
</tr>
</tbody>
</table>

### Greater than (>) Less than (<) Equals to (=)

<table>
<thead>
<tr>
<th>Greater than (&gt;)</th>
<th>Less than (&lt;)</th>
<th>Equals to (=)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Staff initials</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix XIII – Draft TB Recurrence

PID  Visit Code

Date of visit

Date of diagnosis TB Recurrence

TB Recurrence diagnosed on the basis of:  Chest X-Ray  Sputum  Culture

Was a RFLP conducted:  Yes  No

Site of TB:  Lung  Lymph node  Abdominal cavity  CNS  Other

Staff initials  Date
## Appendix XIV - Draft Baseline and Follow up Chest X-Ray and Sputum

<table>
<thead>
<tr>
<th>PID</th>
<th>Visit Code</th>
<th>Date of visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chest X-Ray Date</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Findings:

- Both lungs normal [□] OR Abnormal [□] if abnormal, complete the findings below

<table>
<thead>
<tr>
<th>Right Lung</th>
<th>Left Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- Cavities
- Infiltrates
- Adenopathy
- Pleural Disease

Other

specify ____________________________

specify__________________________

### Sputum Results:

<table>
<thead>
<tr>
<th>Lab Number</th>
<th>Spot</th>
<th>EMS</th>
<th>Sample Date</th>
<th>Smear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Smear: Negative [□] + [□] ++ [□] +++ [□] ++++ [□]

Staff initials | Date |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Form Version 1.0 1 23 January 2009

Principal Investigator: Dr Kogieleum Naidoo

Protocol version 2.1, 22 July 2009
Appendix XV – Draft Sputum Culture and Susceptibility

<table>
<thead>
<tr>
<th>PID</th>
<th>Visit Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Date of visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen date</th>
<th>Lab Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Culture</th>
<th>Neg</th>
<th>Pos</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If Positive and colony count available, complete below

- <10 colonies
- ≥10 colonies

Susceptibility:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETHO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETHIO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Staff initials

Date
### Appendix XVI

#### Draft Follow-up Chest X-Ray and Sputum

<table>
<thead>
<tr>
<th>PID</th>
<th>Visit Code</th>
<th>Date of visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Chest X-Ray Date**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

**Findings:**

- Both lungs normal [ ] OR Abnormal [ ]

  **Right Lung**
  - No [ ] Yes [ ] UK [ ]

  **Left Lung**
  - No [ ] Yes [ ] UK [ ]

- Cavities
- Infiltrates
- Adenopathy
- Pleural Disease
- Other
  - specify ______________________________
  - specify ______________________________

**Sputum Results:**

- Lab Number

<table>
<thead>
<tr>
<th>Spot</th>
<th>EMS</th>
<th>Sample Date</th>
</tr>
</thead>
</table>

  **Smear:**
  - Negative
  - +
  - ++
  - +++
  - ++++

  Staff initials

<table>
<thead>
<tr>
<th>Date</th>
</tr>
</thead>
</table>

---

Principal Investigator: Dr Kogieleum Naidoo

Protocol version 2.1, 22 July 2009
APPENDIX XVII – Planned Tables and Figures

1. Planned figures for the study

Figures 1.1: Illustrates patient participation in the study

Figure 1.2: Kaplan Meier graph of survival analysis: the time to TB relapse vs re-infection from first TB diagnosis

Figure 1.3: Kaplan Meier graph of survival analysis: the time to TB relapse vs re-infection from HAART initiation

Figure 1.4: Kaplan Meier graph of survival analysis: the time to TB relapse vs re-infection from TB treatment cure/completion at previous episode of TB

2. Planned Tables for the study

Table 2.1: Patient Baseline Characteristics: TB reinfection vs TB relapse

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>TB Reinfection</th>
<th>TB Relapse</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min to max</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 count at baseline, cells/µL (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min to max</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log viral load at baseline, copies/mL (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min to max</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO Stage 4 at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR TB cases</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Protocol version 2.1
22 July 2009

Principal Investigator: Dr Kogieleum Naidoo
Table 2.2: Hazard ratios comparing the risk factors for TB Reinfection and TB Relapse, results from proportional hazards regression

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB Recurrence (Relapse as Reference group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO (4 vs 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 at time of recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (females as reference group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of any TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of previous episodes of TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Virologic suppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration on first line ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion on second line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful TB treatment completion at previous episode of TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of previous TB treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of Extra-pulmonary TB at previous episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to ART initiation from previous diagnosis of TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of Extra-pulmonary TB at TB recurrence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.3: Hazard ratios comparing the risk factors for TB Recurrence and Non TB Recurrence, results from proportional hazards regression

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unadjusted</th>
<th></th>
<th></th>
<th>Adjusted</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TB Recurrence</td>
<td>Hazard</td>
<td>95% Cl</td>
<td>p-value</td>
<td>Hazard</td>
<td>95% Cl</td>
<td>p-value</td>
</tr>
<tr>
<td>WHO (4 vs 3)</td>
<td>Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (females as reference group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of any TB Drug resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of previous episodes of TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Virologic suppression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration on first line ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion on second line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful TB treatment completion at previous episode of TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of previous TB treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of Extra-pulmonary TB at previous episode</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to ART initiation from previous diagnosis of TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.4: Presentation at TB recurrence of TB relapse versus re-infection

<table>
<thead>
<tr>
<th></th>
<th>TB Relapse (n=)</th>
<th>TB Re-infection (n=)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiologic features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- parenchymal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- intrathoracic LN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pleural disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scarring at end of treatment (prev TB)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No zones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two or more zones</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cavitation at end of treatment (prev TB)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Virologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- % Viral load undetectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- % with Immunologic recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- suspected IRIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microbiologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Smear +ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Culture +ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- EPTB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- AIDS Defining Illness /HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Progress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug resistant TB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX XVII : Principal Investigator's Curriculum Vitae

Curriculum Vitae Template

This CV template must be completed by the Principal Investigator if this is his/her first submission in the present Calendar year or the application will be considered incomplete and the protocol request will not be reviewed by the REB until received. Do not include the full CV with the application but keep a copy in your study file should the REB require more detail on your qualifications. The REB will consider similar template designed by the pharmaceutical companies in lieu of this form.

Outlines the most relevant experience required for your present research projects only and ensure the form is limited to two pages.

Investigator Name: Kogieleum Naidoo
Investigator Citizenship: South African

Investigator Address: CAPRISA, Nelson R Mandela School of Medicine, P/Bag X07, University of Kwa Zulu Natal, Congella, 4013.

Education (List colleges/universities attended with dates and degree obtained):
University of Natal, Durban – MBChB obtained in 1992 (Medicine)
College of Medicine, South Africa – Diploma – 2003 (HIV Management)

Postgraduate training (List Specialties, give dates, name institutions):
College of Medicine, South Africa – Diploma – 2003 (HIV Management)
Certificate in Advanced Health Management – 2009 (FPD-SA)

Previous appointments/experience (Include all relevant therapeutic, practical experience after gaining qualifications and active professional registration licenses):
1995-2000 (Clinical Investigator – Pediatric), 1999-2000 (Clinical Investigator – SA trial), 2001: Medical Officer Department of Medicine, Coordinator VCT Programme Anglican Church of Kwa Zulu Natal, 2001-2002: Co-director Khanya HIV Treatment St. Andrew Mission Hospital, 2002 (Medical Officer – King Edward Hospital Adult HIV Clinic), 2002 (Co-investigator, HIVEX – 1 study, 2003 Clinical Manager HIVEX study, co-director HIV/AIDS management clinic, Parklands Hospital, 2004 CAPRISA START Project Director at King Edward, 2005 CAPRISA, START/SAPT study Project Director, Project Director CAPRISA AIDS Treatment Programme, 2007 – Head of Treatment Research, CAPRISA, Co-investigator AIDS Clinical Trials Group.

Publications (type appropriate box for number of articles published)

0 □ 1-5 □ 6-10 □ 11-20 □ >20 □

Previous research experience (Example: 3 clinical drug trials in the cardiovascular field and 2 in respiratory field; 3 trials examining Quality of Life post cardiac surgery):
1. [Details of research activities]
2. [Details of research activities]
3. [Details of research activities]

Research Ethics Training and type of Good Clinical Practice (GCP) training (List tutorial, conferences, workshops, meetings attended and dates e.g. Tri-Council Policy Statement online tutorial, NIH online ethics tutorial, ethics conferences, GCP training at investigators meetings, etc.): Note: Although, not required as a condition of approval by the REBs at this time we encourage all researchers to complete the online TCPS Ethics Training at http://www.pre.ethics.gc.ca/english/tutorial/.

Date of signature: [Signature]

CV template
Version October 31, 2006

Protocol version 2.1
1
22 July 2009

Principal Investigator: Dr Kogieleum Naidoo
APPENDIX XVIII : Conflict of Interest

CONFLICT OF INTEREST
Appendix A
CAPRISA
Statement of Financial, Equity and Intellectual Property Interests
Name: Dr Kogie Naidoo
Position held within CAPRISA: Head: Treatment Research

1. **Present Interests:** Please list below any relevant entity (company) in which you or your family member(s) have or have had R50,000 or more of either financial or intellectual property interest, or any shares or ownership interest in any single entity, in the 365 days prior to the date of this document, as defined by the CAPRISA Conflict of Interest Policy.

   *If no present significant interests exist, initial here:*

<table>
<thead>
<tr>
<th>NAME OF COMPANY/ENTITY</th>
<th>TYPE OF INTEREST (PLEASE CHECK)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FINANCIAL</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Future Interests:** Please list below any relevant entity (company) in which you or your family member(s) will have R50,000 or more of either financial or intellectual property interest, or any shares or ownership interest in any single entity, in the future, as defined by the CAPRISA Conflict of Interest Policy.

   *If no future significant interests exist, initial here:*

<table>
<thead>
<tr>
<th>NAME OF COMPANY/ENTITY</th>
<th>TYPE OF INTEREST (PLEASE CHECK)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FINANCIAL</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. The statements I have made are true, complete, and correct. I give my permission to disclose this information to any appropriate individual or organization.

Signature: [Signature]
Date: 26/01/09

Principal Investigator: Dr Kogieleum Naidoo

Protocol version 2.1  2  22 July 2009
Appendix XIX : Locator Information

LOCATOR INFORMATION.

Name & Surname ___________________________ DATE ___________
Educator ______________________________

<table>
<thead>
<tr>
<th>Alternative Name or Nickname</th>
<th>Name of a friend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth</td>
<td>Age:</td>
</tr>
<tr>
<td>I.D. Number</td>
<td>Closest contact person.</td>
</tr>
<tr>
<td>Present Address—Door No.</td>
<td>Door Number</td>
</tr>
<tr>
<td>Building Name</td>
<td>Building Name</td>
</tr>
<tr>
<td>Street Name</td>
<td>Street number</td>
</tr>
<tr>
<td>Landlord Name</td>
<td>Street name</td>
</tr>
<tr>
<td>Area/west or east</td>
<td></td>
</tr>
<tr>
<td>Phone number</td>
<td>Area</td>
</tr>
<tr>
<td>Cell phone</td>
<td>Phone number</td>
</tr>
<tr>
<td>Occupation</td>
<td>Cell phone</td>
</tr>
<tr>
<td>Work Address-door no.</td>
<td>Second contact person</td>
</tr>
<tr>
<td>Building name</td>
<td>Name</td>
</tr>
<tr>
<td>Street name</td>
<td>Name of a closest neighbor</td>
</tr>
<tr>
<td>Street no.</td>
<td>Phone number</td>
</tr>
<tr>
<td>Area</td>
<td>Bus stop</td>
</tr>
<tr>
<td>City</td>
<td>Area’s nickname e.g. point/Jacobs</td>
</tr>
<tr>
<td>Name of friend at work.</td>
<td>Nearest Tuck shop</td>
</tr>
<tr>
<td>Friend’s phone number.</td>
<td>Nearest Church</td>
</tr>
<tr>
<td>Name of relative staying with.</td>
<td>Nearest tavern</td>
</tr>
<tr>
<td>Relatives phone number.</td>
<td>Nearest clinic</td>
</tr>
<tr>
<td>Nearest school</td>
<td>Directions to your place</td>
</tr>
</tbody>
</table>

1. Telephone tracking: All patients are introduced to the nurse responsible for tracking on enrolment into the program. Patients provide direct and alternate contact numbers to site staff. If alternate contact numbers are provided patients indicate whether or not their HIV status is known to the alternate contact. This information is annotated on the patient Locator log, which is kept in the patients file. Three attempts are made to reach patients using these numbers, before physical tracking attempts are made.
made. If we are successful in getting hold of the patient, the caller then identifies herself as a nurse from a clinic, and the patient is reminded to come to clinic and the appointment is rescheduled.

2. Physical tracking: Patients are visited at their home address. The counselor ensures that there is privacy before embarking on counseling on the need to keep appointments, and adhere to prescribed treatment schedules. The patient is reminded to come to clinic and the appointment is rescheduled. If the patient is found to be ill, depending on the condition of the patient, transport is arranged for the patient to the clinic or hospital. If the patient is not home, we identify ourselves as Nurses, and leave a message that the patient needs to call the clinic.