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AN EPIDEMIOLOGICAL EVALUATION OF ATYPICAL MYCOBACTERIUM AND TB/HIV-AIDS STATUS IN MALAYSIA- CLINICAL AND MICROBIOLOGICAL OUTCOMES OF THE DISEASES

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
ARVT	Anti Retroviral Therapy
ATT	Anti Tuberculosis Therapy
BCG	Bacille Calmette Guerin
DOT	Directly Observed Therapy
DOTS	Directly Observed Therapy-Short Course
EPTB	Extrapulmonary Tuberculosis
ETH	Ethambutol
GRID	Gay Related Immune Deficiency
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
INH	Isoniazid
IVDUs	Intravenous Drug Users
MDRTB	Multi Drug Resistant Tuberculosis
PAS	Para-Amino Salicylic Acid
PCP	*Pneumocystis carinii* Pneumonia
PPD	Purified Protein Derivative
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
RIF	Rifampicin
SM	Streptomycin
STDs	Sexually Transmitted Diseases

TB	Tuberculosis
TST	Tuberculin Skin Test
WHO	World Health Organization

LIST OF PUBLICATIONS & SEMINARS

1.1 Angelina Gurunathan, Pazilah Ibrahim, Syed Azhar Syed Sulaiman and Kuppusamy Iyawoo.
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1.2 A. Gurunathan, P. Ibrahim, S.A. Syed Sulaiman and K. Iyawoo.
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AN EPIDEMIOLOGICAL EVALUATION OF ATYPICAL MYCOBACTERIUM AND TB/HIV-AIDS STATUS IN MALAYSIA: CLINICAL AND MICROBIOLOGICAL OUTCOMES OF THE DISEASES

ABSTRACT

In view of the heterogeneous nature of the epidemiology of tuberculosis, the increasing number of cases associated with AIDS and the spread of resistance to antibiotics, all methods of combating the disease must be mobilized. BCG does not prevent reactivation of latent forms and has no impact on transmission of tuberculosis; it is of great value in preventing the most serious forms, miliary and meningeal tuberculosis.

The Atypical Mycobacterium in TB/HIV status in Malaysia is still in vague as most hospitals do not routinely cultured this organisms and will only do so if they highly suspicious about the existence of the organisms. Majority of the Health Institutions will only looking at the matter if other sources of TB cannot be ruled out. Majority of the microbiological evaluation for TB and TB/HIV situation does not focused on these atypical organisms. Some of the observed atypical organisms are *M. kansasii* ,*M. xenopi*, *M. genavense* , *M. haemophilum, M. fortuitum, M. chelonei.*, and *M. intracellulare,*. Hopefully in future, the trend of evaluating these organisms will be routinely done together with the common organisms. The threat of TB seemed to have become increasingly imminent with the lethal symbiosis of TB and human immunodeficiency virus (HIV)-acquired immune deficiency syndrome (AIDS) (Saltini; 1999). This danger is further compounded with the fact that HIV-AIDS is the foremost cause of death from infectious disease in the world; seconded only by TB. (Corbett *et. al.*, 2003). Co-infection with HIV and TB is a phenomenon that is becoming rampant worldwide and Malaysia is no exception. However there is no substantial data

concerning the co-infection of both the diseases in the country. This study's main aim was to obtain a baseline data pertaining to the epidemiology of TB/HIV-AIDS in Malaysia. Records of 231 patients co-infected with TB/HIV-AIDS between the months of January 1999 and June 1999, and between the months January 2000 and December 2002 were obtained retrospectively from the Institute of Respiratory Medicine and the Infectious Disease Clinic at Hospital Kuala Lumpur. Data obtained was analyzed with Statistical Package for the Social Sciences (SPSS) software for Windows release 11.5. Results obtained indicated that the majority of patients were males (222), intravenous drug users (IVDUs) (179), Malays (129) and aged between 31-40 years (114). A total of 63 patients were employed and 54 patients were unemployed. The rest comprised of prison inmates (36), drug rehabilitation centre inmates (6) and those whose occupation status remained undetermined (72). The presence of BCG scar (indicating that the vaccine had been administered) was found in 92 (39.8%) patients. Most of the patients (175 patients) were treated for tuberculosis with 2 months of daily doses of ethambutol, isoniazid, rifampicin and pyrazinamide followed by 4 months of biweekly doses of rifampicin and isoniazid (2EHRZ, 4RH2). There were only 14 patients who underwent antiretroviral therapy (ARVT) for HIV infection at the Infectious Disease Clinic, Kuala Lumpur Hospital. The results of this study indicated that the prevalence of TB/HIV co-infection was high among IVDUs and Malay males who were in the economically productive age group. There was no significant relationship between the various lifestyle of the patients (IVDU, smoking and alcohol consumption) and the different stages of the TB disease. However, this could have been due to the large number of unknown data in this study.

General Introduction

The discovery of *Mycobacterium tuberculosis* (*M. tuberculosis*) as the causative agent of tuberculosis (TB) in 1888 by Robert Koch marked the advent of important developments in the field of bacteriology. Now over a century from that eventful year, TB stubbornly remains a bane to the human population worldwide.

This bacillus, which exists in the human reservoir, is capable of infecting certain animal species living in the vicinity of man (cats, dogs, birds, monkeys). The organism is extremely sensitive to heat and sunlight but is resistant to cold and dryness and may remain alive for several days in contaminated products such as expectoration.
Other species of mycobacteria are present in the environment and are able to infect man: Mycobacterium africanum, Mycobacterium ulcerans, Mycobacterium avium and Mycobacterium bovis.

Following contamination, generally airborne, the bacteria grows in the pulmonary alveoli and in macrophages, thus initiating local inflammatory response.
The immune response to the bacteria is essentially cellular and is associated with positive results in a tuberculin skin test. Activation of Th1 and Th2 lymphocytes stimulates the activity of macrophages through the secretion of various cytokines and gamma interferon. Where immune response is unable to prevent replication of the bacteria, the active disease begins. This stage is enhanced by immunodepressed states such as AIDS, anti-cancer chemotherapy, intensive corticosteroid therapy, badly controlled diabetes, renal failure, malnutrition, or vitamin A or D deficiency.

The tuberculin skin test is currently the best method of screening for latent tuberculosis. After initial infection, this test is positive within two to twelve weeks.

In the majority of cases, initial infection remains asymptomatic and infection may remain latent for months or years. Although the majority of subjects with latent tuberculosis do not go onto develop the clinical disease, some 5 to 10% develop and active form of tuberculosis during there life

The nontuberculosis mycobacteria are often naturally resistant to the conventional antibiotics and to antituberculosis drugs. In addition, providing advice for the treatment of nontuberculosis is complicated by the variable and changing designations of these organisms, the heterogeneity of the clinical syndromes and patients, and the relative lack of controlled clinical trials. This chapter discusses the management of these difficult infections.

The clinical importance of Mycobacterium tuberculosis as a major cause of death has meant that microbiologists have rightly focused on this organism. The remaining Mycobacterium species, which appeared to lack the potential to cause infection in healthy individuals, were often dismissed as "anonymous" or "atypical". This approach was neither accurate nor clinically helpful. As environmental organisms, their low pathogenic potential and failure to produce diseases that resemble tuberculosis is expected. Thus, the term nontuberculosis mycobacterium (NTM) is preferred

The threat of TB seemed to have become increasingly imminent with the lethal symbiosis of TB and human immunodeficiency virus (HIV)-acquired immune deficiency syndrome (AIDS). This danger is further compounded with the fact that HIV-

AIDS is the foremost cause of death from infectious diseases in the world; seconded only by TB. (Corbett *et. al.*, 2003).

M. tuberculosis has become the most common opportunistic pathogen found among HIV positive individuals. According to the World Health Organization (WHO) about a third of the 36 million people living with HIV worldwide are co-infected with *M. tuberculosis* (WHO, 2002a). Therefore, it is not unforeseen that a third of deaths worldwide is caused by AIDS and TB is the leading cause of death among people with HIV infection. (UNAIDS, 2002). TB may as well be one of the first signs of AIDS manifesting itself in HIV positive individuals as it often occurs at an earlier stage in the course of HIV infection and may precede the diagnosis of AIDS by several months. (Mastroianni, 1998). More than 95% of all TB cases and 97% of all deaths occur in developing countries. In sub-Saharan Africa owing to the HIV/AIDS epidemic, an increase of up to 10% of new TB infections a year is recorded. (Kurth & Haas, 2002)

There is a possibility that it is not only the HIV that provides a conducive milieu for the *M. tuberculosis* to thrive and proliferate, for it has been shown that TB may act as a cofactor in the progression of HIV infection. It was also found that HIV-infected patients with active TB have a shorter survival than HIV-infected patients without TB. (Pape *et al.,* 1993).

1.2 Epidemiology

1.2.1 Tuberculosis (TB)

In general TB can be identified as a disease of the poor. The less developed health systems are, the higher the rates of new cases of TB. The WHO has identified 22 high burden countries in the developing areas of the world which carry

about 80% of the disease burden. The countries are; Afghanistan, Bangladesh, Brazil, Cambodia, China, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, Uganda, United Republic of Tanzania, Vietnam and Zimbabwe. It is worth noting that 4 (Cambodia, China, Philippines and Vietnam) of the 22 global high TB burden countries are in the Western Pacific Region to which Malaysia belongs.

In the year 1990, it was estimated that there were 7, 537, 000 incident cases of TB in the world. This included over 4.9 million cases (65%) which occurred in South-East Asian and Western Pacific regions. Out of the 4.9 million cases, 2.1 million occurred in India, 1.3 million in China and 0.4 million in Indonesia. In the Sub-Saharan African region, 1 million cases occurred, Eastern Europe and independent states of former USSR had 0.2 million cases, while Western Europe and other industrialized countries had 0.2 million cases. (Dolin *et. al.,* 1994).

In the year 2000, it was estimated that 8-9 million new cases of TB occurred globally. However, only less than half of these estimated cases were reported. It is further daunting to note that out of the 8-9 million new cases of TB, 3-4 million cases were of the infectious type. (Corbett *et. al.,* 2003).

In the developing countries in Asia, TB seemed to have disseminated itself evenly for it is found in all age groups of native-born populations. The same cannot be said in developed and industrialized countries as a substantial proportion of TB cases occur in foreign-born residents who are mostly from developing nations. (Castro, 1998). In 1998 for example, 38% of patients with TB in England and Wales were from the Indian Sub Continent, 13% were of black African ethnic, 2.2% were black Caribbean and 1.8% were from the Chinese ethnic group. (Rose *et. al.,* 2001)

In Malaysia TB was the number one cause of death in the early 1940s and 1950s. In the year 1961 the Malaysian government launched its National TB Control Programme (NTP) to counter the disease. The programme played an important role in controlling the disease. However, over the past 10 years there has been a steady increase in the number of TB notifications in Malaysia. The incidence of TB in 1997 was 63.6 per 100,000 population as compared to 61.0 per 100,000 population in 1996. (MOH, 1998). In the year 2000 a total of 15, 057 cases of all forms of TB were notified in the country with an incidence rate per 100,000 population of 64.7. The state with the highest disease burden was Sabah, followed by Wilayah Persekutuan, Sarawak and Pulau Pinang. (MOH, 2000). According to the World Health Organization (WHO), there were 14,389 notified TB cases in Malaysia in the year 2002. This included 7,958 new cases with sputum smear positive results. (WHO, 2004). Preliminary reports from the MOH indicates that the incidence rate of all TB forms was 63.3 per 100,000 in Malaysia for the year 2003. (MOH, 2004).

1.2.2 Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome (HIV/AIDS)

The first cases of AIDS were identified in 1981 in the United States of America (USA) among gay young men. Initially before discovering the agent which caused the damage to the immune system was found, the disease was called gay related immune deficiency (GRID). Later it became clear that whatever was causing this condition was transmitted through sexual activity as well as through the use of contaminated needles. Cases among individuals who had received blood transfusions or blood products, particularly haemophiliacs were also noted. Since people other than gay

men were being diagnosed with the condition, it became known as acquired immunodeficiency syndrome (AIDS). (Ford, 1992).

Since then the HIV has killed over 20 million people worldwide. The effect of this disease is most prominent in the African continent. The Sub Saharan Africa is home only to just over 10% of the world's population but contains almost two thirds of all people living with HIV. (UNAIDS, 2004).

In Asia, an estimated 4-7 million people are living with HIV and around ½ a million are believed to have died of AIDS in 2003 while as many as 1 million people are thought to have become newly infected with HIV in this continent in the same year. India which has the largest number of people living with HIV in Asia and in any country outside South Africa, was estimated to have 4.6 million people living with HIV in 2002. The HIV epidemic in Asia, remains largely concentrated in injecting drug users, men who have sex with men, sex workers, clients of sex workers and their immediate sexual partners. (UNAIDS, 2004).

In Malaysia the first case of HIV/AIDS was identified in 1986, and in the year 1999 HIV had an incidence rate of 20.80 per 100,000 population, this number increased to 30.35 per 100,000 population in the year 2002. (MOH, 2003). Preliminary reports from the MOH indicates that the incidence rate of HIV in Malaysia for the year 2003 is 26.9 per 100, 000 population. (MOH, 2004). The epidemic is fuelled by drug use mainly due to the country's proximity to the Golden Triangle (an area along the borders of Thailand, Myanmar and Laos where production of heroine flourishes) and the easy accessibility of the country by both land and sea. (Huang & Hussein, 2004).

1.2.3 TB/HIV Co-Infection

The report by Dye *et. al.,* (1999) stated that in 1999 an estimated 1.87 million people died of TB and the global case fatality rate was 23% but exceeded 50% in some African countries with high HIV rates. Prevalence of *M. tuberculosis* (MTB)/HIV co-infection worldwide was 0.18% (10.7 million people) and 640,000 incident TB cases (8%) were associated with HIV infection. Africa had by far the highest fraction of TB cases that were HIV-positive (32%) and persons with MTB/HIV co-infection (1.2%). Only less than half (42%) of all estimated TB cases and about one third (37%) of smear positive cases were reported to the WHO.

The threat of these two dangerous infections has become bigger with rapid travelling and immigration. TB cannot be viewed as a singular entity anymore. The ominous partnership of TB-HIV/AIDS is becoming increasingly prevalent globally. The United States of America (USA) recorded a 6.7% annual decline in TB cases during the years 1981-1984. However in 1985 to 1991 the number of cases increased by 18%. It was found that the occurrence of TB among persons with HIV infection was a major factor contributing to this significant change in the pattern of decline of the TB disease. (American Thoracic Society, 1992). A total of 61 cases of TB/HIV co-infection were recorded in England and Wales in the year 1993. However this number nearly doubled in the year 1998 to 112. While only 2.15% of the total cases of TB patients were co-infected with HIV in the year 1993 3.26% of all TB cases in the year 1998 were TB/HIV co-infection. This indicated that HIV alone had contributed to 8.5% of the increase in TB between the years 1993 and 1998. In London between the years 1993 and 1998, the

number of cases with both TB and HIV infection more than doubled from 39 (3.3%) cases in 1993 to 86 (5.4%) cases in 1998. (Rose *et. al.,* 2002).

In Malaysia, the number of cases of TB with HIV/AIDS continues to increase since 1990. In 1990, the percentage of HIV/AIDS co-infection with TB was 0.05% and in 1997 this increased to 2.2%. In 1990 there were only 6 reported TB cases with HIV infection but in the year 1997 there were 322 cases reported. (MOH, 1998). In the course of three years this number more than doubled to 734 cases in the year 2000. (Iyawoo, 2004).

Historical background to vaccination and vaccinal strategy

The story of BCG began in 1908 when Albert Calmette and Camille Guérin cultured a pathogenic strain of Mycobacterium bovis isolated from a cow and taken from a tubercular udder lesion. This strain is regularly injected into animals. After several passages, the strain lost its virulence, no longer provoking extensive lesions in the receiving animals. In 1920, after 232 passages at a rate of one every 3 weeks for 13 years (between 1908 and 1921), the cattle in which the vaccine was administered proved capable of resisting a virulent strain. Efficacy was confirmed in a study in young heifers left in contact with tuberculous cows: the vaccinated heifers did not develop the disease.

In 1921, an infant living in a tubercular setting received BCG. It was after this year that BCG came to be used for vaccinal purposes for the first time in France. Use of the vaccine became more widespread in the 1950s.

In 1974, it was introduced into the extended vaccination programme (EVP); it is

administered at birth in countries in which tuberculosis is endemic, resulting in rapid achievement of vaccinal cover rates in excess of 80%. Some 100 million children throughout the world receive BCG vaccinations each year.

Collective analysis of the clinical trials performed to investigate the efficacy of BCG has confirmed the value of this vaccine in preventing meningitis and disseminated forms of the disease

Several strains are used in the manufacture of BCG vaccines, with the most widespread strains being the French Pasteur strain, the Danish strain, the Glaxo strain and the Tokyo strain. There is no worldwide consensus concerning the optimal use of one strain in relation to any others.

The vaccine is administered by the intradermal route. Vaccination schedules in the industrialised countries differ according to the epidemiological profile of each.

1.3 Risk Groups

1.3.1 Age And Gender

Kurth and Haas (2002) reported that in Germany the incidence of TB was at about 9 cases per 100,000 population in the year 2002. TB cases if grouped by age, it became apparent that the disease was a disease of the elderly population in Germany. The observed incidence in people above 69 years was 4-8 times higher than the average incidence in adults younger than 30 years of age. This phenomenon is assumed to be present because in old age, the efficacy of the defense by the immune

system declines allowing in some cases, old contained infections to reappear. In England the number of patients with TB aged 16-54 years reported from outside London increased by 11% between 1993 and 1998 and half of all patients with TB in this age group were women. (Rose *et. al.*, 2002).

In other parts of the world, both HIV and TB has dramatically and specifically zoomed in on the young (15-49 years), and particularly on women. The overall proportion of HIV positive women increased from 41% in 1997 to almost 50% by 2002. In Sub-Saharan Africa, 57% of adults infected with HIV are women and 75% of young people infected were women and girls.

The situation in South and South East Asia however is different. The HIV epidemic is concentrated among injecting drug users who were mostly males. At the end of 2003 women accounted for 28% of HIV infection in these regions. (UNAIDS, 2004). In Malaysia cumulative numbers from the year 1986-2002 showed that males made up more than 90% of those infected with HIV, 91.8% with AIDS and 93.3% of AIDS deaths. This could be caused by the fact that most HIV infected individuals in Malaysia are IVDUs who are also mostly males. Therefore, these individuals who are apprehended by the police are placed in prisons and rehabilitation centres where they are routinely screened for HIV. (Huang & Hussein, 2004).

1.3.2 Ethnic Groups

Several studies have identified several risk groups who seem to have a higher chance of being infected with TB and HIV. A study done by Gampper *et. al.*, 1998 in Rhode Island, United States of America identified certain groups of people to be at a greater risk of being diagnosed with MTB and HIV co-infection. The study showed that

Hispanics were at higher risk for having MTB co-infection. In the United States African Americans and Hispanics were disproportionately affected by HIV infection and TB. This is because African Americans and Hispanics were more likely than whites to be poor, uninsured and more likely to use public sources of care that lack adequate resources. (Brown, 1996; Diaz *et. al.,* 1994). Between the years 1993 and 1998 the number of 16-54 year old patients co-infected with HIV reported from outside London increased by 18% and most were of white ethnicity. (Rose *et. al.,* 2002).

In London the proportion of white patients with TB aged between 16-54 years increased between the years 1993 and 1998 (from 5.2% to 9.8%), while the proportion of black African patients with TB who were co-infected with HIV increased by about one third (from 7.4% to 10.0%). Female black African patients with TB were more likely to be co-infected with HIV than white female patients, but it was found that this was not the case for men. (Rose *et. al.,* 2002).

1.4 Pathogenesis

1.4.1 The Pathogenesis Of The HIV Infection

The human immunodeficiency virus (HIV) is an intracellular parasite, which means that the virus needs a host cell (i.e. human cells) to replicate and propagate. There are two types of HIV virus; HIV-1 and HIV-2. HIV-1 is the more aggressive virus and is responsible for the AIDS pandemic. HIV-2 is much less pathogenic than HIV-1 and it rarely causes AIDS preferring to cause a latent infection instead. (D'Aquila, 1996). Therefore all further discussions on HIV from this point onwards refer to the HIV-1 virus.

The human immunodeficiency virus, upon entry into the human body seeks out the CD4 receptors on T-helper lymphocytes and other cells with CD4 molecule. The target host cell of HIV is the CD4 class of T lymphocyte (T helper cells) and HIV infection prevents normal division processes in these cells. The specificity of HIV for CD4 T cells is due to the fact that the CD4 molecule acts as a cell surface receptor for HIV. Besides this one class of T lymphocytes, several other cell types in the human body have the CD4 molecule on their surface in small amounts and can also be infected with HIV. HIV usually does not immediately kill and lyse its host cell. HIV is a retrovirus and it uses the enzyme reverse transcriptase to form a complementary single stranded DNA molecule using RNA as a template and converts the complementary DNA (cDNA) that was formed into double-stranded DNA, which can enter the CD4 T cells. Following reverse transcription to produce DNA from the RNA genome, the viral cDNA integrates into host chromosomal DNA and exists as a provirus. Provirus refers to a complete viral genome that has been integrated into the host cell chromosome. (Jensen & Wright, 1993).

The cell may show no outward sign of infection, and HIV DNA can remain in a latent state for long periods. Eventually, productive virus synthesis occurs and new HIV particles are produced and released from the cell. T cells producing HIV no longer divide and eventually die. The end result of HIV infection is that CD4 cells progressively decline in number and this has serious health consequences. As CD4 cells decline in number, this leads to gradual reduction in all types of lymphocytes, effectively shutting down the immune system in those suffering from clinical AIDS. With the decline in CD4 T lymphocytes, the body's defense mechanism will be compromised. This will allow opportunistic organisms to cause life-threatening infections. (Madigan *et. al.,* 1998).

1.4.2 The Pathogenesis Of Tuberculosis

The first line of defense against *M .tuberculosis* is the alveolar macrophages, for these alveolar macrophages line the alveoli. Once the organism is engulfed by the macrophage through a complicated process of phagocytosis (Schluger *et al.,* 1998), *M. tuberculosis* can be killed by several different mechanisms involving interactions between lymphocytes and phagocytes. These cellular interactions in TB involve Th1 and natural killer lymphocytes that secrete INF-γ in response to mycobacterial antigens. (Judson, 2002). INF- γ activates alveolar macrophages to produce a variety of substances including reactive oxygen and nitrogen species that are involved in growth inhibition and killing of mycobacteria. (Schluger *et al.,* 1998).

However *M. tuberculosis* organisms that are able to survive the intracellular host defences may grow to a certain limited extent within alveolar macrophages. During the time required to develop cell mediated immunity (CMI) to contain bacterial growth, *M. tuberculosis* infection can spread by lymphohaematogenous dissemination to other sites, including the upper lung fields. With the development of cellular immunity which could take 4 to 6 weeks, small granulomas form at the sites of initial *M. tuberculosis* inoculation and dissemination and this causes the tuberculin skin test (one of the tests used to diagnose tuberculosis infection) to convert to a positive. (Toosi *et al.,* 2001).

Alternatively, and especially if anti - *M. tuberculosis* immune responses fail to develop satisfactorily in the most appropriate time or in a timely manner, the bacilli may continue to replicate and manifest as progressive primary TB. In the majority of

infected individuals, the development of CMI leads either to local destruction of *M. tuberculosis* or persistence of the organisms in a latent phase within tissue macrophages, often for a lifetime. Latent foci of *M. tuberculosis* infection retain the ability to undergo reactivation, most commonly in the lung. (Toosi *et. al.*, 2001). Reactivation of quiescent bacilli can develop years later when the immunologic responsiveness wanes, either due to old age or to immunosuppressive disease or therapy. (Belisle & Brennan, 2000).

1.4.3 The Pathogenesis Of TB/HIV Co-Infection

It is estimated that one third of the total world population is infected with *M. tuberculosis* and out of these; fewer than 10% will develop the disease. This means those who do not develop the disease still have the pathogen (*M. tuberculosis*) in them, but have it contained in discrete lesions. WHO reported that two billion persons around the world have latent TB infection (WHO, 2000). The immune system is very effective in containing the pathogen, but fails to eradicate it. When the immune system is weakened, disease develops through reactivation. (Kaufmann, 2002). HIV infection can reactivate previously acquired *M. tuberculosis* infection or latent TB as the patient becomes immunocompromised. This is because HIV appears to be the most potent known risk factor for reactivation of latent TB. (Fitzgerald *et. al.*, 1999).

Dolin and associates (1994) reported that the coinfected individuals have a marked increase in the overall annual risk of developing active TB. Individuals who are coinfected with *M. tuberculosis* and HIV are 20 times more prone to develop active TB compared to individuals who are only infected with *M. tuberculosis* as the risk of developing active disease for the former is 8% whereas for the latter it is only 0.4% (Dolin *et al.*, 1994). Infection with *M. tuberculosis* in HIV infected patients will activate

viral production in white blood cells latently infected with HIV. This inevitably leads to an increase in the viral load thus hastening the deterioration and eventual collapse of the immune system in the body (Miller, 1996).

1.5 Transmission

1.5.1 Transmission Of The HIV

The principal sources of HIV are the blood and genital secretions of HIV infected persons. Other body secretions or fluids may contain HIV in low concentrations and are probably unimportant in transmission. Three main modes of transmission have been recognized,

1. sexual contact with an infected person
2. inoculation of blood or blood products contaminated by HIV (mainly through needle sharing among intravenous drug users)
3. perinatal transmission from an infected woman to her foetus or infant

Hitherto there is no effective vaccine against HIV, therefore prevention depends on the interception of transmission. HIV infection can be prevented by avoiding the type of behaviour that permits HIV transmission, such as needle sharing with another person, having sex with a person known to be at risk for HIV infection, avoiding sex with casual partners and with multiple partners, avoiding anal intercourse, and by using condoms. (Baron *et. al.*, 1994).

1.5.2 Transmission Of Tuberculosis

TB is a disease that can be spread through the air. An individual can be infected by inhaling a small number of viable tubercle bacilli contained in small aerosolized droplets. (Belisle & Brennan, 2000). Aerosolized droplets are emitted

through coughing, sneezing, talking and even singing. Aerosolized droplets containing *M. tuberculosis* are known as airborne droplet nuclei and minute infectious droplets could measure between 1-5 µm in diameter. (Frieden *et. al.,* 2003). Large droplets get deposited in the upper airways (trachea and bronchi). These droplets are then removed by mucociliary clearance mechanisms. Droplets which are smaller, (1-5 µm in diameter) may contain 3 or fewer bacilli and have a higher chance of reaching the alveoli. (Smith *et al.,* 1970). When a healthy individual inhales this infectious droplet nuclei, the nuclei is lodged in the alveoli in the distal airways. (Frieden *et.al.,* 2003).

In human beings a single exposure to a source of TB is sufficient to contract infection and develop active disease. (Saltini *et. al.,* 1999).

1.6 Clinical Manifestations

1.6.1 Symptoms Of HIV Infection

An individual infected with HIV may develop a transient illness characterized by fever, swollen lymph nodes, a rash and inflammation of the meninges (the three connective tissue membranes which surround the spinal cord and brain). This only happens to 15% of infected individuals. The remainder of infected individuals is asymptomatic at the time of initial infection. Progressive generalized lymphadenopathy (PGL) may develop as time passes. PGL is the swelling of lymph nodes and individuals with PGL as well as those who are asymptomatic may have progression of the infection to fever, night sweats, weight loss and minor infections such as yeast organisms in the mouth which is called thrush. Thrush is caused by the yeast *Candida albicans* and is commonly found in HIV infected individuals. Depending on the individuals, major opportunistic infections will start setting in at varying length of time. These include *Pneumocystis carinii* pneumonia (PCP), mycobacterium infections, toxoplasmosis,

genital and herpes simplex. Karposi's sarcoma a tumour of endothelial cells that give rise to prominent purplish spots on the skin and B-cell lymphomas also may develop and are among the most prominent malignancies observed in patients with AIDS. (Roitt *et. al.,* 1996).

1.6.2 Symptoms And Types Of Tuberculosis

Pulmonary TB may present with a variety of signs. There are certain classic signs of TB that physicians look out for. These include low-grade fevers, rising in the afternoon and accompanied by night sweats, malaise and loss of appetite, cough that becomes productive with purulent sputum or with moderate haemoptysis when caseation (necrotic degeneration of tissues into a soft, cheeselike substance) of the infiltrates results in cavitation. In some patients localized pleuritic pain (sharp, stabbing, pain which is worsened on deep breathing and coughing, caused by pleural inflammation or chest wall lesions) is also present. (Saltini *et. al.,* 1999).

The tubercle bacillus causes the production of a characteristic and unique lesion identified as the tubercle, in the tissues of infected animals and man. In its typical form the tubercle shows a peripheral zone of fibroblasts (cells that make the structural fibres and ground substance of connective tissue) and lymphocytes, an inner zone of epithelioid cells and in its centre one or more giant cells. As it increases in size necrosis of the central portion occurs. The necrotic material is not normally digested, consequently it has a cheesy appearance and consistency on account of which it is known as caseous i.e. cheesy material. Normally when necrosis of tissue occurs the necrosed tissue is digested by tissue proteolytic enzymes. In caseous lesions however, this normal proteolyses is inhibited presumably due to the inhibition of tissue proteases.

It has been suggested that the inhibitor is a lipid component of the bacillus. (Stewart, 1968)

M. tuberculosis can cause pulmonary as well as extrapulmonary tuberculosis. Pulmonary tuberculosis happens when *M. tuberculosis* infects the lungs while extrapulmonary tuberculosis happens when the bacteria infects other parts of the body. Miliary tuberculosis refers to disseminated TB in organs such as lungs, liver, spleen, bone marrow and brain. Unlike the chest radiograph in pulmonary tuberculosis, miliary tuberculosis in the lung shows reticulonodular shadowing in the chest x-ray, similar to the appearance of millet seeds, hence the name miliary tuberculosis. (Carrol *et. al.,* 2001). Lymphatic tuberculosis is another form of extrapulmonary tuberculosis which affects the lymph nodes. At present it is also known as tuberculosis of the lymph nodes or tuberculous lymphadenitis. However previously, this form of tuberculosis was known as scrofula and was widely believed for many centuries (since the 13th century) that the Royal Houses of England and France had a supernatural gift to cure scrofula by merely touching the sufferers. It was for this reason that scrofula was also known as the king's evil. (Grzybowski & Allen 1995).

The most serious clinical manifestation of tuberculosis is the involvement of the central nervous system. This could include inflammation of the meninges, as well as space-occupying lesions (tuberculomas) of the brain. Tuberculosis meningitis is fatal in almost all cases without chemotherapy. Another form of extrapulmonary tuberculosis, the genitourinary tuberculosis (including involvement of the renal and male and female genital tracts) is uncommon and is difficult to distinguish from other infections of the genitourinary tract. (Frieden *et. al.,* 2003). Tuberculosis can also affect any bone or joint, but the spine (i.e. Pott's disease) is the most common bony structure involved. Pott's

disease comprises about 50% of all cases of skeletal TB. (Paradisi & Corti, 1999). Another unusual manifestation is tuberculosis of the skin. Tubercles in the skin can appear as tiny papules with 'apple jelly centres' most commonly on the trunk, thighs and face. These lesions are similar to popular urticaria or early chicken pox lesions. (Carrol *et. al,* 2001).

1.6.3 Clinical Manifestations Of TB/HIV Co-Infection

In an individual infected with both *M. tuberculosis* and HIV, TB could develop at any juncture in the course of the HIV infection. Therefore it could occur during the initial course of HIV infection, which is often before a substantial and significant drop in CD4 lymphocyte cell counts is recorded. Therefore TB could present itself even before clinical conditions suggestive of HIV infection or AIDS appear. (Zumla *et. al.,* 2000).

In the HIV-positive patient the pathologic and clinical features of TB varies with the patient's CD4 lymphocyte count. Reactivation TB occurs early in the course of immune depression in HIV infected individuals. In cases such as these, the formation of "hard" nodules with epitheloid cell granulomas, little caseous necrosis and few bacilli characterize the pathology. Cavitation may also occur as the expression of typical reactivation disease. The pathology is characterized by miliary acinar nodules composed of aggregates of macrophages with scanty lymphocyte reaction, little granuloma formation, marked necrosis and numerous extracellular bacilli in the more advanced stages of the HIV infection. Patients with CD4 lymphocyte cell counts > 200/mm^3, apical infiltrates with cavitation as well as pleural effusions are common. In those with CD4 lymphocyte counts <200/mm^3, there is a higher prevalence of adenopathies and extrapulmonary and disseminated TB with positive blood cultures for *M. tuberculosis*.

(Saltini, 1999). In individuals with normal or immune functions which are still well, intact and with a relatively high CD4 lymphocyte count, classical caseating granulomas which are characterized by mature epithelioid cells and Langhans' giant cells (fused macrophages) but with few or no visible bacilli can be found. (Kaufmann, 2002).

The radiologic findings in pulmonary TB may also be altered in the presence of HIV co-infection. (Long *et. al.,* 1991). Lower lobe involvement is seen more often, pleural effusion is more common, cavities are less common and intrathoracic adenopathy (enlargement of the lymph glands) in adult TB is observed more frequently than among HIV-seronegative patients. (Long *et. al.,* 1991). However, an entire negative chest radiograph may be found in individuals with positive *M. tuberculosis.* (Saltini, 1999).

M. tuberculosis may cause disease in individuals with CD4 lymphocyte cell counts ranging from normal to very low. Extrapulmonary sites are more often involved in HIV-infected patients, particularly in those whose CD4 lymphocyte cell count is markedly depressed. (Fitzgerald *et. al.,* 1999). Nonetheless pulmonary TB is present in well over half of HIV-infected TB patients. (Fitzgerald *et. al.,* 1991).

Microscopy

The most rapid and simple means of detecting the presence of *M. tuberculosis* is through microscopy examination of sputum specimen subjected to staining. The techniques used for staining mycobacteria are based on the resistance of the organisms to decolorization by acids after staining by an arylmethane dye. The most widely used staining technique is the Ziehl and Neelsen technique. (Grange, 1984) Mycobacterial cells that have taken up fuchsin (triaminotriphenylmethane chloride;

pararosanilin), crystal violet (hexamethylpararosanilin chloride), or auramine O (tetram ethyldiaminodiphenyl ketoimine) in phenol-water (as carbol fuchsin, carbol crystal violet, or carbol auramine O) usually resist decolorization by acidic ethanol as applied in the Ziehl-Neelsen stain. (Barksdale *et. al.,* 1977). This distinctive staining property of acid-alcohol fastness is due to the presence on the surface of the mycobacterial cell of unique lipid components called mycolic acids and is found only in the genus Mycobacterium. (Madigan *et. al.,* 1997).

Besides sputum, microscopy is also applied to bronchoalveolar lavage fluid, gastric washings, laryngeal swabs, cerebrospinal fluid, pleural, pericardial and peritoneal effusions, fine needle lymph node aspirates, bone marrow aspirates and tissue biopsies. Ideally 3 sputum specimens collected on successive days should be examined. Patients with HIV related TB particularly those with more profound immunosuppression and no cavity formation, are more likely to be sputum negative than those with typical cavitating post primary disease. (Zumla *et. al.,* 2000).

1.7.2.2 Culturing

Microscopic examination of sputum samples, although rapid and simple, identifies only about 50% of pulmonary TB cases. Sensitivity of detection is greatly increased when culturing of the sputum is performed. Culture remains the most reliable method for the diagnosis of TB and detection of the bacilli. (Belisle & Brennan, 2000).

Microscopic examination of specimen should always be followed by culturing. Culture is imperative as it differentiates *M. tuberculosis* from other acid fast organisms. Drug-susceptibility studies too can only be performed with the availability of cultures of the *M. tuberculosis* from the respective specimens collected from individuals.

Most importantly microscopic examination could be erroneous if the number of bacilli present in specimen is small. Culture often reveals the presence of bacilli in these situations even after direct smear of the same specimen gave a negative result. (Farzan, 1985). An egg-based medium called the Lowenstein-Jensen medium is used in the traditional method of culturing. This method, although cheap is very time consuming as growth may not be visible until after 3 or more weeks after incubation. Rapid results can be obtained by using radiometric assays such as BACTEC whereby test samples are inoculated into vials containing enriched liquid medium. In this case, the presence of the mycobacteria is determined by calculating the radioactivity of $^{14}CO_2$ which is a gas released into the atmosphere above the medium when the mycobacteria utilize a ^{14}C labeled substrate (fatty acid) present in the liquid medium. This radiometric assay is sensitive and can produce results within 1-2 weeks. (Venkatraman *et. al,* 1998)

1.7.2.3 Chest Radiography

The radiographic appearance of TB gives important diagnostic information to the physician. However it is non-specific in HIV infected patients. This gives rise to the danger of overlooking TB as a disease present in the HIV infected individual. Unrecognized pulmonary TB poses a serious risk of transmission. Therefore for any HIV-infected patient with unexplained pulmonary disease, strong consideration should be given to testing respiratory secretions for *M. tuberculosis* and until infectious TB is ruled out respiratory isolation should be applied. (Fitzgerald *et. al.,* 1999). Culture positive pulmonary TB in the presence of a normal chest X-ray is not uncommon, and the incidence appears to be increasing and patients with this presentation are typically symptomatic and or are detected by contact tracing. (Marciniuk *et. al.,* 1999). Therefore Marciniuk and associates (1999) proposed that patients presenting with a cough for more than a month, a fever for more than a week or with a documented skin-test conversion less than 2 years after known exposure to infectious TB should have sputum

submitted for an *M. tuberculosis* smear and culture and investigated further for pulmonary TB even if the patients have a normal chest X-ray.

1.7.2.4 Tuberculin Skin Test (TST)

The *M. tuberculosis*-specific delayed-type hypersensitivity response subsequent to the establishment of intracellular infection can be investigated *in vivo* by skin testing with *M. tuberculosis* extracts or tuberculins. (Saltini *et. al.,* 1999) The tuberculin skin test is an imperative diagnostic tool in identifying latent TB or a TB infection. The tuberculin is a mixture of substances extracted from *M. tuberculosis*, which is called Purified Protein Derivative (PPD) consisting of proteins with estimated molecular weights of about 10500. Its capability to evoke a delayed-type hypersensitivity reaction in sensitized persons or animals form the very basis for the TST.

The Mantoux test and the Heaf test are among the most precise and reliable methods of tuberculin testing available. In the Mantoux test graded amounts of PPD are injected intradermally while in the Heaf test the reagent is introduced into the skin by a multiple puncture spring release gun. In both tests the development of areas of redness and swelling in the skin around the sites of introduction of the tuberculin indicates a positive reaction, in both the tests. This reaction reaches its maximum in about 72 hours after the performance of the test. (Stewart, 1968).

A false negative tuberculin skin test is more likely in an HIV-infected patient and is increasingly likely with increasing immunosuppression. (Markowitz *et. al.,* 1993). This is due to a condition known as anergy which is found among individuals with immune deficiency. Anergy is an immunological term that implies impaired cell-mediated immunity leading to a disruption of delayed-type hypersensitivity (DTH) skin reaction.

This state contributes to the decrease in dermal reaction when challenged with foreign antigens, such as tuberculin. (Hegde & Robbins, 2001).

Nontuberculous Mycobacteria

Nontuberculous mycobacteria or atypical mycobacteria are mycobacteria that do not cause the TB disease. The key difference between *M. tuberculosis* and nontuberculous mycobacteria, which are also called atypical mycobacteria, is that while *M. tuberculosis* and the other mycobacteria of the TB complex (*M. bovis*, *M. paratuberculosis*, *M. africanum*) are obligate parasites found only in mammalian hosts and are contagious to immunocompetent individuals, the nontuberculous mycobacteria species are saprophytes in soil and water and are pathogenic only to individuals with altered immune defenses. (Saltini *et. al.,* 1999).

Nontuberculous mycobacteria disease affects >90% of AIDS patients with severe immune deficiency. In a healthy immunocompetent host, atypical mycobacteria reveal low virulence. Colonizing the respiratory and digestive tracts, they cause no symptoms. In an immunocompromised patient, the situation is reversed, as these bacteria can cause disease in the lungs, esophagus or intestines. Therefore in HIV-infected patients with severe immunodeficiency such infections can progress to disseminated disease. (Rozsypal & Stankova, 1995).

Among HIV-infected patients disseminated *Mycobacterium avium* complex (MAC) is the most common systemic bacterial infection. (Chin, 1993). Depending on where MAC presents a variety of symptoms and signs may occur. Patients with disseminated MAC infection frequently have non specific symptoms, signs and laboratory abnormalities. Persistant fever, fatigue, night sweats, anorexia,

abdominal pain, chronic diarrhoae are some of the symptoms. Many patients will have progressive wasting and weight loss from their initial diagnosis to death. (Chin, 1993).

The various nontuberculous mycobacteria that have been reported to cause disease in HIV-infected patients are grouped according to the Runyon classification, a classification that is based on the rate of growth, pigment production and colonial morphology. (Table 1.1)

Prophylactic treatment has reduced the incidence of *Pneumocystis carinii* pneumonia therefore *M. avium* complex (MAC) disease may present as the first opportunistic infection in AIDS patients. Besides MAC other nontuberculous mycobacteria infections in AIDS patients are chronic pulmonary infections caused by *M. kansasii* and *M. xenopi*, disseminated infections by *M. genavense* and diffuse skin and joint septic lesions by *M. haemophilum*.(Saltini; 1999). *M. kansasii* more often than not presents as a slowly-progressive pulmonary infection in patients with underlying lung disease such as chronic obstructive pulmonary disease (COPD), bronchiectasis, or pulmonary fibrosis. (Chin, 1993). Among the rapid growing mycobacteria, *Mycobacterium fortuitum* and *Mycobacterium chelonei* are the only organisms associated with human disease. These two organisms are often grouped together as *Mycobacterium fortuitum* complex. In HIV infected patients, these organisms cause skin diseases and localized abscesses as a result of puncture wounds or surgical procedures. (Chin, 1993). HIV when accompanied by disseminated atypical mycobacterioses, worsen the quality of life and survival in patients with AIDS.

Diagnostic Criteria of Nontuberculosis Mycobacterium Lung Disease in HIV-Seropositive and Seronegative Hosts.

The following criteria apply to symptomatic patients with a chest x-ray showing infiltrate, nodular or cavitary disease, or a high resolution computed tomagraphy scan that shows multifocal bronchiectasis and/or multiple small nodules.

A.If three sputum/bronchial wash results are available from the previous 12 mo:

1. Three positive cultures with negative AFB smear results or
2. Two positive cultures and one positive AFB smear

B.If only one bronchial wash is available:

1. Positive culture with a 2+, 3+, or 4+ AFB smear or 2+, 3+, or 4+ growth on solid media

C.If sputum/bronchial wash evaluations are nondiagnostic or another disease cannot be excluded:

1. Transbronchial or lung biopsy yielding a NTM or
2. Biopsy showing mycobacterium histopathologoc features (granulomatous inflammation and/or AFB) and one or more sputum or bronchial washings are positive for an NTM even in the numbers.

List of common mycobacterium:

M.avium, M. gordonae, M. fortuitum, M. kansasaii, M. chelonae

Case classification

Confirmed: A clinically compatible illness that is culture confirmed.

Table 1.1 Nontuberculous Mycobacteria Causing Disease in HIV-infected Patients

Classification	Mycobacterium species
Photochromogens (Runyon Group I) (Actively growing cultures which develop yellow pigment on exposure to light, but fail to produce pigment in the dark. Cultures require 2 - 6 weeks incubation before visible growth can be seen).	*M. kansasii, M. simiae, M. marinum*
Scotochromogens (Runyon Group II) (Pigment can be produced in the light and dark. Cultures require 2 - 6 weeks incubation before visible growth can be seen. The temperature range is 25 to 42 degrees Celsius).	*M. gordonae, M. scrofulaceum*
Non photochromogens (Runyon Group III) (These organisms are a heterogeneous group containing both pathogenic and non-pathogenic species. Most are non-pigmented and extremely slow growers).	*M. avium, M. intracellulare, M. haemophilum, M. terrae, M. malmoense*
Rapid growers (Runyon Group IV) (with the exception of the *M. fortuitum* complex, the mycobacteria in Group IV are saprophytes and are considered to be non-pathogenic. They are characterized by their ability to grow rapidly (2 - 7 days) at temperatures ranging from 25 to 42 degrees celsius. Colonies are generally smooth but rough variants may occur. They may be pigmented or non-pigmented).	*M. fortuitum, M. chelonei, M. fortuitum complex*

Source: Chin, 1993

1.11 Opportunistic Infections

Candida albicans and *Penumocystis carinii* as well as *Toxoplasma gondii* are common opportunistic microorganisms causing infections in HIV/AIDS patients. The yeast *Candidia albicans* is a normal saprophyte of the human digestive tract. Oropharyngeal and esophageal infection is common in those with AIDS and is the reason for patients complaining of an uncomfortable feeling in the mouth, hypersensitive mucosa and loss of appetite. This can also be the first clinical sign in HIV infection. (Lucht &Nord, 1996).

Pneumocystis carinii is an extracellular fungus that causes severe interstitial pneumonia in immunocompromised patients with AIDS. This condition is called *Pneumocystis carinii* pneumonia (PCP). Infection with *Pneumocystis carinii* may represent either reactivation of latent infection or failure of host defense mechanisms to suppress this environmentally ubiquitous organism, It is presumed that the organism is acquired by airborne transmission. *Pneumocystis carinii* infection elicits an inflammatory response in the lung where alveolar macrophages are probably the primary cells for recognition and removal of the parasite. (Kasper & Buzoni-Gatel, 1998).

Toxoplasma gondii is a unicellular protozoan. The definitive hosts are cats and ingestion by a non feline (e.g. humans) leads to parasitemia or latent infection with the formation of tissue cysts in skeletal muscle, heart muscle and central nervous system (CNS) tissue. Toxoplasmosis is transmitted to humans by ingestion of tissue cysts in raw or inadequately cooked infected meat. Immunosuppressed patients may experience severe symptoms including splenomegaly, encephalitis and multisystem organ failure. (Gagne, 2001).

Aim And Objectives

Aim

- To have a baseline epidemiological data on the occurrence of TB co-infection with HIV/AIDS in Malaysia so as to assist in management of TB among immunosuppressed patients with HIV/AIDS.

Objectives

- To obtain epidemiological data on TB-HIV/AIDS co-infected patients in Malaysia which includes;

  - demographic data encompassing age, race, gender, occupation and lifestyle etc. This is to evaluate the socioeconomic status of these patients.
  - clinical data which includes the symptoms, treatment and management of the patients etc. This is to assist in evaluating the clinical outcomes of these patients

- To evaluate the microbiological aspects of the TB/HIV co-infection, including, drug susceptibility of the *M. tuberculosis* and the presence of atypical mycobacterium in this group of patients

CHAPTER 2

METHODOLOGY

2.1 Location Of Study

The study was a retrospective epidemiological study on human immunodeficiency virus (HIV) infected tuberculosis (TB) patients and vice versa. The study was carried out on two main locations, with few other hospitals to support the data, namely;

1. The Institute of Respiratory Medicine (IRM), Kuala Lumpur Hospital, Malaysia. The IRM is the nations centre for the treatment of respiratory diseases (which includes TB). Apart from cases from the Klang Valley, patients with complicated chest problems which require tertiary management , including cases of complicated TB were also referred to IRM from all over Malaysia.

2. The Infectious Diseases (ID) Clinic, Kuala Lumpur Hospital, Malaysia. The Kuala Lumpur Hospital (KLH) is the main hospital for treating HIV/AIDS in the country. The ID clinic at KLH treats patients with HIV infection and all information on the patients in this study pertaining to antiretroviral therapy for the HIV infection was obtained from here.

The initial and the major part of the study was carried out at the IRM where all 231 records of the patients were obtained. There were a total of 25,798 outpatients attendances in IRM for the year 2002 which included 1587 new TB and 2465 new non TB cases. The rest of the cases were old cases of both TB and non TB. Based on the list of patients given, the relevant patients' profiles were obtained after sieving through over hundreds of records of patients which included new cases of TB for the year 2002 as well as old cases of TB from the previous years.

The records of patients obtained from IRM were cross checked with the list of patients at the ID clinic. Information obtained from these two locations were then incorporated into the research data.

The records were first perused at IRM and the identification number of the patients noted. These were subsequently used to obtain their corresponding records at the ID clinic later. The IRM provided information regarding the TB disease for a patient, while the Infectious Disease clinic gave information regarding the HIV infection for the same patient.

2.1.1 Duration Of Study

The study was based on the records of 231 patients co-infected with TB/HIV-AIDS between the months of January 1999 and June 1999, and between the months January 2000 and December 2002. The records of patients between the months July 1999 and December 1999 could not be obtained due to certain inevitable problems faced.

2.2 Sampling Technique

The sampling technique employed in this study was the simple sampling technique. This technique made use of the records or patient profiles only available at the record office. No information was gathered from the wards of patients.

The patient records were sorted out according to the inclusion and exclusion criteria employed in this study. These criteria are elaborated below;

2.2.1 Inclusion criterion

Registered cases for tuberculosis with HIV from January 1999 till December 2002 at the particular institutions

2.2.2 Exclusion criteria

a. Tuberculosis co-infected with HIV cases registered before or after the time frame specified

b. Incomplete data or record

2.2.3 Type of Information Taken

The records of patients at the IRM were contained in an envelope which was referred to as the patients' wallets. Aside from containing the record file of the patient, the wallet also contained x-ray films, laboratory test results and referral letters of doctors. At the ID clinic the records of patients were obtained from a file.

The data collected from the patients were classified as follows;

A. Demographic data

B. Lifestyle and Habits

C. Disease

D. Other Relevant Information

The data forms used in this study is included in Appendix A.

2.2.3.1 Demographic Data

The demographic data included particulars such as name, identification number, gender, race, age, weight, marital status, address and occupation of the patient. Demographic data is needed to get an overview of the patients' socioeconomic status which plays an important role with regards to both TB and HIV/AIDS. Financial stability as well as a good social support could influence the likelihood of successful management of the diseases.

2.2.3.2 Lifestyle And Habits

Lifestyle and habits were especially important to note due to the mode of transmission of the HIV as well as the risk factors associated with the tuberculosis disease. By determining these risk factors conclusions can be drawn by establishing the relationship between the lifestyle and habits and the presence of the diseases as well as the progression of the diseases. This is imperative in management of patients. This section included information regarding smoking, alcoholism, drug abuse and sexual promiscuity

2.2.3.3 Disease

The disease section was divided into two parts;

i. Tuberculosis

ii. HIV/AIDS

All information regarding diagnosis and treatment of the patients were noted here.

2.2.3.4 Other Relevant Information

All other additional information regarding the patients were placed here. The clinical outcome of the patients i.e. status of the TB disease (active, inactive), surviving or dead was recorded in this section along with footnotes of doctors and referral letters which further explained the patients' status.

2.2.4 Data Analysis

Data obtained from the patient records was transferred to a specially prepared form (Appendix A) and then keyed into a computer data sheet of the statistical package SPSS for Windows release 11.5. and the statistical significance level used was 0.05. All data were taken from the records of the patients and no personal communication was made with the patients for the study was retrospective.

CHAPTER 3

RESULTS

This study was an epidemiological evaluation of patients co-infected with tuberculosis (TB) and human immunodeficiency virus (HIV) and the existence of atypical mycobacterium among this category of patients. The study was carried out in various hospitals inclusive the Institute of Respiratory Medicine (IRM), Infectious disease (ID) clinic, both under the Kuala Lumpur Hospital, Hospital Universiti Sains Malaysia in Kubang Kerian Kelantan, various hospitals in Sabah and Sarawak including few districts hospitals. However, majority of the cases were obtained from IRM. At the end of 2002, there were 25, 796 outpatients were included. Out of this 4052 were new cases for the year 2002. Out of all the new cases, 1587 were new tuberculosis cases.

The patients at IRM and ID clinic were mostly from the Federal Territory of Kuala Lumpur and the state of Selangor. The rest were from the rehabilitation centres and prison in these two areas.

A retrospective evaluation of patient records at the ID clinic and IRM was carried out. Records of 231 patients co-infected with TB/HIV-AIDS between the months of January 1999 and June 1999, and between the months of January 2000 and December 2002 were obtained. The amount of data obtained was subject to the hospital staff attending to the patients, as well as the co-operation of the patients themselves, thus there were quite a number of patient charts with some missing data. In these cases the missing data was categorized as unknown.

3.1 Demographic Data

3.1.1 Age, Gender, Race And Weight

The results indicated that males formed the majority with 96.1% (222) while females only made up 3.9 % (9) of the total number. The age of patients ranged between the minimum of 18 and maximum of 68 years. The mean age of patients was 37.4 years. However, a high percentage (49.0%) of patients was in the range of 31-40 years. (Figure 3.1).

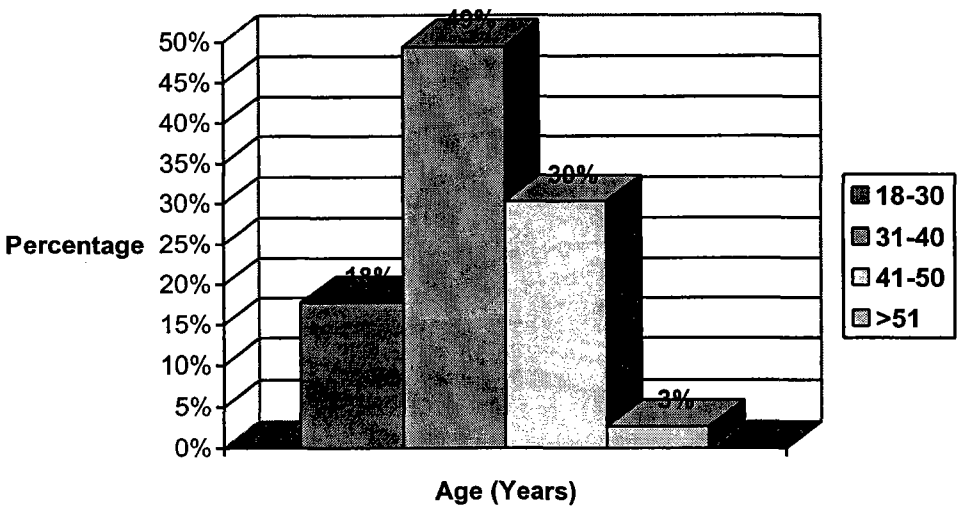

FIGURE 3.1 PERCENTAGE OF PATIENTS ACCORDING TO AGE

As with the general population of the country, the patients in this study could also be divided into three major races; Malay, Chinese and Indian. More than half the patients were Malays [129 (55.8%)], followed by the Chinese [64 (27.7%)] and Indians [33(14.3%)]. Besides the three major races there were also 4 Indonesians and one Indian citizen who have been grouped as others (2.1%). (Figure 3.2).

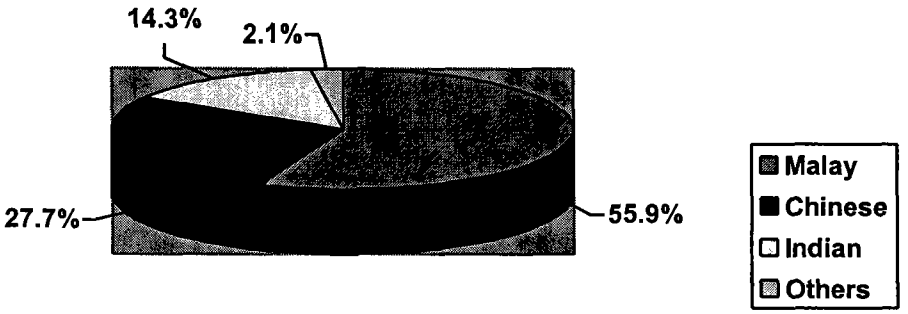

FIGURE 3.2: DISTRIBUTION OF PATIENTS ACCORDING TO RACE

Table 3.1 below shows the number of patients according to both the age group and the race. Majority of patients were Malays in the age group of 31-40 years. Statistical analysis showed that there was a significant relationship between the various races and age groups in this study. (P value= 0.004)

TABLE 3.1: NUMBER OF PATIENTS ACCORDING TO RACE AND AGE GROUP

Age (years)	Race				Total
	Malay	Chinese	Indian	Others	
18-30	24	9	5	3	41
31-40	67	31	15	1	114
41-50	38	18	13	1	70
>51	0	6	0	0	6
Total	129	64	33	5	231

In this study information regarding the weight of patients was also taken to monitor the progression of the disease. This is because tuberculosis is also known as

'wasting disease', which refers to loss of weight experienced by those inflicted and "consumption" which refers to the disease as consuming the patient's body.

The information regarding the weight of patients was taken from the charts of each patient. However, patients who were wheelchair bound and could not stand were not weighed. In such cases, the weight of these patients was categorized as unknown.

The results obtained indicated that most patients (65.0%) weighed between 41-60 kilograms. The exact amount of weight lost by the patients could not be determined due to the absence of data. Therefore the weight of the patients upon registering at the hospital was noted. However the weight of a substantial number of patients (53) remained unknown. (Figure 3.3).

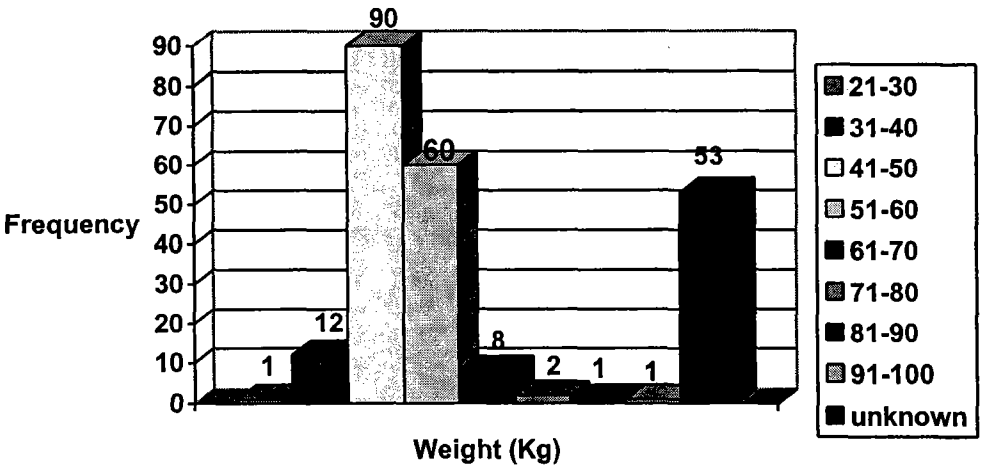

FIGURE 3.3: DISTRIBUTION OF PATIENTS ACCORDING TO WEIGHT

3.1.2 Marital Status

Patients who were single (unmarried) formed the majority [140 (60.6%)] of the patients in this study. Details are shown in table 3.2 below.

TABLE 3.2 FREQUENCY AND PERCENTAGE OF PATIENTS ACCORDING TO THEIR MARITAL STATUS

Marital Status	Frequency	%
Single	140	60.6
Married	57	24.7
Divorced	12	5.2
Unknown	22	9.5
TOTAL	231	100

3.1.3 Lifestyle And Habits

The lifestyle and habits of patients may be used to assist in the investigation to determine the mode of transmission of the diseases as well as their progression. Patients were investigated for habits that may be considered as contributing or risk factors for tuberculosis and HIV infection. All the patients were questioned on their lifestyle and habits by the doctor or medical assistant attending to them. The answers given were subject to the patient's honesty. In the event of a patient denying a particular habit or lifestyle, it was written so in the chart. However, there were charts which had no information regarding the patient's lifestyle and habits, therefore the missing data was categorized as unknown.

In this study the smoking habit was found in 110 (47.6%) of the patients, while 10 (4.3%) patients when asked by the doctor, nurse or the medical assistant denied smoking. There were 30 (13.0%) patients who admitted to consuming alcohol and 40 (17.3%) patients who denied it. A total of 179 (77.5%) patients admitted to being an intravenous drug user (IVDU) while 10 (4.3%) patients denied it. There were 35

(15.2%) patients who confessed to being sexually promiscuous and 3 (1.3%) patients who denied it.

The results obtained also indicated that there was a difference in the pattern of HIV transmission among the different races. IVDU and sexual promiscuity are two very distinct modes of HIV transmission. The majority of IVDUs in this study were Malays, while the majority of sexually promiscuous patients were Chinese. Table 3.3 shows the breakdown of the different races according to their lifestyle and habits.

TABLE 3.3: NUMBER OF PATIENTS CONSUMING ALCOHOL, SMOKING, WHO ARE INTRAVENOUS DRUG USERS (IVDUs) AND WHO ARE SEXUALLY PROMISCUOUS ACCORDING TO THEIR RACES

Race	Consuming Alcohol	Smoking	IVDU	Sexually Promiscuous
Malay	13	61	116	11
Chinese	12	30	33	22
Indian	5	19	29	1
Others	0	0	1	1
Total	30	110	179	35

The findings in this study indicates that young people belonging to the economically productive bracket, made up the majority of alcohol consumers, smokers, IVDUs as well as sexually promiscuous individuals. Table 3.4

TABLE 3.4: NUMBER OF PATIENTS WHO CONSUME ALCOHOL, SMOKE, ARE INTRAVENOUS DRUG USERS AND ARE SEXUALLY PROMISCUOUS ACCORDING TO THEIR AGE

Age (years)	Alcohol	Smoking	IVDUs	Sexual Promiscuity
18-30	3	18	27	7
31-40	19	60	90	17
41-50	7	29	60	9
≥51	1	3	2	2

Total	30	110	179	35

The marital status of patients was important to determine the risk they posed to their spouses. At the ID clinic patients were counselled to notify their spouse or sexual partners of their HIV status. During counseling, the patients were given basic knowledge on HIV infection, on the definitions of CD4 count and viral load and its significance it had to their condition, modes of HIV transmission, safe sex and harm reduction strategies in their sexual activities. Patients were also informed of the working hours of the ID clinic and were also briefed on the mode of action to take in the event of an emergency.

Among the married patients there were 11 patients who admitted to being sexually promiscuous in this study. However, there was a large number of patients whose information regarding their sexual activities remained unknown. (Table 3.5). This was because there was no information regarding this in their records.

TABLE 3.5 FREQUENCY OF PATIENTS WHO ARE SEXUALLY PROMISCUOUS VERSUS THEIR MARITAL STATUS

MARITAL STATUS	SEXUAL PROMISCUITY			TOTAL
	YES	NO	UNKNOWN	
Married	11	1	45	57
Single	20	2	118	140
Divorced	1	0	11	12
Unknown	3	0	19	22
Total	35	3	193	231

3.1.4 Occupation And Social Status

Information regarding the occupation status of patients were obtained by the hospital staff. Most of the records viewed, had the occupation status column left

blank. These were categorized as unknown. It should also be noted that some of the patients were brought in for treatment to IRM by officers from the prison or rehabilitation centres. In such cases, these patients were categorized as prisoners and rehabilitation centre inmates respectively. (Table 3.6)

TABLE 3.6: THE OCCUPATION STATUS OF THE PATIENTS ACCORDING TO AGE

Age (Years)	Employed	Unemployed	Prisoner	Rehabilitation centre	Unknown	Total
18-30	14	11	2	2	12	41
31-40	26	25	21	4	38	114
41-50	21	16	13	0	20	70
≥51	2	2	0	0	2	6
Total	63	54	36	6	72	231

Prisoners and inmates of drug rehabilitation centres made up 15.6% (36) and 2.6% (6) of the total number of patients respectively. There were 63 (27.3%) patients who claimed to have an occupation to support themselves, while 54 patients (23.4%) were unemployed. Among the 54 unemployed patients and the 36 prisoners, 49 (77.8%) and 30 (83.3%) were also IVDUs respectively.

TABLE 3.7: THE OCCUPATION STATUS OF THE PATIENTS ACCORDING TO RACE

		Occupation Status					Total
		Yes	No	Prisoner	Drug rehabilitation centre inmate	unknown	
Race	Malay	36	32	22	4	35	129
	Chinese	20	12	5	1	26	64
	Indian	6	8	9	1	9	33
	Others	1	2	0	0	2	5
Total		63	54	36	6	72	231

The occupation status of the different races in this study was proportionate to the number of patients from different races. Most unemployed patients were Malays, followed by the Chinese and Indians. (Table 3.7)

3.2 Symptoms And Type Of Tuberculosis

3.2.1 Symptoms

The evaluation of symptoms experienced by a patient greatly contributes to the accurate diagnosis of the tuberculosis disease. Patients in this study complained mainly of loss of weight (155), cough(147), fever (119), night sweats(47) and heamoptysis (32). (Fig 3.4). Heamoptysis is the coughing up of blood from the respiratory tract. The blood can come from the nose, mouth, throat, the airway passages leading to the lungs, or the lungs.

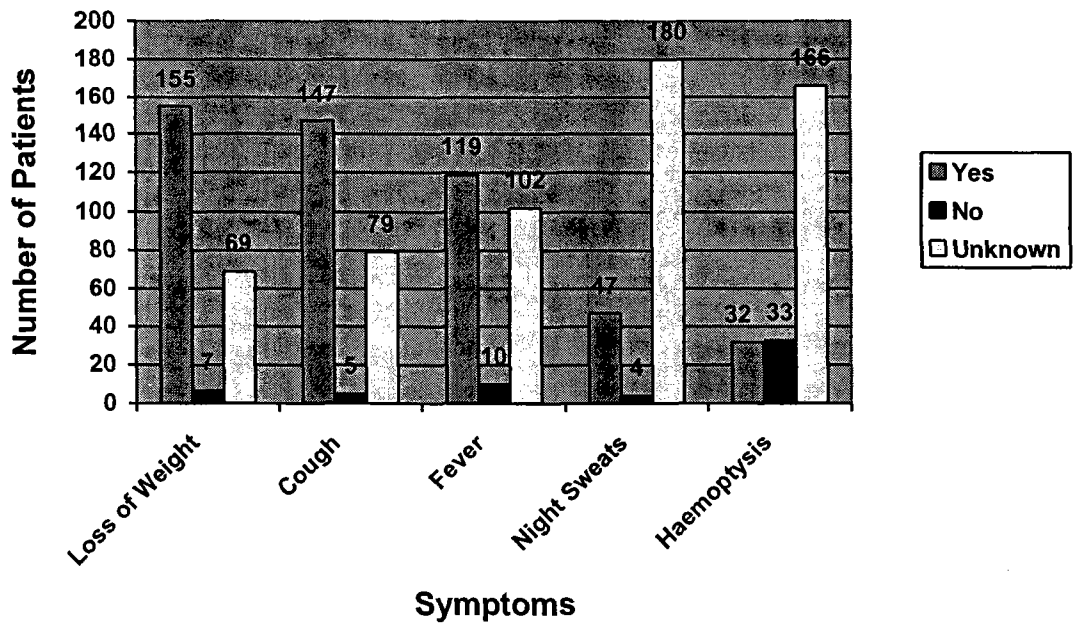

FIGURE 3.4: NUMBER OF PATIENTS ACCORDING TO THE SYMPTOMS EXPERIENCED

The most common symptom that the patients in this study reported experiencing was loss of weight. This is probably because loss of weight is a major symptom of both tuberculosis and HIV infection. The majority (150) of patients in this study weighed between 41-60 kgs and out of this 94 patients experienced loss of weight. (Table 3.8).

TABLE 3.8: NUMBER OF PATIENTS WHO EXPERIENCED LOSS OF WEIGHT VERSUS THEIR WEIGHT

		Loss of Weight			Total
		Yes	No	unknown	
Weight (Kgs)	21-30	1	0	0	1
	31-40	13	0	2	15
	41-50	66	2	22	90
	51-60	28	3	29	60
	61-70	5	1	2	8
	71-80	2	0	0	2
	81-90	1	0	0	1
	91-100	1	0	0	1
	unknown	38	1	14	53
Total		155	7	69	231

3.2.2 Types Of Tuberculosis

Tuberculosis is a systemic infection with varying clinical manifestations. *M. tuberculosis* can infect many sites in the body; however, the lung is the most common site. When the infected site is the lung, it is called pulmonary tuberculosis (PTB). Extrapulmonary tuberculosis, which is not as common as PTB, is the disease caused when *M. tuberculosis* infects an organ outside of the lung. This includes disseminated disease and bacteremia, pleural disease and intrathoracic lymphatic disease. It may occur in the presence or absence of pulmonary involvement.

Figure 3.5 below represents the frequency of patients with pulmonary and extrapulmonary tuberculosis as well as patients with both pulmonary and extrapulmonary tuberculosis. A total of 175 (75.8%) patients had pulmonary tuberculosis (PTB) only, 34 (14.7%) patients had extrapulmonary tuberculosis (EPTB)

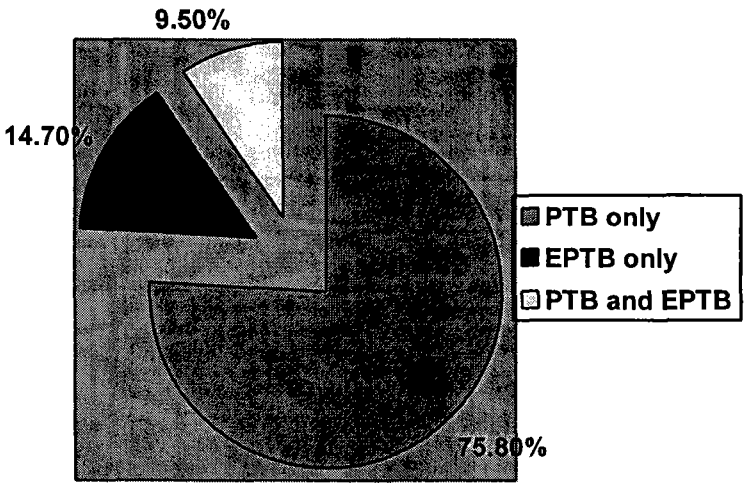

FIGURE 3.5: PERCENTAGE OF PATIENTS ACCORDING TO PTB AND EPTB

Extrapulmonary tuberculosis (with or without PTB) was found in 56 (24.2%) patients. Miliary tuberculosis (22 patients) and tuberculous lymphadenitis (20 patients) were the most common EPTB found in this group of patients. Miliary tuberculosis is a potentially life-threatening type of tuberculosis which may result when a large number of the tubercle bacilli spread throughout the body by the way of the bloodstream. The infection is known as miliary tuberculosis because the millions of tiny lesions formed are the size of millet, the small round seeds in bird food. Tuberculous lymphadenitis is the swelling of the lymph nodes due to the infection of the tubercle bacilli. This indicates that the tubercle bacilli has entered the lymphatic system of the individual. Figure 3.6 shows the percentage represented by each type of EPTB.

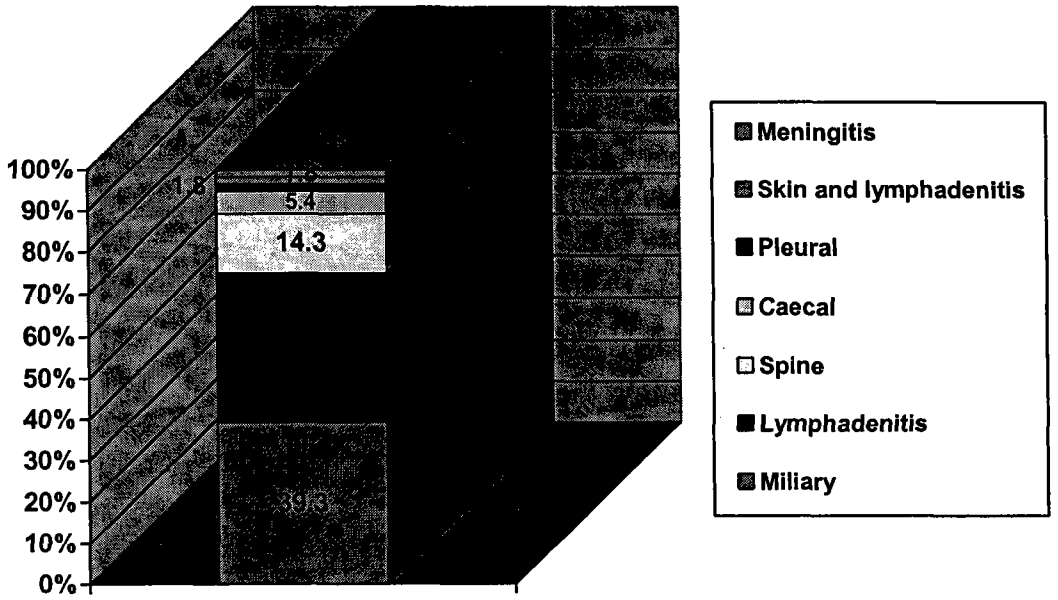

FIGURE 3.6: PERCENTAGE OF THE DIFFERENT TYPES OF EXTRAPULMONARY TUBERCULOSIS

Out of the 34 patients with only EPTB, one patient had 2 forms of EPTB, tuberculosis of the skin and tuberculous lymphadenitis. Tuberculosis of the skin is a type of infection that occurs in the skin cells of the individual. Table 3.9 shows the frequency of the types of EPTB found in both the patients with EPTB only and in the patients with EPTB and PTB as well.

TABLE 3.9: FREQUENCY OF PULMONARY TUBERCULOSIS AND THE TYPES OF CO-EXISTING EXTRAPULMONARY TUBERCULOSIS

		Pulmonary Tuberculosis		Total
		Present	Absent	
Type(s) of Extrapulmonary Tuberculosis	Miliary	9	14	23 (10.0%)
	Spine	2	6	8 (3.5%)
	Lymphadenitis	9	10	19 (8.2%)
	Caecal	1	2	3 (1.3%)
	Meningitis	1	0	1 (0.4%)
	Pleural	0	1	1 (0.4%)
	Skin and Lymphadenitis	0	1	1 (0.4%)
SUBTOTAL		**22**	**34**	**56 (24.2%)**
No Extrapulmonary Tuberculosis		175	0	175 (75.8%)
TOTAL		**197 (85.3%)**	**34 (14.7%)**	**231**

3.3 *Laboratory Results*

3.3.1 *Direct Smear And Culture*

Direct smear is the test that is done to ascertain the presence of *Mycobacterium spp.* in the sputum or other clinical specimen of patients. It is also known as acid fast microscopy, referring to the unique characteristic of Mycobacteria to retain the primary stain used in staining when treated with acid alcohol. It is the foremost diagnostic investigation that is done in the mycobacteriology laboratory. It is rapid,

inexpensive and simple. Direct smear also identifies potentially infectious patients and helps monitor the effects of therapy. However microscopical examination alone cannot differentiate the

staining is the Ziehl-Neelsen method. The presence of red acid fast bacilli confirms the presence of *Mycobacteria spp.*

In this study a total of 54 (23.4%) patients had positive results for direct smear while 166 (71.9%) patients had negative results for direct smear examination. The results for direct smear of 11 other patients were unknown because there were no records of the results in the patients' records. Figure 3.7 shows the percentage of patients according to their direct smear results.

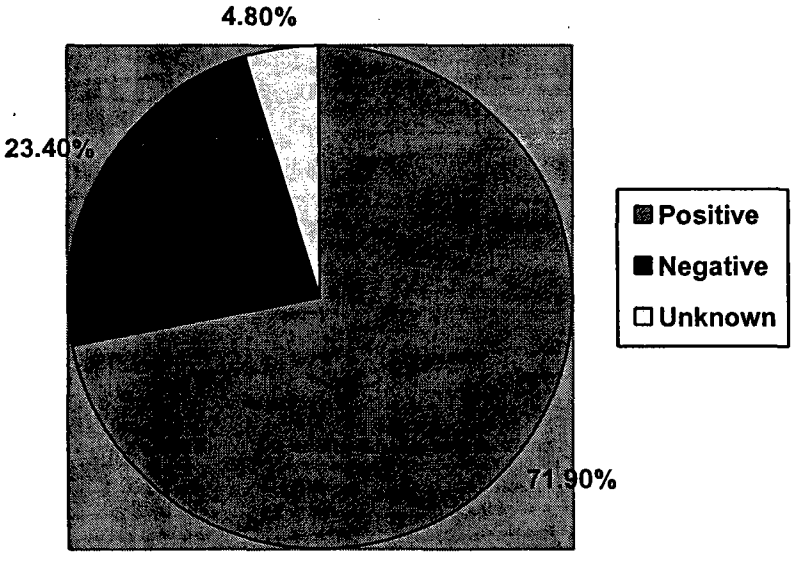

FIGURE 3.7 PERCENTAGE OF PATIENTS ACCORDING TO THEIR DIRECT SMEAR RESULTS

The subsequent procedure in the laboratory following direct smear, is culturing. Isolation of *Mycobacteria spp.* by culture on artificial media is essential in

determining the species of the Mycobacterium causing the disease. An egg-based growth medium known as Lowenstein-Jensen (L-J) medium is the common medium used. It is composed of whole eggs, glycerol, other nutrients and trace elements, plus a dye called malachite green which inhibits contaminant growth.

A positive culture for *M. tuberculosis* was obtained from clinical specimen of 95 (41.1%) patients and no culture obtained from 128 (55.4%) patients. If no culture is obtained it indicates that there were no tubercle bacilli in the clinical specimen provided by the patient. The culture results for the rest of the patients (8) were unknown for there were no results available in their records. Owing to the difference in sensitivity of the two procedures (direct smear and culture), there were 60 patients with positive results for culture but negative results for direct smear. However, there were also 21 patients who had negative results for direct smear but positive results for culture. Eventually patients with a positive result for any of the two tests were started on tuberculosis treatment. (Table 3.10).

TABLE 3.10: FREQUENCY OF PATIENTS ACCORDING TO THEIR DIRECT SMEAR AND CULTURE RESULTS

		Culture			Total
		Positive	Negative	Unknown	
Direct Smear	Positive	32	21	1	54
	Negative	60	105	1	166
	Unknown	3	2	6	11
Total		95	128	8	231

3.3.2 Chest X-Ray

The chest X-ray is an important tool in diagnosing PTB as it shows if there are lesions or cavities which are common in lungs of tuberculosis patients. The

radiological extent of disease in the chest x-ray is standardized by the Ministry of Health Malaysia as minimal, moderately advanced and far advanced.

TABLE 3.11 FREQUENCY AND PERCENTAGE OF PATIENTS ACCORDING TO THEIR CHEST X-RAY READING

X-Ray Reading	Frequency	Percent
Minimal	64	27.7
Moderately advanced	90	39.0
Far advanced	28	12.1
None	49	21.2
Total	231	100

In this study most of the patients (90) had moderately advanced chest x-ray reading followed by 64 patients with minimal chest x-ray reading and 28 patients with far advanced chest x-ray reading. However, there were 49 patients whose chest X-ray results could not be found in their records. Among these 49 patients, there were 5 patients with tuberculosis of the spine, 10 with tuberculosis lymphadenitis, 2 caecal tuberculosis and 1 with tuberculosis of the skin and lymphadenitis. Table (3.11).

3.3.3 Tuberculin Skin Test (TST)

The tuberculin test is a test that indicates the immunologic response of the individual towards tuberculin. Tuberculin is the protein component of *M. tuberculosis* which acts as antigen that induces the secretion of the appropriate antibodies as an immunological response. The rate of reaction is measured by the diameter of induration produced in an individual. The tuberculin or Mantoux test is carried out in government hospitals in Malaysia using two tuberculin units (T.U>) in 0.1 ml of prepared solution. The test is carried out by injecting the tuberculin under the skin in the lower part of the arm. The result is read after 72 hours. A diameter of indurations of less than 10mm is graded as negative but this does not exclude a diagnosis of tuberculosis. A reading of 10

mm or more in a child or adult is considered positive. A positive Mantoux test merely indicates tuberculosis infection and not necessarily active disease. (Ministry of Health Malaysia, 2002).

In this study there were 30 (13.0%) patients who were positive for the tuberculin test and 148 (64.1%) patients who were negative for the test. (Table 3.12). False negative (the result is negative even though the individual is infected by *Mycobacteria spp.*) tuberculin test result may also occur in individuals with immunosuppressive disease such as HIV infection due to a condition called anergy. Anergy is the inability to mount a delayed type hypersensitivity (DTH) response to several skin test antigens, including the tuberculin test. The study done by Girardi *et. al.,* (1997) indicated that in identifying HIV-infected patients who are at an increased risk of TB and who may benefit from preventive therapy, a response to PPD of 5mm is an appropriate cutoff point.

TABLE 3.12 FREQUENCY AND PERCENTAGE OF PATIENTS ACCORDING TO THEIR MANTOUX TEST RESULTS

Test Results	Frequency	Percentage
Positive	30	13.0
Negative	148	64.1
Unknown	53	22.9
Total	231	100

3.3.4 Bacille Calmette Guérin (BCG)

BCG or Bacillus of Calmette & Guérin is a weakened or attenuated strain of bovine-type tubercle bacillus used as a vaccine against tuberculosis. Given the high incidence of tuberculosis in many developing countries and the inability to control the

spread of infection, WHO recommends the use of BCG vaccine on a worldwide basis. In Malaysia, BCG vaccination is given to babies as soon as after delivery, and if there is no scar at school going age (7 years) a repeat dose is given.

In this study the presence of the BCG scar which indicates that the vaccine had been administered to the individual, was found in 39.8% (92) of patients. However, a total of 90 (39.0%) of the patients did not have a BCG scar while the status of the rest of the patients (49) is unknown. Figure 3.8 shows the percentage of patients in each age group according to BCG scar. The highest percentage of patients with BCG scarring are from the 41-50 years age group.

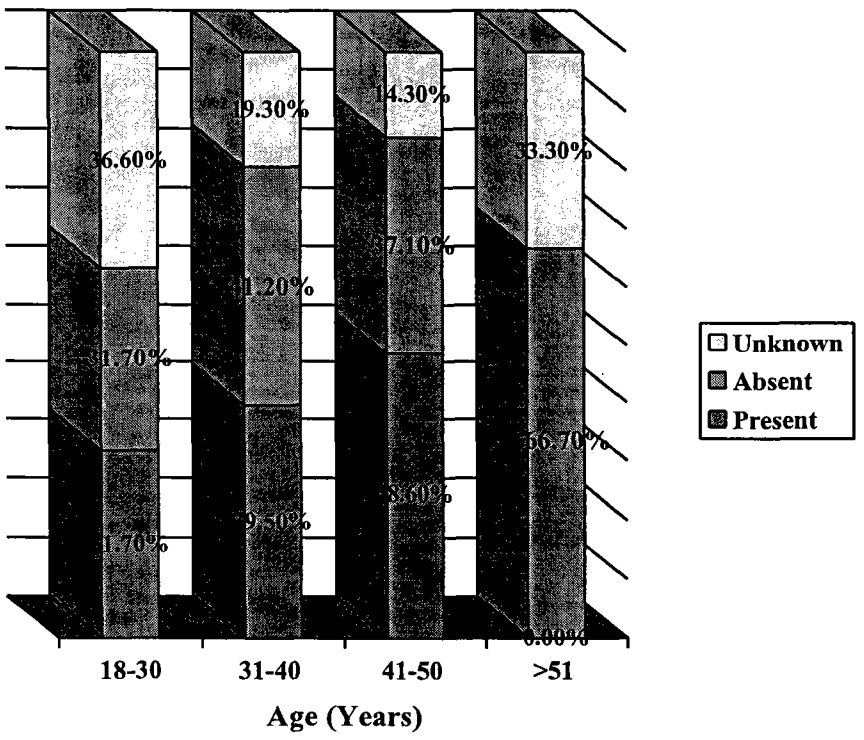

FIGURE 3.8 PERCENTAGE OF PATIENTS IN EACH AGE GROUP ACCORDING TO BCG SCAR

3.3.5 CD4 Cell Counts

The CD4 cell which is a type of T lymphocyte performs essential functions in the immune system of humans. They recognize antigens or foreign entities in the body such as microbes which have invaded the body, and they multiply while releasing a variety of proteins known as lymphokines that regulate other immune system cells. After receiving the signals from CD4 cells, the B cells or B lymphocytes secrete specific antibodies to neutralize or eliminate antigenic bacteria and viruses as they travel through body fluids between cells. Similarly, following recognition of antigens and signaling from CD4 cells, some CD8 cells called cytotoxic T cells become activated to kill cells infected with intracellular pathogens; the suppressor T cells dampen an ongoing immune response. The CD4 cells are also known to modulate the activities of immune system cells known as natural killer cells and macrophages, which are involved in responses to infection.

HIV attacks and proliferates in the white blood cell known as T lymphocyte or T cells. Thus patients with AIDS have reduced numbers of CD4 cells. The normal range of CD4 cells for a healthy individual is between 561-1075.9 cells cu/mm. In this study there were only 2 patients with CD4 cell counts within this range while a large number of patients [188 (81.4%)] did not have their CD4 cells counted. This is probably because CD4 cells counts are done at the ID clinic, and not at the IRM and since not all the patients were being treated at the ID clinic, most of the patients' records perused did not have this information. (Table 3.13).

It is interesting to note that the CD4 cell counts have been found to be related to the type of tuberculosis an individual has. This is mainly because

extrapulmonary tuberculosis is indicative that the immune system has failed to localize the infection thus allowing the tubercle bacilli to spread to other parts of the body. Table 3.14 shows the association of CD4 counts with the extrapulmonary tuberculosis types involved. Although the numbers shown are small, it can be seen that all individuals with miliary tuberculosis individuals who have had their CD4 count done have a low level of CD4 cells in their system. Unfortunately a clearer picture of this association could not be determined due to the lack of data.

TABLE 3.13 FREQUENCY AND PERCENTGAE OF PATIENTS ACCORDING TO THEIR CD4 CELLS COUNT

		Frequency	Percent
CD4 Cells Count	<100 cells cu/mm	19	8.2
	100-560 cells cu/mm	22	9.5
	561-1075.9 cells cu/mm (normal)	2	.9
	unknown	188	81.4
	Total	231	100.0

TABLE 3.14 CD4 CELLS COUNT OF PATIENTS ACCORDING TO THEIR EXTRAPULMONARY TUBERCULOSIS TYPE

		CD4 (cu/mm)				Total
		<100 cells	100-560 cells	561-1075.9 cells	unknown	
Type of ExPTB	miliary	3	0	0	20	23
	spine	1	0	0	7	8
	lymphadenitis	2	2	0	15	19
	caecal	0	1	0	2	3
	meningitis	0	0	0	1	1
	pleural	0	1	0	0	1
	skin and lymphadenitis	0	0	0	1	1
	none	13	18	2	142	175
Total		19	22	2	188	231

3.3.6 Atypical Mycobacteria

Atypical mycobacteria are also known as nontuberculous mycobacteria and the key difference between *M. tuberculosis* and non-tuberculous mycobacteria, is that *M. tuberculosis* is an obligate parasite found only in mammalian hosts and can infect immunocompetent individuals. Non-tuberculous mycobacteria (mycobacteria that do not cause tuberculosis) species are ubiquitous saprophytes in soil and water and are pathogenic only to individuals with altered immune defenses. (Saltini & Vezzani, 1999).

In this study atypical mycobacterium was found in 6 patients and all 6 had atypical mycobacterium belonging to Group IV of the Runyon classification system. In the laboratory at IRM, identification of atypical mycobacterium was done to determine the Runyon group to which the mycobacteria belonged. Most of the atypical mycobacteria encountered at IRM belonged to Runyon Group IV. These mycobacteria are further identified as either *M. fortuitum-chelonei* complex or "not - *M. fortuitum-chelonei* complex". No further identification is done to determine the species of the mycobacterium.

Out of the 6 atypical mycobacteria found in this study, two belonged to *M. fortuitum-chelonei* complex, while 4 were not *M. fortuitum-chelonei* complex. All six strains were resistant to the anti tuberculosis drugs. (Table 3.15).

TABLE 3.15: DRUG SUSCEPTIBILITY PATTERNS OF THE ATYPICAL MYCOBACTERIA

STRAIN		DRUGS				
		Isoniazid	Streptomycin	Kanamycin	Ethambutol	Rifampicin
M. fortuitum-chelonei complex	1	HR	HR	R	R	R
	2	HR	HR	R	R	R
Not *M. fortuitum-chelonei* complex	3	S	HR	S	S	R
	4	HR	HR	R	R	R
	5	HR	HR	R	R	R
	6	HR	HR	R	R	R

S = sensitive HR = highly resistant

R = resistant

A sensitive strain indicates that there was no growth of the *Mycobacterium sp.* found on the medium containing a certain concentration of drug. A strain that is found to be resistant or highly resistant is a strain of *Mycobacterium sp.* which grows on drug incorporated media. Usually 20-100 colonies of the microorganism are found on the medium depending on the concentration gradient of the drugs.

3.4 Therapy

3.4.1 Anti Tuberculosis Therapy (ATT)

3.4.1.1 Treatment Regimen

The aims of treatment are to cure patients and render them non-infectious, to reduce morbidity and mortality, and to prevent relapse and emergence of resistant tubercle bacilli. Five drugs are considered essential to the treatment of tuberculosis; isoniazid (H), rifampicin (R), pyrazinamide (Z), streptomycicn (S) and

ethambutol (E). Treatment regimens are divided into the initial or intensive phase and the continuation phase.

In this study the three most common regimens encountered were 2EHRZ, 4RH2 (two months of daily doses of the drugs E,H,R and Z for the initial phase, followed by four months of biweekly doses of the drugs R and H for the continuation phase), 2RHZ,4RH (two months of daily doses of the drugs R, H and Z for the initial phase, followed by four months of daily doses of the drugs R and H for the continuation phase) and 2RHZ, 4RH2 (two months of daily doses of the drugs R, H and Z for the initial phase, followed by four months of biweekly doses of the drugs R and H for the continuation phase). Other regimens of drugs used on patients with problems such as adverse drug reactions are grouped as miscellaneous. All patients were also given pyridoxine or vitamin B complex supplementing their antituberculosis therapy to minimize the side effects of the drug INH. In this study most of the patients [75.8% (175)] in this study were under the 2EHRZ, 4RH2 therapy regimen. (Figure 3.9)

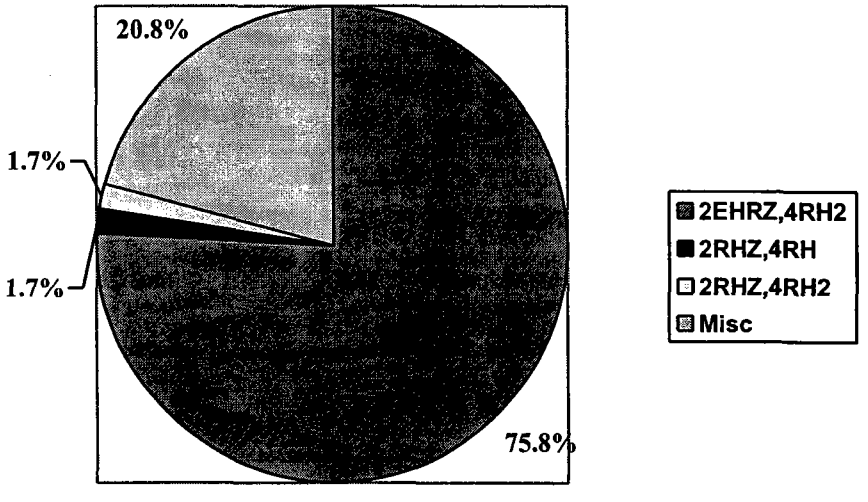

FIGURE 3.9 FREQUENCY OF PATIENTS UNDER THE DIFFERENT REGIMENS OF THERAPY

3.4.1.2 Adverse Drug Reactions (ADR)

Major adverse reactions to anti tuberculosis drugs can cause significant morbidity, and compromise treatment regimens for tuberculosis (TB). Adverse drug reactions usually associated with anti tuberculosis drugs include rashes, blurring of vision and nausea. In this study a total of 21 (9.10%) patients had adverse drug reaction (ADR) to anti tuberculosis therapy.

Majority of the 21 patients had rashes and drug induced hepatitis. Patients with drug induced hepatitis had their medications stopped and their liver functions monitored. Once it returned to normal, the patients were started on the same drugs, but with constant monitoring of their liver functions. Patients with rashes were given topical creams to apply to relieve their itch and discomfort. Patients were also advised to continue their treatment if the side effects were not too serious. In cases where patients were found to be allergic to the drugs, the drug involved was withheld and treatment was continued with other drugs which included second line anti tuberculosis drugs such as ofloxacin.

Table 3.16 shows the various adverse drug reactions experienced by the 21 patients.

TABLE 3.16 PERCENTAGE OF PATIENTS ACCORDING ADVERSE DRUG REACTIONS (ADR) TO ANTI-TB DRUGS

ADR	%
Thrombocytopenia - a condition where the number of platelets (the component in the blood that aids in the clotting of blood) is decreased causing excessive bleeding	14.3 (3)
Rashes & Itchiness	42.9 (9)
Drug Induced Hepatitis	19.0 (4)
Blurring of Vision	9.5 (2)
Nausea and Rashes	14.3 (3)
TOTAL	100 (21)

3.4.1.3 Treatment Defaulting

In the treatment of tuberculosis, it is imperative that patients adhere to the treatment completely. All the anti-tuberculosis drugs have to be taken correctly as prescribed by the physician to ensure treatment success, failing which will result in a relapse of the disease or an increased risk of multiple drug resistant tuberculosis (MDRTB). In IRM, patient supervision through Directly Observed Treatment, Short Course (DOTS) was carried out on all patients. Arrangements for patient supervision were made by hospital staff (nurse or medical assistant) at nearby local health facilities, family practitioner or with a reliable person or relative. In situations where the patients were homeless, drug addicts and those whose compliance was suspect hospitalization was done for the initial intensive chemotherapy. To encourage patient adherence to therapy, they were given counselling on tuberculosis and its treatment. Education was also provided for family members who were present with the patient.

Patients who defaulted treatment were identified if they failed to attend for daily supervision or biweekly chemotherapy, failed to collect their supply of drugs, or failed to attend follow-up appointments. Home visit would be made by hospital staff, if not a letter would be dispatched or a phone call made. In this study defaulting of treatment was found in 28.1% (65) of patients. Figure 3.10 shows the percentage and number of patients who defaulted treatment according to the number of times they have defaulted.

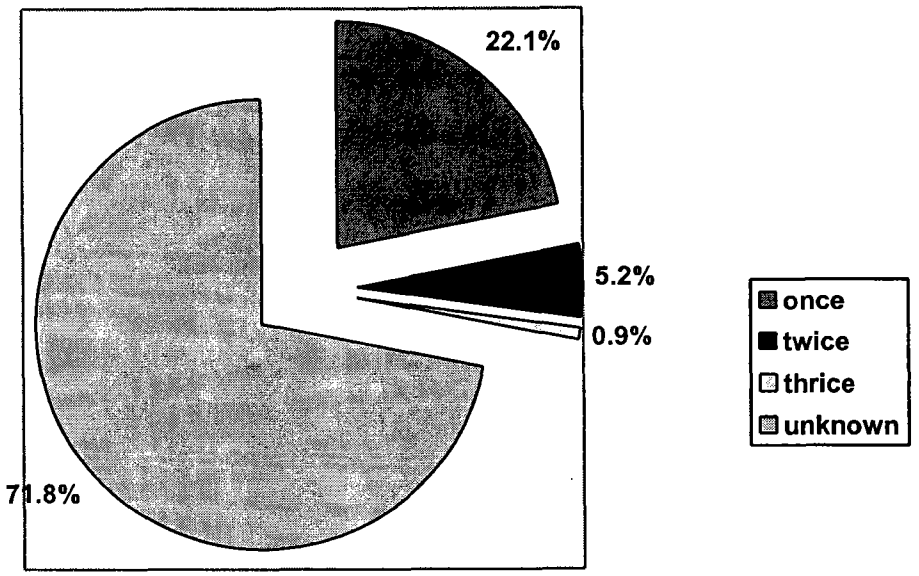

FIGURE 3.10 PERCENTAGE OF PATIENTS WHO DEFAULTED AND THE NUMBER OF TIMES THEY DEFAULTED

3.4.1.4 Multidrug Resistant Tuberculosis (MDRTB)

All mycobacteria cultures isolated from clinical specimens of the patients were sent for drug susceptibility test. The test is done to determine the susceptibility of the mycobacteria to the anti tuberculosis drugs. The result of this test enables the physician to determine the suitable drug regimen to treat the patient concerned. All *M.*

tuberculosis strains isolated from the patients in this study were sensitive to the anti tuberculosis drugs. When a *M. tuberculosis* strain is resistant to at least INH and RIF the patient is considered to be having MDRTB. There were no cases of MDRTB in this study. However there was one patient who had a *M. tuberculosis* strain which was highly resistant to the drug SM. Therefore the drug SM was not included in the treatment regimen of this patient.

3.4.2 Antiretroviral Therapy (ARVT)

In Malaysia it is mandatory for all tuberculosis patients to be tested for the HIV. While there is no cure for AIDS, treatment of HIV infection, with highly active antiretroviral therapy (HAART), results in suppression of viral replication and partial restoration of cell-mediated immunity. There are three groups of antiretroviral drugs; nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI). HAART is an ARVT which combines the different group of drugs to treat patients. The three groups of drugs have specific roles in HAART. NRTI inhibits an enzyme called reverse transcriptase that enables HIV to infect healthy cells, PI and NNRTI slow down the duplication of the virus and preventing infection of healthy cells. Therefore for optimum results drugs from each group are used in treating HIV infection.

Patients under antiretroviral therapy made up 14 (6.1%) of the total patients in this study. Most of the patients were taking ddI, d4T and Efavirenz. One patient however was on a herbal trial. (Table 3.17).

TABLE 3.17 PERCENTAGE AND NUMBER OF PATIENTS ACCORDING TO ARVT

ARVT	Drug Group	Number of Patients
ddI, d4T, Efavirenz	NRTI, NRTI, NNRTI	4
Herbal	-	1
3tc, d4t, Indinavir, Norvir	NRTI, NRTI, PI, PI	1
ddI, AZT	NRTI, NRTI	1
AZT	NRTI	1
ddI,AZT, Efavirenz	NRTI, NRTI, NNRTI	2
ddI,d4T, stocrin	NRTI, NRTI, NNRTI	1
ddI,d4T, indinavir	NRTI, NRTI, PI	1
3TC, AZT, Stocrin	NRTI, NRTI, NNRTI	1
Combivir, stocrin	NRTI, NNRTI	1
Total		14

NRTI - nucleoside reverse transcriptase inhibitors
PI - protease inhibitors
NNRTI - non-nucleoside reverse transcriptase inhibitors
Herbal - the details of this therapy was not found in the records as it was a trial that was being carried out at the Institute of Medical Research (IMR)

3.5 Other Infections

The immunologic damage caused by the HIV infection instigates many opportunistic infections to arise in the patients. Apart from the Mycobacteria species, other microorganisms take advantage of the lowered immunity to cause disease otherwise seldom encountered in persons with normal defense mechanisms.

Due to the decreased immune competency, the patients are exposed to *Pneumocystis carinii* pneumonia (PCP), systemic fungal infections such as candidiasis

as well as toxoplasmosis. They are also predisposed to hepatitis B and C virus infections as well as syphilis, depending on their lifestyle.

3.5.1 *Pneumocystis carinii* (PCP) And Candidiasis

There were 9 patients under antifungal medication for *Pneumocystis carinii* pneumonia (PCP), 2 for thrush (candidiasis) and 44 patients under antifungals for both PCP and thrush in this study.

3.5.2 Toxoplasmosis

Toxoplasmosis is a disease that affects the central nervous system causing disfunction of the brain and seizures or affect nerve functions. It is caused by the protozoan parasite *Toxoplasma gondii* and is a major complication of HIV induced immunosuppression and the leading cause of focal cerebral lesions in patients with AIDS. Toxoplasmosis usually affects the brain and causes a disease called toxoplasma encephalitis. Toxoplasmic encephalitis is the most common clinical presentation of toxoplasmosis and is fatal unless promptly treated. (Luft & Remington; 1992). The organism can also infect and cause disease in other organs, including the eyes and lungs. Some of the symptoms of toxoplasma encephalitis include headache, fever, confusion, seizures, abnormal behavior and coma.

The parasite *Toxoplasma gondii* and is detected through specific antibodies found in the blood. IN this study a total of 24 (10.4%) patients had been detected to have toxoplasmosis. *Toxoplasma gondii* was not detected in 5 (2.2%) patients and the rest of the patients (202) had no information (unknown) regarding toxoplasmosis in their records.

3.5.3 Hepatitis

Hepatitis B and C are caused by the hepatitis B and C viruses. They are transmitted when blood or body fluids from an infected person enters the body of a person who is not immune. The viruses can be spread through sexual contact and sharing of needles.

A total of 87 (37.7%) patients were found to have viral hepatitis in this study. Out of this, 6 (2.6%) patients had hepatitis B, 68 (29.4%) had hepatitis C and a total of 13 (5.6%) patients had both hepatitis B and C. A total of 18 patients were negative for both viruses (hepatitis B and C), 4 patients were negative for the hepatitis B virus but had no information (unknown) regarding the hepatitis C virus and 122 patients had no information regarding both the viruses. (Table 3.18).

TABLE 3.18 NUMBER OF PATIENTS WITH HEPATITIS B AND HEPATITIS C

		HEPATITIS C			Total
		Positive	Negative	Unknown	
HEPATITIS B	Positive	13	4	2	**19**
	Negative	58	18	4	**80**
	Unknown	10	0	122	**132**
TOTAL		**81**	**22**	**128**	**231**

The majority of patients with either hepatitis B or C were also intravenous drug users and only a fraction, sexually promiscuous. This could indicate that most of them got infected by the hepatitis viruses through needle sharing. A total of 3 patients with hepatitis B were IVDUs, and 2 patients were sexually promiscuous. (Tables 3.19).

TABLE 3.19 PATIENTS WITH HEPATITIS B ACCORDING TO IVDU AND SEXUAL PROMISCUITY

		Sexual Promiscuity			TOTAL
		Yes	No	Unknown	
IVDU	Yes	0	0	3	3
	No	0	0	0	0
	Unknown	2	0	1	3
TOTAL		2	0	4	6

Among patients with hepatitis C, 60 patients were IVDUs, and 1 patient was sexually promiscuous. (Table 3.20)

TABLE 3.20 PATIENTS WITH HEPATITIS C ACCORDING TO IVDU AND SEXUAL PROMISCUITY

		Sexual Promiscuity			TOTAL
		Yes	No	Unknown	
IVDU	Yes	0	1	59	60
	No	0	0	0	0
	Unknown	1	0	7	8
TOTAL		1	1	66	68

Among patients with both hepatitis B and C, a total of 12 patients were IVDUs of which 2 were also sexually promiscuous. (Table 3.21)

TABLE 3.21 PATIENTS WITH HEPATITIS B AND C ACCORDING TO IVDU AND SEXUAL PROMISCUITY

		SEXUAL PROMISCUITY			TOTAL
		Yes	No	Unknown	
IVDU	Yes	2	0	10	12
	No	0	0	0	0
	Unknown	0	0	1	1
TOTAL		2	0	11	13

3.5.4 Syphilis

Sexually transmitted syphilis is caused by the spirochete *Treponema pallidum pallidum.* Two tests are used to detect syphilis in patients. These are rapid

plasma reagin (R.P.R.) and *Treponema pallidum* haemagglutination assay (T.P.H.A.). The former is a non-treponemal test which detects non-specific treponemal antibodies. Non specific treponemal antibodies include antibodies for *T. pallidum endemicum, T. pallidum pertenue* and *T. carateum*. They cause non-venereal treponematoses known as bejel (endemic syphilis), yaws and pinta respectively. The latter is a treponemal test which detects specific treponemal antibodies. The T.P.H.A is used as a confirmatory test for syphilis.

In this study, there were 2 patients confirmed to be having syphilis (RPR reactive and TPHA detected) and 1 patient with non-venereal treponematose (R.P.R reactive and T.P.H.A. not detected) indicting that this individual could be infected with bejel, yaws or pinta. (Table 3.22).

TABLE 3.22 PERCENTAGE AND NUMBER OF PATIENTS WITH SYPHILIS

Syphilis Test Results	Frequency	Percent
R.P.R. non-reactive	29	12.6
RPR reactive & TPHA-detected	2	.9
RPRreactive & TPHA-not detected	1	.4
Unknown	199	86.1
Total	231	100.0

3.6 Clinical Outcomes

3.6.1 Status Of TB

At the time of the study 80 (77.9%) patients in this study had active tuberculosis. Active tuberculosis indicates that tuberculosis is present in a communicable or infectious stage as established by chest x-ray, laboratory examination of sputum or

other fluids, or tissues from the patient. A total of 33 (14.3%) patients had inactive TB and 18 (7.8%) had completed their treatment and were taken off the anti tuberculosis therapy. (Table 3.23).

TABLE 3.23 NUMBER OF PATIENTS ACCORDING TO THEIR STATUS OF TB

	STATUS OF PATIENT			TOTAL
NUMBER OF PATIENTS	TB active	TB inactive	Off treatment	
	180	33	18	**231**

Table 3.24 shows that almost equal numbers of patients who were employed and unemployed had active TB, although a higher number of employed patients (14) had inactive TB compared to unemployed patients (4). In this study more unemployed patients had been taken off treatment compared to employed patients. Analysis showed that no significant relationship was found between the occupation status and the TB disease stage of the patients. (P value= 0.178)

TABLE 3.24: OCCUPATION STATUS VERSUS STAGE OF TB DISEASE

Occupation Status	Stage of disease			Total
	TB active	TB inactive	Off Treatment	
Yes	44	14	5	63
No	43	4	7	54
Prisoner	28	6	2	36
Drug Rehab. Centre Inmate	4	2	0	6
Unknown	61	7	4	72
Total	180	33	18	231

Crosstabulation of TB disease stages and the various lifestyle showed that most of the patients who were with active TB were IVDUs. (Table 3.25). Statistical analysis showed that no significant relationship was found between the various lifestyles and the different stages of the TB disease. [IVDU (P value=0.060), Alcohol consumption (P value=0.097), Smoking (P value=0.668) and Sexual promiscuity (P value= 0.205)

TABLE 3.25: STAGES OF TB DISEASE VERSUS LIFESTYLE

	TB active	TB inactive	Off Treatment
IVDU	146	20	13
Alcohol consumption	23	6	1
Smoking	89	14	7
Sexual Promiscuity	30	1	4

3.6.2 Mortality

By the end of the study a total of 4 patients died. Out of this 3 patients were having active tuberculosis while the other had already completed treatment. One patient had passed away in the surgical ward of HKL after completing one year of ATT for pulmonary tuberculosis, 10 months before he passed away. The cause of death was not stated in his record. Out of the three who had active TB, one patient was under biweekly treatment of RIF and INH (RH) when he passed away in IRM. He had miliary tuberculosis. Another patient who was taking daily doses of EHRZ was found dead by the police in an empty house. However, there was no date of his death stated in his record. He had active pulmonary tuberculosis. The other patient was on biweekly doses of RH and was referred from Bentong hospital for management regarding his adverse drug reaction (thrombocytopenia) to RIF. He was later discharged form IRM, and sent back to Bentong hospital. He died of PTB at HKL 5 months later.

CHAPTER 4

DISCUSSION

Malaysia is a multiracial nation which is made up of three main races along with other minority racial groups. The population of Malaysia in the year 2002, was estimated to be 24.5 million. The predominant race is Malay (50.2%), followed by the Chinese (24.0%) and Indians (7.0%). (Department of Statistics, 2003).

At the time of this study there was no published data on the epidemiology of HIV/AIDS-TB co-infected patients in Malaysia. This study which was carried out in the Institute of Respiratory Medicine (IRM) and the Infectious Disease (ID) Clinic (both under the Kuala Lumpur Hospital), Kuala Lumpur aimed to fill this void as much as possible.

4.1 HIV And TB In Malaysia

The first case of the human immunodeficiency virus (HIV) infection in Malaysia was detected in 1986, and since then, the country has been seeing a steady increase in the cases of people living with HIV. At the end of 2001, there was an estimated of 42,000 people living with HIV in Malaysia (UNAIDS, 2004). In the year 2002 it was reported that each new day saw an average of 17.4 new cases in Malaysia (Huang & Hussein, 2004) and by the end of the year 2003, there were an estimated 52,000 people living with HIV in the country (UNAIDS, 2004).

As for TB, it was the number one cause of death in Malaysia in the early 1940's and 1950's. Patients with the disease were managed by surgical means before TB chemotherapy became available in the late 1950's. (Iyawoo, 2004). In the year 2000, a total of 15,057 of all forms of TB were notified in the country. In the year 2001, the incidence rate of TB was second highest after dengue fever among communicable diseases in Malaysia, recording an incidence rate of 61.7% per 100,000 population. TB however had the highest mortality rate (5.52%), followed by AIDS in the same year. (Department of Statistics Malaysia, 2003).

The single most important risk factor for the development of active TB is the HIV infection. In the year 1990, there were 6 TB cases with HIV infection in the country, and in the year 2000, there were 734 such cases reported. (Iyawoo, 2004).

In this study only patients with TB-HIV/AIDS co-infection were included. The majority of the patients in this study were single Malay males with a mean age of 37.4 years, who were intravenous drug users (IVDUs). There were 63 (27.3%) patients who were employed and 54 (23.4%) unemployed. A total of 72 (31.2%) patients had no record of occupation, thus their occupation status was classified as unknown. The remaining patients comprised of inmates of drug rehabilitation centres (2.6%) and prisoners (15.6%).

4.2 Age And Mode Of Transmission

At present the youth generation consists of a large proportion of the global population, with nearly half of the global population being less than 25 years old (UNFPA, 2003). It is therefore a cause for concern when two debilitating diseases; HIV/AIDS and TB affect this economically productive and valuable population. For

example in this study 155 (67.1%) patients were between the ages of 18 and 40 years. Globally, HIV and AIDS increasingly ravage the economically productive young citizens. Data released by the UNAIDS showed that an estimated 37.8 million adults and children were living with HIV globally at the end of 2003, and that out of this an estimated 35.7 million comprised of adults aged between 15 and 49 years of age. In Malaysia, at the end of 2003, it is estimated that 52,000 adults and children were living with HIV and a startling 51,000 were adults between 15-49 years of age. (UNAIDS, 2004). In Malaysia, over the years from 1990-2000, a total of 80.2% of those living with the virus and 65.9% of those who have AIDS were in the 20-29 year old age group. (Ministry of Health Malaysia, 2003).

Similar to HIV infection, the prevalence of TB is also high in the group which affects the economy of a nation most. A review by Bates *et. al.,* 2004, found that the greatest mortality and morbidity related to TB in poorer countries is concentrated in the economically productive 15-59 years age group. The majority of TB cases in the year 2000 in Malaysia, were in the 15-54 years range. (Iyawoo, 2004). In the year 2001, a total of 7958 smear positive cases of TB in Malaysia were reported and 52.9% of these cases were of individuals between the ages of 15 and 44 years (WHO, 2004).

The HIV/AIDS epidemic is also impacting TB incidences among the young globally and it is a major cause for the increased prevalence of TB among them. In the year 2000, a total of 560 cases of HIV/AIDS were reported in Taiwan and among them 240 cases (43.2%) were from the 25-34 years age group. Similarly the largest increase in the incidence of TB from the year 1994 through 2000 was also found in the 25-34 year old group in a study in Taipei, Taiwan. (Wang, 2002). The HIV epidemic also seems to be spreading alongside the TB disease. This is seen in the African continent, (which

contains 13 out of the 15 countries with the highest estimated TB incidence rates per capita in the world) where the prevalence of HIV infection among TB patients is high. (WHO, 2004).

An association between HIV/AIDS and TB is well established as HIV compromises the immune system of an individual and exposes the individual to an opportunistic disease such as TB. If efforts to curb the dual epidemic among the young in this country are to be successful the mode of transmission of the diseases, particularly of HIV has to be identified. The findings of this study suggested that the main mode of HIV transmission among the patients is intravenous drug use. A total of 179 (77.5%) patients were intravenous drug users (IVDUs) and out of this number, 117 (50.6%) patients were from the ages ranging between 18 and 40 years.

A total of 36,996 IVDUs were identified in Malaysia by the end of 2003 and out of this 20,194 cases were new cases of IVDUs. A total of 15, 647 IVDUs were between 20 to 49 years of age. The Malays make up the majority (68.6%) of IVDUs in the country that year, followed by the Chinese (14.8%) and the Indians (10.1%). In the same year the number of IVDUs in the state of Selangor alone was 3509 while in the Federal Territory of Kuala Lumpur 6073 IVDUs were noted. (National Drug Agency, 2004).

Similarly in this study, the Malays who formed the majority of patients were also the majority of IVDUs (64.8%) followed by the Chinese (18.4%) and the Indians (16.2%). This is an indication that intravenous drug injection is a major mode of transmission among the young in the country. Risk behaviours among IVDUs which are usually linked to misconception about drug use and addiction, social settings, societal

attitudes and stigmatization markedly increase the risk of being infected by HIV (Stajduhar *et. al.,* 2004). Better and stringent steps have to be taken to curb the spread of the HIV epidemic and subsequently TB if risk behaviours among IVDUs in this country were identified. In comparison, a study on the risk factors for HIV infection among drug injectors in Southern Thailand showed that out of the 272 (165 Thais and 107 ethnic Malays) active injecting drug users (IDUs) interviewed, 138 tested positive for HIV. A total of 88 (64%) out of this 138 were ethnic Malays. The risk factors and behaviours associated among the Malay IDUs to be infected by HIV were injecting immediately at drug onset and not carrying new needles. The risk factors identified among the Thai IDUs were past history of needle sharing, injecting immediately at drug onset as well as starting first injection at younger age. (Perngmark *et. al.,* 2003).

Although intravenous drug using is the main mode of transmission found in this study, the other mode of HIV transmission identified is sexual promiscuity. For example in this study 62.9% of sexually promiscuous patients were Chinese. This is because the Chinese were more likely than Malays to visit sex workers both within and outside the country. On the other hand the Malays and Indians got infected mainly through intravenous drug use. (Huang & Hussein, 2004).

4.3 Gender And Stigma

The issue of gender as a risk factor for both TB and HIV is important to decipher the evolution of both the diseases. In the early stages of the HIV/AIDS pandemic, infection was predominantly among men worldwide. However, at the end of 2003, a total of 17 million (47.6%) out of the 35.7 million adults between the ages of 15-49 years living with HIV, were women. (UNAIDS, 2004). Women's vulnerability to the HIV infection includes biological as well as socio-cultural determinants. Young women

are especially vulnerable to HIV infection through sexual intercourse because the immature genital tract of girls is more likely to sustain tears during sexual activity, creating a higher risk of HIV transmission (UNAIDS, 1998). Young women too most commonly have more experienced partners who are more likely to have sexually transmitted infections (STIs) from previous sexual encounters. (UNAIDS, 2004). This situation is worsened if poverty is involved. A study in Malawi showed that two thirds of 168 sexually active young women reported having sex for money or gifts (UNAIDS, 1998). Gender inequalities such as deprivation of education among women in some cultures who see females as housebound caretakers affect women's ability to take informed decisions regarding their sexual activities.

In Malaysia in the year 2001, a total of 32.3% of smear positive TB cases were from women aged 15-44 years. Globally, it was found that women aged 15-24 years made up a higher proportion of TB cases in countries with higher rates of HIV infection. (WHO, 2004). Although women have a high risk of contracting HIV/AIDS and subsequently TB, findings of this study showed that a very low number of women (9) were infected with the two diseases. There could be a few possibilities that contributed to this situation. It is possible that women who were infected by their partners were not aware of the HIV status of their partner. Married monogamous women could also been unaware of their HIV status as they were oblivious to their spouse's sexual activity. In this study, most patients (60.6%) were single while 24.7% were married. The onus of notifying their HIV status to their partner does not only lie on the individuals who are married, but also on individuals who are single or divorced. In this study it was also found that there were 20 single patients who admitted to being sexually promiscuous.

At the Infectious Disease Clinic at KLGH, married individuals were counselled on safe sex and advised to inform their spouse of their HIV status and to bring their spouse in to the clinic for HIV screening as well. This is important because for every married individual who fails to inform his family of his HIV status, there is an imminent risk of that individual infecting his or her spouse or even children. In a study in India on the spread of HIV infection in married monogamous women, prevalence of HIV among these women was 13.6%. It was confirmed that the spouse of these women were the source of their HIV infection as the women had sexual contact with no one else but their spouse. (Gangakhedkar *et. al.,* 1997). While some women remain oblivious to the risks their sexually promiscuous partners pose to them, others who are fully aware of their HIV status often shun treatment and counseling for fear of stigmatization and even the threat of violence.

TB as a disease causes stigmatization as well. In Vietnam, perception of and attitudes to TB were found to be different between males and females. Female TB patients were more likely to perceive stigma and suffer social consequences of the disease such as social ostracism whereas men with TB had only financial concerns to contend with. (Long, 2001). A longer delay in the diagnosis of TB among female patients could also be a contributing factor contributing to the conspicuously few TB cases being reported. This was shown in the study by Thorson & Johansson, 2004 which was carried out in the Bavi District, Ha Tay province in north-west Vietnam. The findings of this study revealed that the Vietnamese women in the district were self-conscious and shy especially when attended to by male doctors, causing difficulty in communication to relate symptoms which were useful to diagnose them. A previous study in the same district also found that TB was under diagnosed among both men and women. However women ran a significant risk of underdetection. Women also more often chose

healthcare providers operating outside the nationally controlled health care system for reasons such as easy accessibility and increased privacy. (Thorson *et. al.*, 2000).

The combination of stigma associated with both the diseases, could be a strong reason why the number of women patients were low in this study.

4.4 Poverty, Employment And Institutionalization

The association between poverty and disease, especially infectious disease, is not novel, and poverty most often creates the right environment for easy transmission of communicable diseases. Lack of infrastructure and proper sanitation system are most often the bane of poverty in a society. TB is also known as the poor man's disease, due to the improper sanitation, infrastructure and overcrowding which the poor contend with in their live, which provides an environment that is conducive for the disease to spread. A study in the USA found that the risk of developing TB was 2-3 times higher in the poorest individuals than the richest. (Cantwell *et. al.*, 1998).

Although every individual is susceptible to the tubercle bacilli, both HIV/AIDS and TB however is prevalent among the socially and economically down trodden. WHO identified that the 1.2 billion people worldwide living in absolute poverty, are those most vulnerable to infectious diseases such as malaria, TB and HIV infection. (WHO; 2002).

The employment status is often an indicator of the economic standings of an individual. Employment status has been found to be the strongest determinant of both poverty and economic hardship. A national survey of 925 people living with HIV/AIDS (PLWHA) in Australia was used to examine the relationship between disease progression, employment status, poverty and economic hardship. The findings of the survey indicated that the loss of income as a consequence of the loss of employment is a more important determinant of financial distress than the additional expenses incurred as a consequence of disease progression. (Ezzy *et. al.*, 1999)

In this study 63 (27.3%) patients were employed, and 54 (23.4%) patients unemployed. It can be postulated most unemployed individuals in this study could probably not hold a job to support themselves due to their drug addiction, considering the fact that such a high percentage (77.8%) of the unemployed were IVDUs. The two diseases might have prevented them from working due to their poor health. Although the monthly incomes of the patients as well as their educational status could not be determined in this study; (taking into consideration their employment status or the lack of it) it is highly probable that the majority of the patients in this study did not have a steady income that they could depend on to sustain a livelihood. In the long run, this will reduce the productivity of the nation for most of these individuals belong to the economically productive age group.

A lower socioeconomic status usually points to a low level of education. Although the education level of the patients could not be determined however, based on their economic standings most patients in this study were probably not well educated and this could be a reason why they had engaged in risky behaviours that exposed them to HIV infection.

Apart from the poor and economically marginalised, the other risk group is the institutionalized which includes prisoners and individuals in correctional facilities. The spread of infectious diseases among the incarcerated and institutionalized could also be attributed to the lack of infrastructure and overcrowding usually found in these places. In this study, prisoners and inmates of drug rehabilitation centres made up 15.6% (36) and 2.6% (6) of the total number of patients in this study respectively. Among the 36 prisoners, 30 were also IVDUs, indicating the risk they pose to other inmates. Although the number of prisoners and drug rehabilitation inmates did not seem to be very high,

this could very well be the tip of the iceberg. A study by Baillargeon *et. al.,* (2004) in a Texas prison in the USA showed that latent TB infection was the most prevalent infectious disease reported among the inmates, followed by hepatitis C, HIV/AIDS and syphilis. The situation in Malawi was more worrying for in a prison there, a high rate of pulmonary TB was found. This finding led to the implementation of interventions in eight prisons in Malawi to improve TB control, including collection of health data, education of prisoners and clinical staff about TB, active screening of prisoners for pulmonary TB and active case-finding in the prisons. (Nyangulu *et. al.,* 1997).

4.5 Alcoholism And Smoking

There are several factors that pose greater risk for an individual to contract TB. If sexual promiscuity as well as IVD using poses a great risk for HIV, smoking on the other hand causes a great risk for TB. Smoking has been associated with TB and in this study 47.6% of the patients smoked. A study done in India in the year 2003, to determine the effects of smoking on mortality in men, showed that male smokers between the ages of 25 to 69 years who smoked cigarettes or *bidis* which resemble small cigarettes, were significantly more likely than non-smokers to have died of TB, other respiratory disease, vascular disease and cancer. The study concluded that about half the male TB deaths and a quarter of all male deaths in India can be attributed to smoking and that smokers were 4.5 times more likely to die of TB than non-smokers. (Gajalakshmi *et. al.,* 2003). According to a study by Matteos *et. al.,* (1998) individuals smoking one packet of cigarettes a day inhales 1.12 µg of iron. Boelaert *et. al.,* (2003) proposed iron loading in the bronchoalveolar macrophages the primary residence of *M. tuberculosis* and which promotes the growth of *Mycobacterium tuberculosis*, as the reason for tobacco smoking being a risk factor for pulmonary TB, resulting on severe clinical disease and eventually death.

Alcoholics were found to have an increased susceptibility to infectious diseases, for chronic ingestion of ethanol can cause a wide variety of physiological changes which includes the alteration of immune functions thereby leading to an increased potential for susceptibility to bacterial infection. (Brecher *et. al.,* 1995). Individuals consuming alcohol could be further contributing to the advancement of an infection to the disease stage. In this study there were 13.0% patients who admitted to consuming alcohol. It was difficult to determine the amount of alcohol the patients consumed as apart from stating that the patients consumed alcohol, there was no other information in their records. A study on the effect of alcohol consumption with HIV and AIDS however, found that there was no relationship with the progression of HIV infection to AIDS. (Penkower *et. al.,* 1995). Alcohol consumption can however lead to a state where an individual feels less inhibited (disinhibited) making the individual more likely to engage in risky behaviour such as casual sex. Research on predictors of high-risk behaviour, has indicated a consistent relationship of alcohol use with sexual risk taking. (Kalichman *et. al.,* 2002).

4.6 Types Of Tuberculosis

Pulmonary tuberculosis is the most common type of tuberculosis in Malaysia. In its annual report in 1998 the Ministry of Health Malaysia reported that 87% of all tuberculosis cases were pulmonary tuberculosis, 9% were extrapulmonary tuberculosis, and 4% were cases where both pulmonary tuberculosis and extrapulmonary tuberculosis co-existed.

Incidences of extrapulmonary tuberculosis were found to be higher among HIV infected individuals in certain countries. In some African countries, 20-50% of

patients with pulmonary tuberculosis and 60-90% of those with extrapulmonary tuberculosis were found to be HIV positive. (Narain *et. al.,* 1992). The influence of HIV/AIDS on the epidemiology of extrapulmonary tuberculosis had been earlier questioned through a study by Mehta *et. al.,* (1991) in Tennessee. The study found that the incidence of extrapulmonary tuberculosis remained unchanged from the pre-AIDS era. However a recent study found that HIV positive individuals have indeed a significantly higher risk for extrapulmonary tuberculosis (Yang *et. al.,* 2004).

In this study extrapulmonary tuberculosis (with or without pulmonary tuberculosis) was found in 24.2% (56) of the patients. The most common types of extrapulmonary tuberculosis in this study are miliary tuberculosis and tuberculosis of the lymph nodes (tuberculous lymphadenitis). Similar findings were observed in a study in Malawi, where out of 38 patients diagnosed with tuberculosis lymphadenitis, 32 (84%) were HIV seropositive individuals. (Bekedam *et. al.,* 1997). In a study by Houston *et. al.,* (1994) in Zimbabwe, TB at two sites, lymph node, pericardial and miliary TB, were significantly more common in HIV seropositive patients compared to HIV negative individuals.

The clinical manifestations of extrapulmonary tuberculosis are often non specific and insidious delaying diagnosis for years. Therefore a high index of suspicion is needed on the part of the physician to diagnose and treat extrapulmonary tuberculosis. (Elder, 1992). Due to the difficulty in detecting and diagnosing EPTB, there is a possibility that the number of EPTB cases found in this study were more than the ones recorded. This could probably be due to the fact that the patients were still asymptomatic and showed no apparent signs of EPTB. A study in Tanzania for instance, found that

4.7 Clinical Investigations And Laboratory Results

4.7.1 Symptoms

According to the Practice Guidelines for the Control and Management of Tuberculosis by the Ministry of Health and the Academy of Medicine Malaysia (2002), symptoms which suggest pulmonary tuberculosis include;

a. cough persisting for more than two weeks

b. cough with sputum which is occasionally bloodstained

c. Loss of appetite and loss of weight

d. Fever

e. Dyspnoea, night sweats, chest pain and hoarseness of voice, all of which are uncommon

The symptoms for extrapulmonary TB are often non-specific and include lassitude, anorexia, fever and weight loss. The symptoms also vary with the different organs that are involved.

The guidelines indicate that patients with the above symptoms should be screened for tuberculosis. In this study, loss of weight, cough and fever were the three most common symptoms the patients in this study complained of. HIV positive individuals with TB have double the chances of experiencing loss of weight compared to their HIV negative counterparts as weight loss is a symptom of both HIV and TB. A total of 150 patients weighed between 41-60 kgs and more than half experienced loss of weight. Unfortunately the exact amount of weight lost by the patients could not be determined due to insufficient data available in the records of the patients.

4.7.2 Chest X-Ray

The Ministry of Health Malaysia and the Academy of Medicine Malaysia has classified the radiologic extent of tuberculosis as follows;

RADIOLOGICAL CLASSIFICATION	CRITERIA
Minimal	Slight lesions without demonstrable cavitations confined to a small part of one or both lungs. The total extent of the lesions should not exceed the volume of lung on one side which lies above the second chondrosternal junction and the spine of the fourth or the body of the fifth thoracic vertebra.
Moderately advanced	One or both lungs may be involved but the total extent of the lesions should not exceed the following limits: i. Disseminated lesions of slight to moderate density not exceeding the total volume of one lung or the equivalent in both lungs ii. Dense and confluent lesions not exceeding one third the volume of one lung

	iii. Total diameter of cavitations, if present, must be less than 4 cm.
Far advanced	Lesions are more extensive than moderately advanced

Source: Ministry of Health Malaysia & Academy of Medicine of Malaysia, 2002

In this study the chest x-ray of 64 (27.7%) patients showed that the extent of the disease was minimal, on the other hand the disease was found to be far advanced in 28 (12.1%) of the patients. Tuberculosis patients with HIV infection are more likely to have atypical chest radiographic appearances (pulmonary infiltrates with no cavities, lower lobe involvement, intrathoracic lymphadenopathy and even normal appearance) than tuberculosis patients without HIV infection. (Harries *et. al.,* 1998b)

Due to the atypical presentations in their chest x-ray, it has been suggested that using chest radiography as a screening tool for tuberculosis in HIV infected individuals who were asymptomatic could be excluded. (Mosimaneotsile *et. al.,* 2003). However, in this study the patients at IRM were showing symptoms of the TB disease to a certain extent, therefore the results of the chest X-rays was used alongside other diagnostic investigations for a more accurate diagnosis.

4.7.3 Tuberculin Skin Test (TST)

In this study a high percentage of patients [64.1% (148)] were found to be negative for the tuberculin or Mantoux test in this study. This indicates the high

possibility of anergy in the patients as the human immunodeficiency virus induces this state in its host. Anergy is an immunological term that can be generally interpreted as impaired cell-mediated immunity leading to disruption of delayed-type hypersensitivity (DTH) skin reaction. (Hedge & Robbins, 2000). An anergic individual does not have the immunologic capacity to give out any reaction to a test like the tuberculin skin test, rendering it meaningless or useless. The cutaneous reactivity is partially or completely negative due to the state of anergy in the majority of AIDS patients with dual infections. (CDC, 1991b). Results similar to the one in this study were also found in a study of HIV positive hospitalized patients in Baltimore, Maryland, USA, an area where both TB and HIV infection are prevalent. The study found that 63% of HIV infected patients were anergic. (Janis *et.al.,* 1996). In a study by Duncan *et. al.,* (1995) which was carried out at a sexually transmitted diseases clinic in Lusaka, Zambia, it was found that the percentage of HIV positive patients without a response to tuberculin (indicative of a negative result for the tuberculin skin test) was double (67%) the percentage of HIV negative patients with negative results for the tuberculin test which was 33%.

4.7.4 Bacille Calmette Guérin (BCG)

BCG vaccination was given for the first time in Malaysia as mass vaccination in 1958 to everyone who came forward including children. The National Tuberculosis Control Programme was launched in Malaysia in the year 1961, and one of its objectives was to protect at least 95 % of the susceptible population of less than 20 years of age by BG vaccination. (Ministry of Health Malaysia, 1998).

At present, in Malaysia, BCG vaccination is given only once to all newborns as soon as after delivery. At primary schools, when the children start their

primary education at age seven, they are given a repeat dose of the BCG vaccine if a scar is not found.

In this study the number of patients having a BCG scar and the number of patients not having the scar is almost the same; 92 and 90 respectively. The results in this study also indicated that no patients in the age group of more than 51 years had the BCG scar. This could probably be due to the lack of a systematic tuberculosis control program in the country prior to the year 1961. The other patients without the scar might not have had formal education in schools. However, the fact that even those vaccinated were also afflicted by the tuberculosis disease could be an indication of the inefficacy of the vaccine in controlling the disease among adults, and in this case, HIV positive adults.

4.7.5 Direct Smear And Culture

The results for direct smear and culture play important roles in the diagnosis and treatment of the tuberculosis disease. In this study 54 (23.4%) patients had positive results for direct smear while 166 (71.9%) patients had negative results. A total of 95 (41.1%) patients had positive results for culture and 128 (55.4%) patients had negative results. The reason as to why the positive results for culture is higher than that for direct smear could probably be explained by referring to the sensitivity of the tests. The AFB (acid fast bacilli - the detection of which indicates the presence of *M. tuberculosis*) smear examination has a sensitivity of only 50-60%, partly because a positive smear requires 5000-10,000 AFB per µL sample. To obtain a culture of the mycobacteria, only 10-100 AFB per µL is needed and culturing can detect pulmonary tuberculosis in around 80% of true cases. (Levy *et, al.,* 1989). The difference in the efficacy of the two procedures (direct smear and culturing) is probably the reason why in

this study there were 60 patients with positive results for culture but negative results for direct smear.

The high percentage of patients with negative results for direct smear in this study could also be explained with reference to the influence of the HIV infection on the immune reactions of the patients. It has been found that in countries with high prevalence of both PTB and HIV infection, the detection rate of tuberculosis through direct smear is low owing to the paucibacillary nature of PTB in patients with HIV infection. (Siddiqi *et. al.,* 2003). An immunocompetent individual's immune system will mount the suitable reactions against *M. tuberculosis* and this usually results in pulmonary inflammation and cavitation. The tubercle bacilli which are lined along the walls of the cavities are coughed up by the individual and would be present in the sputum. However in HIV positive individuals the tubercle bacilli do not appear in sputum because of the paucity of pulmonary infection and also due to the decreased cavitation in the lungs. (Harries *et. al.,* 1998a).

Less bacilli in the sputum means less likelihood of transmission as TB (pulmonary) is spread through droplets exuded while coughing, talking or singing. The findings of the study by Espinal *et. al.,* 2000 indicated that HIV positive individuals with TB were less likely than HIV negative individuals with TB to transmit *M. tuberculosis* to their close contacts. The study however concluded that apart from lower bacillary load found in the sputum smear of HIV positive TB co-infected individuals, the weakened cough among these individuals (due to a high degree of illness) which resulted in less effective dissemination of *M. tuberculosis* into their surroundings, could also be a possible reason for the less infectious nature of the individuals concerned.

4.7.6 CD4 Cell Counts

There were only 2 patients with normal CD4 counts. Considering the fact that both HIV and TB weigh down the immune system, this figure is not unexpected. However, in this study most of the patients did not have their CD4 cells counted. Only those who were under the care of the Infectious Disease Clinic at the Kuala Lumpur Hospital had the count done. This is the reason why there were 188 patients without information regarding their CD4 count.

A study by Ackah *et. al.,* (1995) in Abidjan, Cote d' Ivoire, showed that 43 % of HIV positive patients were diagnosed with tuberculosis at a CD4 lymphocyte count below 200/uL and 39% with a count of 200-499 /ul. The CD4 count of the patients in this study was matched with the type of tuberculosis they had and it showed that none of the patients with extrapulmonary tuberculosis had CD4 cell count in the normal range. Patients with EPTB have been noted to have lower CD4 counts than patients with PTB. A study by Castilla *et. al.,* (1997), involving 6161 AIDS cases in Spain found that pulmonary tuberculosis presented with higher CD4+ lymphocyte counts than extrapulmonary tuberculosis.

The lower level of CD4 count is a direct indication of the lowered efficacy of the immune system. Due to the immune system's inability to contain and localize the tubercle bacilli (e.g. in granulomas) the *M. tuberculosis* spread to various organs in the body causing extrapulmonary tuberculosis.

4.7.7 Atypical Mycobacteria

In this study atypical mycobacteria belonging to Runyon Group IV was found. They were classified as "belonging to *M. fortuitum-chelonei* complex" and "not belonging to *M. fortuitum-chelonei* complex". The mycobacteria *M. fortuitum* and *M. chelonei* which make up the complex very often are found together and have very similar morphologies. They are among the non-tuberculous mycobacteria that affect humans. In patients without HIV infection, these organisms, cause skin diseases and localized abscesses as a result of puncture wounds or surgical procedures (Chin, 1993). In patients with HIV infection, both *M. fortuitum* and *M. chelonei* have been reported as a cause of disseminated infection and have also been isolated from cervical lymph node, sputum and pleura. (Shafer & Sierra, 1992).

The most common atypical mycobacteria that cause infections in humans are *M. abscessus*, *M. chelonei* and *M. fortuitum*. (Howard & Byrd; 2000). Atypical mycobacterioses, especially the disseminated forms accompany HIV infection and worsen the quality of life and survival in patients with AIDS. Disseminated infection is detected antemortem in 25% of patients with AIDS and postmortem in 50% of these patients. (Rozsypal & Stankova, 1995).

Atypical mycobacteria are mostly resistant to all the first line drugs of anti tuberculosis therapy (ATT). The atypical mycobacteria (M. fortuitum and M. chelonei) in this study were found to be resistant to anti tuberculosis drugs. This is not uncommon as rapidly growing mycobacteria, to which *M. fortuitum* and *M. chelonei* belong to, are generally resistant to most first-line antituberculosis drugs. Treatment may involve months of antibiotic therapy and surgical removal of infected tissue. (Wallace *et. al.*, 1997).

4.8 Therapy

4.8.1 Anti Tuberculosis Therapy (ATT)

Modern chemotherapy has been very successful in conquering the tuberculosis disease. At the present time, tuberculosis can be cured in most cases with drugs given daily or two to three times weekly for 6 months. (Chaisson, 2003). In fact anti tuberculosis chemotherapy is so effective that afflicted patients are rendered non-infectious after only the first two weeks of initiating chemotherapy. (Jidani *et. al.,* 1980). The remaining months are to kill a population of slowly-metabolizing persistant bacilli as well as to permit the host to develop protective immunity to control the remaining number of bacilli which escaped annihilation by the drugs. (Zhang & Amzel, 2002).

The treatment of HIV infected individuals with tuberculosis is the same with their HIV negative counterparts. A study in Africa (Murray *et. al.,* 1999) had shown that the treatment of active susceptible tuberculosis with first line anti tuberculosis drugs (SM, ETH, INH, RIF and PZA) is as effective and reliable at curing tuberculosis in people infected with HIV in the absence of highly active anti retroviral therapy (HAART), as in those not infected with HIV. However, the mortality rate will be higher for those with HIV infection, for their compromised immune system ravaged by the HIV exposes them to other various opportunistic infections. (Murray *et. al.,* 1999).

In this study most of the patients (75.8%) were under the regimen of two months of daily doses of the drugs ETH (E), INH (H), RIF (R) and PZA (Z) for the initial phase, followed by four months of biweekly doses of the drugs R and H for the continuation phase.

4.8.2 Adverse Drug Reactions (ADR)

The continuity of anti tuberculosis chemotherapy is at times disrupted by adverse drug reactions encountered by patients. There are some major adverse effects associated to the first line of anti tuberculosis drugs. The common drug reaction that is associated with the drugs INH, PZA and SM is rash. Nausea is associated to RIF and PZA, drug-induced hepatitis is associated to the drugs INH, RIF and PZA, thrombocytopenia is associated to RIF and blurring of vision is associated to ETH and SM. (Chan & Iseman, 2002).

Some drugs are more prone to cause adverse drug reactions than others as found by a study by Yee and associates (2003) In the mentioned study PZA-induced hepatoxicity and rash during treatment for active tuberculosis was substantially higher than with other first line anti tuberculosis drugs. However some side effects are reversible, and this includes the most significant side effect of ETH - optic neuritis. Symptoms of optic neuritis include blurred vision and colour blindness. If the reactions are detected early and the medication stopped promptly these symptoms can be reversed. (Hershfield; 1999).

In this study a small percentage (9.1%) of patients were found to have experienced adverse drug reactions to their anti tuberculosis drugs. Similarly the study on 430 tuberculosis patients by Yee *et. al.,* (2003) showed that 9% of patients experienced adverse drug reactions to the anti tuberculosis drugs. Adverse drug

reactions could pose a problem to therapy as it can result in modification or discontinuation of therapy. This will affect the effectiveness of the therapy itself.

4.8.3 Treatment Defaulting

Patients who have missed more than 25% of their tuberculosis treatment doses in one month are considered to be defaulters. This means that an individual who missed more than 6 doses of daily treatment or more than 2 doses of biweekly treatment qualify to be defaulters. (Ministry of Health Malaysia & Academy of Medicine of Malaysia, 2002).

Defaulting of treatment add to the complication of treating HIV infected individuals with tuberculosis. In the year 2000, there was a defaulter rate of 9.80% in Malaysia and 50.3% of these defaulters were retrieved and put on their treatment again. (Ministry of Health Malaysia, 2000) Despite the efforts of the hospital staff and physicians to keep the patients coming for treatment regularly, some patients elude their treatment. In New York City, many of the most difficult tuberculosis patients to manage are co-infected with HIV and many of these have been detained until cured, because of their frequent habit of defaulting treatment. (Coker; 1998).

4.8.4 Directly Observed Therapy-Short Course (DOTS)

Although tuberculosis is curable, the disease has not been eradicated successfully. The only way to annihilate TB is through stringent adherence to ATT. Patients who fail to stick to their treatment regimen by defaulting, weaken the fight against TB. To resolve the huge problem of non-adherence by TB patients, the World Health Organization (WHO) implemented the Directly Observed Treatment, Short-Course (DOTS) in the year 1996 after announcing tuberculosis as a global health

emergency in the year 1993. DOTS was introduced to increase the cure rate of the disease and to ensure that tuberculosis patients adhered to treatment avoiding treatment failure. The DOTS strategy comprises five elements for its success;

1. Government commitment to a National Tuberculosis Control Programme
2. Case detection through sputum smear microscopy examination of tuberculosis suspects in general health services
3. A standardized short-course tuberculosis treatment regimen of six months under direct observation by a trained supervisor to ensure the patient takes every dose of medication.
4. A regular, uninterrupted supply of quality anti-tuberculosis drugs
5. A monitoring and reporting system to evaluate treatment outcome for each and every patient with proper documentation

Source: Ministry of Health Malaysia & Academy of Medicine of Malaysia, 2002.

The fact that the patients were directly observed taking the medication, by health personnel, reliable friend or a relative, has greatly improved the adherence of patients to their treatment. DOTS has a cure rate of up to 95%, and takes at least 6 months. Presently DOTS is the best treatment for TB (Zhang & Amzel; 2002). A study in a teaching hospital in Nigeria found that the cure rate and compliance rate was 86.1% and 93.8% respectively with DOTS. The study concluded that DOTS is an effective mean of administering anti-TB drugs and that efforts should be channelled towards developing strategies for implementing DOTS in a more efficient way. (Erhabor, *et. al,* 2003).

4.8.5 Multidrug Resistant Tuberculosis (MDRTB)

In the early days of tuberculosis chemotherapy, it was found that the use of single drug led to selection of drug resistant bacilli and that a combination of two or more drugs greatly reduced the emergence of drug resistance. (Zhang & Amzel, 2002). This is an important reason as to why multiple drugs are used in the treatment of tuberculosis. Even then, the emergence of drug resistant strains of *M. tuberculosis* that cause MDRTB (multi-drug resistant tuberculosis) could not be stopped completely.

MDRTB is defined as tuberculosis with resistance to at least INH and RIF. (Bastian *et. al.,* 2000). This resistance to the drugs is important to *M. tuberculosis* in order to survive and evade destruction by the drugs. Very often human error provides the suitable situation for the microorganism to acquire drug resistance. Acquired drug resistance of tuberculosis is almost always caused by inadequate treatment. This can include failure of the patient to take the prescribed drugs, failure of the physician to prescribe appropriately, failure of the healthcare system to ensure that drugs are available or malabsorption of the drugs due to dysfunction of the digestive system or substandard bioavailability of the preparation. (Chan & Iseman; 2002).

In this study although a strain of *M. tuberculosis* resistant to SM was isolated from one patient, it was not considered to be a case of MDRTB as indicated by the definition of the term. Since the patient was resistant only to SM, a treatment regimen that excluded this drug was used to treat this patient. However the solution may not be so simple in the case of MDRTB. To treat MDRTB at least two new drugs should be added to the original medications, incurring high costs and difficulties in curing the disease. (Hershfield; 1999).

Transmission and acquisition of MDRTB is in large part preventive as found in a study in USA involving the most unwell MDRTB patients that included those who were treated an average of 6 years and had resistance to an average of 6 drugs. The study showed an average of 4 preventable mistakes per patient. The mistakes included a) failure to obtain drug susceptibility testing, b) failure to modify the regimen when the susceptibility pattern of the isolate indicated change and c) failure to identify and remedy patient non-adherence by the provision of DOT and other adherence promoting strategies. (Mahmoudi & Iseman, 1993).

4.8.6 Antiretroviral Therapy (ARVT)

Antiretroviral therapy improves live quality of HIV infected individuals and improves their prognosis. Highly active antiretroviral therapy is a antiretroviral therapy that involves triple combination therapy. These combinations can be triple nucleoside reverse transcriptase inhibitor (NRTI) regimens, non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens (2NRTI and 1NNRTI), and protease inhibitor (PI) based regimens. Combining agents produces more effective viral suppression, which in turn limits the mergence of drug resistance and provides more effective antiretroviral treatment even when mixtures of drug resistant and drug sensitive strains are present. (Thaker & Snow; 2003).

A study by Ives *et. al.,* (2001) found that although most AIDS-defining illnesses decreased with the introduction of HAART in a London clinic over a 9 year period, there was a non-significant increase in the incidence of tuberculosis. This indicated that the tuberculosis disease continued to affect the HIV positive individuals regardless of whether they were on HAART or not. The effect of HAART on the incidence of tuberculosis in South Africa conducted by Badri *et. al.,* (2002) gave a

different result. It was found that HAART reduced the incidence of HIV-1-associated tuberculosis by more than 80% in an area endemic with tuberculosis and HIV-1. Another study by Schluger *et. al.,* (2002), found that HAART restores immune responses to *M. tuberculosis* in HIV infected individuals, although this restoration was delayed and did not reach levels seen in healthy, HIV-negative individuals.

In this study it was found that only a very small percentage (6.1%) patients were under antiretroviral therapy. The high cost of ARVT is a major obstacle to most of the patients who have social problems such as drug addiction and alcoholism which prevents them from maintaining a job to support themselves. However those patients who were under ARVT had supportive family members who were willing to spend the money required for the therapy.

4.9 Other Infections

Most patients with AIDS die from infections other than human immunodeficiency virus (HIV). Most of these infections are caused by organisms that do not normally afflict healthy individuals and are thus considered to be opportunistic.

4.9.1 *Pneumocystis carinii* Penumonia (PCP) And Candidiasis

Among the major problems confronting patients with AIDS are opportunistic fungal infections. The most common infections encountered are PCP and candidiasis. In this study, 55 patients were under antifungal medication, with 44 patients taking medication for both PCP and thrush, 9 for PCP alone and 2 for thrush alone.

The opportunistic yeast *Candida albicans* which is a normal saprophyte of the human digestive tract can cause oropharyngeal and esophageal infection in those

with AIDS and is the reason for patients complaining of an uncomfortable feeling in the mouth. Mucosal candidiasis in HIV-infected patients affects more than 95% of patients with HIV infection. As the immune status deteriorates, thrush becomes more frequent and recur within weeks after antifungal therapy is stopped. (Rinaldi; 1996).

Pneumocystis carinii is an extracellular fungus that causes severe interstitial pneumonia and is the commonest opportunistic infection of HIV-infected adults in developed countries. (Hargreaves *et. al.*, 2001). *Pneumocystis carinii* infection elicits an inflammatory response in the lung and PCP is the predominant disease suffered by about 20% of AIDS patients and 50% of HIV-infected patients experience at least one bout of PCP during the course of their disease. (Kasper & Buzoni-Gatel; 1998).

4.9.2 Hepatitis

The viral infection, hepatitis was found in a total of 87 (37.7%) patients with a total of 6 patients with hepatitis B, 68 patients with hepatitis C and 13 patients with both hepatitis B and C. The majority of patients infected with hepatitis B and C in this study could have been infected through sharing of needle. Hepatitis B is the most common viral hepatitis infection in people with HIV, but hepatitis C is more likely than any other form of hepatitis to result in chronic or long term disease, liver failure or death. (Piliero & Faragon; 2002). In a study conducted by Seaton (2003), a total of 25% of Americans with HIV also have hepatitis C virus infection and people with co-infection have higher levels of hepatitis virus in the blood, more rapid progression of liver damage and a greater rate of death due to hepatitis than people with only hepatitis C virus infection.

4.9.3 Syphilis

Syphillis is a sexually transmitted disease caused by the spirochete *Treponema pallidum pallidum*. In this study 2 patients had syphilis and both admitted to being sexually promiscuous. Since the year 1997, there has been several outbreaks globally of syphilis among men who have sex with men, many of whom were co-infected with HIV. (CDC, 2001). Eliminating syphilis would reduce the likelihood of HIV transmission, for sexually transmitted infections facilitates HIV transmission by increasing HIV shedding in the genital mucosa in individuals co-infected with HIV and STI. (Cohen *et. al.,* 1997).

4.9.4 Toxoplasmosis

Toxoplasmosis is caused by infection with the obligate, intracellulare parasite, *Toxoplasma gondii.* In the immunocompromised individual, this parasite is responsible for the development of a variety of clinical syndromes, the most frequent of which is toxoplasmic encephalitis. A total of 24 (10.4%) patients were found to have toxoplasmosis in this study. Toxoplasmosis detection is done in the ID clinic only, this explains why so many patients had no information regarding this infection in their files. These patients have a good chance of being infected and developing the disease as been found by several studies on HIV and AIDS patients. In the USA, between 18% and 25% of patients with AIDS suffer from symptomatic toxoplasmosis during the course of their illness. (Kasper & Buzoni-Gatel; 1998). In a study in Mexico of patients with neurological complications related to HIV-Infection /AIDS, brain toxoplasmosis was the most common neurological complication found, with 32.2% (the highest percentage) of the patients afflicted by it.. (Gongora-Rivera *et. al.,* 2000).

4.10 Clinical Outcomes

Tuberculosis was the number one cause of death in Malaysia in the early 1940's and 1950's. The availability of chemotherapy in the late 1950's as well as the launching of the National TB Control Programme (NTP) in 1961 set the pace for the curbing of the disease. Since then, tuberculosis has dropped from being the number one cause of death to being number 11 in the year 1998. (Iyawoo, 2004)

By the end of this study there were 180 patients with active TB, 33 patients with inactive TB and 18 patients had completed their treatment successfully. A total of 4 patients died; 3 patients of which had active TB while the remaining one patient had already completed treatment.

The life expectancy of HIV infected patients has been improving steadily over the years, due to the various treatment available to treat the opportunistic diseases that are encountered in this group of patients. A study of survival trends during the first 12 years of the AIDS epidemic in Mexico, showed that survival improved among patients with HIV infection over the 12 years. (Villasis-Keever *et. al.,* 2001). .

Severity of immune deficiency is the major determinant of mortality in HIV-associated tuberculosis. (Ackah *et. al.,* 1995). An increase in the case fatality rate, is one of the important adverse effects which HIV has upon treatment outcome in patients with tuberculosis as shown by a study in Malawi by Harries *et. al.,* (1998b). The study found that among new patients of tuberculosis, HIV positive patients had higher death rates compared to HIV negative patients.

HIV infection remains the single most important risk factor for the development of active tuberculosis and since most patients with TB/HIV co-infections are seen with advanced tuberculosis in Malaysia, the number of deaths due to TB/HIV has also increased over the years. (Iyawoo, 2004). In the year 1999, there were 14, 907 cases of tuberculosis in Malaysia. A total of 690 cases were TB-HIV co-infection cases, of which 202 were fatal (Ministry of Heath Malaysia, 2000).

4.11 Conclusions

The conclusions that can be drawn from this study are;

- The prevalence of HIV/AIDS-TB co-infection was found to be higher among males compared to females

- Most of the patients were Malays in the age group of 31-40 years and were IVDUs

- The majority of co-infected patients were in the economically productive bracket (31-40 years of age)

- In this study no significant relationships were found between the different lifestyles and the stage of the TB disease as well as the clinical outcomes of the patients. This was probably due to the large number of unknown data which distorted the results of the statistical analysis

4.12 Recommendations

- Since the majority of patients in this study were IVDUs, more research into the risk factors of IVDUs in the country should be done. Identifying the risky behaviours (using unsterilized needles, usage of needles without knowing the source etc) that are practiced by the IVDUs could provide better chances of preventing HIV infection among this group of individuals.

- A systematic procedure for the updating of the patients' profile in hospital settings could be immensely useful for researches as crucial epidemiological data could be left out if no consistent method is followed. Serious implementation of the system should also be adopted so that essential information of patients (e.g weight, lifestyle, socio-economic status) is always obtained.

- Healthcare providers should always be professional in their approach towards the HIV and TB co-infected patients. They should be sensitive towards the fact that stigmatization of this group of patients will only lead to more serious consequences. It is highly imperative that the patients develop a strong bond of trust with their healthcare providers so that they can be completely comfortable to reveal more about themselves. If patients feel they are being treated with biasness they will withhold precious information that could be highly essential for effective management of his or her diseases.

- The Ministry of Health should realize the importance of this group of patients vis-à-vis public health and adopt more vigorous steps in tracking down patients who default treatment so that more patients could be cured of tuberculosis. A change of perception is necessary at all levels of the ministry regarding this group of patients and the importance of managing them should never be clouded by biasness.

4.13 Limitations Of The Study

- Data in this study was obtained retrospectively. This did not allow the researcher to find out all the parameter needed such as the education status and monthly income of patients, reasons of defaulting treatment and reasons for not getting treatment at the ID clinic as well.

- Due to some complications with the filing system, there were some files which were missing.

- Occasional difficulty in deciphering the handwriting of healthcare providers impeded the data collection process

- Time shortage prevented the researcher to obtain more case files

A. DEMOGRAPHIC DATA

<table>
<tr><td colspan="5">1. Patient Biodata</td><td colspan="3">REF NO:</td></tr>
<tr><td colspan="3">Name:</td><td>Age:</td><td>Height:</td><td>Weight:</td><td colspan="2">Race: M/ C/ I/ Others, specify .....</td></tr>
<tr><td colspan="5">Address:</td><td>Urban</td><td>Rural</td><td>Homeless</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>2. Social Status</td><td>Smoker: Y / N</td><td colspan="2">Alcohol: Y / N</td><td colspan="2">Working: Y / N</td><td colspan="2">Drug Abuse: Y / N</td></tr>
<tr><td colspan="4">3. Monthly Income:
< RM 500 / RM 500-RM 999/ RM 1000-RM 1999/ > RM 2000</td><td colspan="4">Job: Govt/ Private/ Own/ Others</td></tr>
<tr><td colspan="8">4. Education: Primary/ Secondary/ Diploma/ Degree/ Higher level</td></tr>
<tr><td colspan="8">5. Family History :</td></tr>
<tr><td colspan="8">6. Allergy: Y / N
If yes, kind of allergy: Food/ Drug/ Environment/ Others, specify .....</td></tr>
<tr><td colspan="8">7. Past Medical History:</td></tr>
<tr><td colspan="8">8. Past Surgical History:</td></tr>
</table>

9. Past Medication History:
10. Present Medication:

B. DISEASE

1. Tuberculosis								
1.1 Clinical Signs			**1.2 Clinical Investigation**					
Symptoms	Y/N	Date	1.2.1 CXR		1.2.2 Laboratory Investigation			
Malaise			Date	Findings	Date	Result	Sensitive	Resistant
Anorexia								
LOW								
Fatigue								
Fever								
Chills/Night Sweats								
Cough Duration								
Pleuritic chest pain								
Hemoptysis								
SOB								
Others								
1.3 Diagnosis : When: __ __ / __ __ / __ __ Where: Govt. Hospital or Clinic / Private Hospital or Clinic / Others, specify								
1.4 Drug Treatment								

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