PULMONARY TUBERCULOSIS TREATMENT OUTCOMES IN HIV INFECTED PATIENTS ON ANTIRETROVIRAL THERAPY

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PULMONARY TUBERCULOSIS TREATMENT OUTCOMES IN HIV-INFECTED PATIENTS ON ANTIRETROVIRAL THERAPY

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ABSTRACT

Objective: To determine the treatment outcomes of pulmonary tuberculosis in HIV- infected patients on antiretroviral therapy (ART)

Method: A retrospective study was conducted among HIV-infected patients aged 15 years and above, who presented with active pulmonary TB (culture-positive cases) and received anti-TB treatment and NNRTI-based antiretroviral treatment.

Finding: There were 65 patients (47 male) with a median age of 32 years (range 20-58). Positive culture results were obtained from sputum (57 patients) and trans-tracheal aspirate (8 patients). At the time of TB diagnosis, the median CD4 count was 33 cells/μL (range 2-342). 50 patients (76.92%) received HRZE anti-TB regimes for at least 2 months in the initial phase and 15 (23.08%) did not receive HRZE for at least 2 months in the initial phase. ART was initiated at a median of 12 weeks (range 0-52) of TB treatment. Eight patients (12.3%) had already received ART before TB diagnosis. 43 patients (66.1%) received NVP-based regimes and 22 (33.9%) received EFV-based regimes. 36 patients (55.4%) received NVP and RFP concurrently, and the median of overlap was 115 days (range 5-394 days). Drug toxicity was observed in 26 patients (40%). There was no significant association between drug toxicity and concurrent use of NVP and RFP. IRIS occurred in 5 patients (7.7%) and opportunistic infections occurred in 4 patients (6.2%) after ART had started. 33 patients (50.8%) were clinically cured, 20 (30.8%) were cured, 5 (7.7%) were transferred out, 3 (4.6%) had treatment interrupted, 3 (4.6%) died, and 1 patient had treatment failure. There were no significant associations between TB treatment outcomes and anti-TB regimes, ART regimes and concurrent use of NVP and RFP, but the schedule for initiating ART was significantly associated with pulmonary TB treatment outcomes.

Conclusion: Initiation of ART in the early course of HIV infection, before TB infection, yields a favorable pulmonary TB treatment outcome. NVP-based ART may be an option for HIV-infected patients receiving RFP.

KEY WORDS: Pulmonary TB/ HIV/ anti-TB/ ART/ treatment outcomes

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LIST OF ABBREVIATION

AFB	= acid fast bacilli
AIDS	= Acquire Immune Deficiency Syndrome
ALT	= alanine aminotransferase
AST	= aspertate aminotransferase
ATS	= American thoracic society
ART	= antiretroviral treatment
ARV	= antiretroviral drugs
AZT	= zidovudine (also known as ZDV)
CDC	= center for disease control and prevention
CD4	= CD4+ T lymphocyte
d4T	= stavudine
ddI	= didanosine
EFV	= efervirenz
EPTB	= extra pulmonary tuberculosis
GPO vir	= generic fixed dose combination of D4T, 3TC and NVP
HAART	= highly active antiretroviral therapy
Hb	= hemoglobin
Hct	= hematocrit
HIV	= Human Immunodeficiency Virus
IDSA	= Infectious Diseases Society of America
IDV	= indinavir
IUATLD	= International Union Against Tuberculosis and Lung Disease
MOPH	= Ministry of public health, Thailand
NRTI	= nucleoside reverse transcriptase inhibitor
NNRTI	= non nucleoside reverse transcriptase inhibitor
NVP	= nevirapine
OI	= opportunistic infections
PCP	= *Pneumocystis carinii* pneumonia
PI	= protease inhibitor

LIST OF ABBREVIATION (Cont)

RFP = rifampicin
SQV = saquinavir
TB = tuberculosis
TTA = Trans tracheal aspirate
3TC = lamivudine
UNAIDS = United Nations program for HIV/AIDS
WBC = white blood cell
WHO = World Health Organization

CHAPTER I

INTRODUCTION

Tuberculosis (TB) is one of the oldest diseases known to affect the human and caused by the bacteria, *Mycobacterium Tuberculosis*. The tubercle lesions have been found in the vertebrate of Neolithic human in Europe and Egyptian mummies perhaps as early as 3700 years BC. The infectious agent was discovered by Robert Koch in 1882. (Horne, 1996) Acquire immuno deficiency syndrome (AIDS) was first recognized in the United States in the summer of 1981. In 1983, human immunodeficiency virus (HIV) was isolated from a patient with lymphadenopathy and by 1984 it was demonstrated clearly to be the causative agent of AIDS. (Fauci and Lane, 2005)

Since the time of its initial description more than two decades ago, HIV/AIDS has spread all around the globe. In 2004, there were 4.9 million new infections and 3.1 million deaths due to HIV/AIDS largely in sub-Saharan Africa and South East Asia. (UNAIDS 2004). Unfortunately, Tuberculosis has been booming since ages and forming a deadly synergy in these regions. TB is the leading cause of morbidity and mortality in patients with HIV/AIDS. (Harris et al., 2004). TB and HIV are also intricately linked to malnutrition, unemployment, alcoholism, drug abuse, poverty and homelessness. (Russell 2004). As a result of HIV/AIDS, incidence rates of TB in certain countries have gone up by more than 6 per cent (Corbett, 2003) and HIV infection increases the risk of developing active TB by a factor of 100. (Fauci and Lane, 2005)

TB is one of the important opportunistic infections in HIV infected patients in developing countries. (Narain et al., 2002). Before the epoch of highly active antiretroviral therapy, TB caused substantial mortality in patients with advanced HIV infection. Although there are effective therapies for both HIV and TB (Hung et al 2003), concomitant administration is difficult due to the problems of drugs interactions, toxic adverse effects and paradoxical worsening of the patients'

condition. (Dean et al 2002) These events can potentially affect the patients' adherence to treatment, which is necessary for successful treatment of TB and HIV infection. (Paterson et al., 2000)

It may not be safe to wait for antiretroviral therapy until the completion of TB treatment as HIV infected patients with low CD4 counts are at increased risk of HIV progression and mortality. However, the optimal timing to start antiretroviral treatment in HIV and TB co-infected patients is not clearly known. (Sungkanuparph et al., 2005)

The current recommendation for TB treatment in HIV infected patients suggests using rifabutin, which offers more flexibility than rifampicin in the choice of antiretroviral drugs. (CDC, 2004) But rifabutin is not easily available in many developing countries where there is high prevalence of TB and HIV infection. Rifampicin is a potent inducer of the hepatic microsomal enzymes and thereby decreases the half-life of a number of drugs, including antiretroviral drugs such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).(Wallace and Griffith, 2005) Therefore patients who have to use rifampicin will have considerable effect on dosage of the drugs and regimes of antiretroviral therapy. At the same time, the patients who have contraindication to use rifampicin may have substantial impact on the clinical outcomes.

Finally, to reduce the morbidity and mortality and to improve the quality and duration of life span of HIV and TB infected patients, early diagnosis and proper treatment is essential. The aim of this study is to describe the outcomes of anti TB and antiretroviral treatment and to compare the results of different kinds of ARV regimes, different kinds of TB treatment regimes and also different timing of initiating ARV in HIV and TB co-infected patients. Therefore, the result of the study is expected to be beneficial for medical personals involved in handling HIV/AIDS patients especially in developing countries.

CHAPTER II
OBJECTIVE

To determine the outcomes of pulmonary TB among HIV and TB co infected patients who received both anti TB and antiretroviral treatment

CHAPTER III
LITERATURE REVIEW

Epidemiology of HIV and TB

Joint United Nations Program on HIV/AIDS (UNAIDS) and WHO estimate nearly 39.4 million people were living with HIV/AIDS worldwide; more than half of them were in the in Sub Sahara Africa and nearly one fifth were in South and South-East Asia by the end of 2004. In Thailand, cumulative HIV infections were 1,092,327; cumulative deaths were 551,505 and the number of people living with HIV/AIDS was 540,822. (Source: The Thai working Group on HIV/AIDS Project, Bureau of Epidemiology, Department of Disease Control, as of Feb 28, 2005)

Prevalence of TB in HIV infected patients

TB is the most common opportunist infection in people with HIV/AIDS in developing countries in contrast to developed countries where *Pneumocystic carinii* pneumonia (PCP) is the commonest. (Narain et al., 2002). By the end 2000, about 11.5 million people were co infected HIV and TB, globally; 70% of co-infected people were in Africa, 20% in South East Asia and 4% in Latin America and Western Pacific . (Harris et al., 2004). In Thailand, TB has been reported as number one opportunistic infection in AIDS patients; 27.1 % of all opportunistic infections. (Source: AIDS Division, MoPH, Thailand, 2000)

Clinical Manifestations of HIV associated TB infection

TB is classified as pulmonary and extra-pulmonary. Before the recognition of HIV infection, more than 80% of all cases of TB were limited to lungs. However, up to two-third of HIV infected patients with TB may have either pulmonary and extra pulmonary disease or extra pulmonary disease alone. TB can appear at any stage of HIV infection, unlike other opportunistic infections which occur at CD4 count less than 200/$mm^{3.}$ Clinical presentation varies with the level of immunosuppression resulting from HIV infection. (Raviglione and O'Brian, 2005)

A retrospective study done in Bamrasnaradura Hospital, Thailand, in 2001 showed that among AIDS patients with TB, the common chief complaints were fever (80.8%), loss of weight (64.6%), loss of appetite (55.4%), cough (55.4%), and enlarge lymph nodes (36.4%), abdominal pain (15.4%), diarrhea (13.1%) and weakness (10%). The other complaints were headache, pallor, shortness of breath, vomiting, cheat pain, drowsiness, hemoptysis, neck stiffness, nausea and abdominal pain. Type of tuberculosis among AIDS patients with TB were Pulmonary TB (43.8%), Disseminated TB (32.3%), and Extra pulmonary TB (23.8%). (Arain, 2001)

In patients with partially compromised cell mediated immunity, pulmonary TB is more frequently seen than extra pulmonary TB. (Zumla et al., 2000) In these patients, chest radiographic finding include upper lobe infiltrates and cavitations, similar to those in HIV negative patients with pulmonary TB. (Perlman et al., 1997) In late stages of HIV late stages of HIV infection, primary tuberculosis like pattern, with diffuse infiltrate, little or no cavitation and intra-thoracic lymph adenopathy is more common. (Raviglione and O'Brian, 2005)

The chest imaging of pulmonary TB in HIV infected patients, who receive ARV, reflects more frequently the classic post primary pattern and this finding probably reflects the partial restoration of cell mediated immunity that can be induced by ARV. In the countries where this therapy is being increasing used, an increased proportion of post primary pattern of Chest X-ray findings may be expected among HIV infected patients with pulmonary TB. (Ruzzi et al., 2003) Sputum smears are often positive for acid fast bacilli (AFB) in these patients. As immnunosupression progress, extra pulmonary TB (EPTB) becomes common. In contrast to HIV negative patients with EPTB, the disease is often disseminated involving two or more non contiguous organs concomitantly, in patients with HIV/AIDS. (Sharma et al., 2004)

In contrast to infection with atypical Mycobacteria, active TB often develops relatively early in the course of HIV infection and may be early clinical sign of HIV disease. In one study, the median CD4+ T cell count at presentation was 326/μL. The clinical manifestation of TB in HIV infected patients are quite varied and generally show different pattern as a function of CD4+ T cell count. (Fauci and Lane, 2005)

Diagnosis of TB in HIV/AIDS

Diagnosis of TB in HIV infected patients is often difficult due to several reasons: (1) frequently negative sputum smear (2) atypical radiographic findings (3) higher prevalence of EPTB especially at inaccessible sites and (4) resemblance to other opportunistic pulmonary infections. However diagnostic approach to suspected TB in a HIV infected individual is similar to that in immuno-competent patients except that invasive diagnostic procedures are more often required to establish the diagnosis. (Sharma and Mohan, 2004)

The standard test for pulmonary TB is morning expectorated sputa for 3 days for AFB smear and culture. Sensitivity of AFB smear is about 50%. With military TB, sputum cultures are positive in only 25% but multiple other specimens are AFB smear or culture positive, including blood in 50 to 60%. Positive cultures for *Mycobacterium tuberculosis* approach 100% sensitivity and 97% for specificity. (Bartlett and Gallant 2004). A considerable proportion of patients (10 to 20%) with advanced immnosupression may have apparently normal looking chest radiographs although *M tuberculosis* can be demonstrated or isolated from their sputum or bronchoaveolar lavage fluid. (Greenberg et al., 1994 and Perlman et al., 1997)

Treatment of active tuberculosis in HIV co-infected patients

Treatment recommendations for tuberculosis are the same for HIV-infected and HIV-uninfected patients. The two main measures of effectiveness for tuberculosis regimens are the treatment failure rate and the relapse rate. Both are low for the standard 6-month regimen consisting of isoniazid, rifampin, ethambutol and pyrazinamide for 2 months followed by isoniazid and rifampin for another 4 months. Any deviation from this regimen is likely to be associated with higher relapse or treatment failure rates unless drugs are given for a prolonged period. (Blumberg et al., 2003)

Studies comparing treatment outcomes have shown that clinical response rates, time to culture conversion from positive to negative, and treatment failure rates differ little between HIV-infected and -uninfected patients treated with standard regimens (Murray et al., 1999. and Ackah, et al., 1995) although the risk of death during treatment is increased by HIV co-infection. Relapse rates in most studies (Chaisson et

al., 1996) are 5% or less for disease caused by drug sensitive *M. tuberculosis*, unless patients have positive cultures beyond 2 months or are noncompliant with their anti mycobacterial regimen (Driver et al., 2001)

Similarly, studies in HIV-uninfected patients reported high relapse rates in patients with cavitations and positive cultures at the completion of 2 months of therapy (Mitchison, 1993). In response to these findings, the new ATS/CDC/IDSA guidelines recommend, regardless of HIV status, prolonging therapy in patients with cavitations noted on initial chest radiograph and a delayed response, defined as positive cultures at completion of 2 months of therapy. These patients should receive rifampin and isoniazid for an additional 3 months for a total of 9 months of treatment. The World Health Organization (WHO) guidelines, however, do not distinguish between cavity and non cavity disease and recommend 6 months of therapy in all cases. (De Jong et al., 2004)

HIV-infected tuberculosis patients are more likely to relapse with rifampicin resistant organisms than HIV-uninfected patients, especially when they are given highly intermittent regimens (CDC, 2002). The lack of rifampicin from the treatment regimen is likely to delay sputum conversion, prolong the duration of therapy, and, in endemic areas, result in higher relapse and mortality rates (Hawken et al 1993 and Wallis et al., 1996). Thus, the ATS/CDC/IDSA guidelines recommend two differences in the treatment of HIV-infected tuberculosis patients as compared with HIV-uninfected tuberculosis patients: Once-weekly isoniazid-rifapentine in the continuation phase should not be used in HIV-infected patients, and twice-weekly isoniazid-rifampin or isoniazid-rifabutin should not be used for patients with CD4 counts less than 100 cells/μL (Blumberg et al., 2003).

There is a small number of specific data about therapy of extra-pulmonary tuberculosis in HIV-infected individuals. However, in general, a standard 6-month course of antituberculous therapy is adequate. Exceptions to this include central nervous system disease (including military tuberculosis with cerebrospinal-fluid evidence of meningitis), which should be treated for 9–12 months, and bone and joint disease, for which treatment can be prolonged to 9 months. Regardless of HIV status, adjuvant corticosteroids are indicated for central nervous system disease and pericardial disease (Blumberg et al., 2003).

Therapy with isoniazid should be supplemented with 25 mg of pyridoxine (B6) per day, or 50 mg twice weekly with intermittent antituberculous therapy (Fujiwara, 1999), a regimen similar to that for HIV-uninfected tuberculosis patients at risk for peripheral neuropathy. Regardless of HIV infection, patients receiving ethambutol should be questioned at monthly intervals regarding visual disturbances; especially those receiving doses higher than the recommended 15–20 mg/kg, or taking ethambutol for more than 2 months, should have monthly testing of visual acuity and color vision (Blumberg et al., 2003).

Some studies found the incidence of serious side effects from antituberculous medications among HIV-infected individuals to be similar to rates in HIV uninfected patients (Chaisson et al., 1996 and El Sadr et al., 1998), whereas others found significantly increased rates of side effects, namely rifampicin-associated rash (Small, 1991) and hepatotoxicity from antituberculous combination therapy (Ungo et al., 1998 and Pedral-Sampaio et al., 1997).

Regardless of having tuberculosis, HIV-infected persons should receive cotrimoxazole for prophylaxis of PCP if their CD4 count is less than 200 cells/ μL. Neither HIV infection nor diarrhea alters pharmacokinetic characteristics of standard anti-tuberculous drugs (Choudhri, 1997). Directly observed therapy (DOT) should be used in all patients with HIV-related tuberculosis. (De Jong et al., 2004)

Recommended Dosage for initial treatment of TB in adults

	Dosage	
Drug	**Daily dose**	**Thrice weekly Dose**
Isoniazid	5mg/kg, max 300mg	15mg/kg, max 900mg
Rifampicin	10mg/kg, max 600 mg	10mg/kg, max 600mg
Pyrazinamide	20-25mg/kg max 2 g	30-40mg/kg max 3 g
Ethambutol *	15-20/kg	25-30mg/kg

In certain setting, Streptomycin (15mg/kg daily with max: dose 1g or 25-30mg/kg thrice daily with max: dose 1.5g) can replace in Ethambutol in the initial phase of treatment. (Source: Based on ATS, IDSA and CDC)

Initiating Anti retroviral treatment in patients with active TB

Simultaneous treatment of TB and HIV should not be initiated due to overlapping of drug toxicities, drug interactions, adherence requirements and possible paradoxical reactions/immune reconstitution syndrome. (Bartlett and Gallant, 2004) Delaying antiretroviral therapy until after completion of tuberculosis treatment has several advantages. Standard regimens can be used for both diseases, and potential drug interactions are avoided. Furthermore, paradoxical reactions may be less common as the time interval between treatment of active tuberculosis and initiation of antiretroviral therapy is increased. A final advantage of delaying antiretroviral therapy is that 90% of anti-tuberculous therapy– induced hepatitis among HIV-infected individuals occurs in the first 2– 4 weeks, as do common side effects such as rash and gastric disturbances and the management of these common side effects before the introduction of antiretroviral therapy is crucial to the success of treatment. (Pedral-Sampaio, 2002 and Dean, 2002)

However, the high mortality rates in the first few months of tuberculosis treatment observed in developing countries concern routinely withholding antiretroviral therapy until after tuberculosis treatment has been completed. . (De Jong et al., 2004) The CDC/ATS recommendation (Bartlett and Gallant, 2004) is to:

1) Continue anti retroviral therapy that was previously started
2) Avoid initiating treatment of both and always treat TB first with HAART introduced at 4-8 weeks.
3) The possible exception is patients with advanced HIV with CD4 count <50/ μL

WHO guideline is:

1) CD4< 200/ μL: Start ART at 2 to 8 weeks after TB treatment with EFV based HAART; alternative third drugs are SQV and ABC, NVP
2) CD4 200 to 350μL: Consider ART. If given start after initial TB phase using EFV(or NVP in rifampin free continuation)
3) CD4>350 μL: Defer ART

The ATS/CDC/IDSA guidelines suggest an individualized decision on timing of antiretroviral therapy in patients with CD4 counts below 350 cells/ μL and advise delaying antiretroviral therapy for 4–8 weeks if possible (Blumberg et al., 2003).

Specific treatment of *M. tuberculosis* can confer immunological benefit without antiretroviral therapy; a likely mechanism to explain the observed improvements in CD4 counts and plasma viral load is that, as tuberculosis is effectively treated, a decrease in immune activation leads to down regulation of viral replication (Dean et al., 2002).

Dose Adjustments

As a consequence of drug-induced alterations in hepatic cytochrome P450, dose adjustments are needed when co-administering rifampicin and some antiretroviral drugs. Rifabutin at 150–300 mg/day can safely and effectively be exchanged for rifampicin in patients who receive ART concomitantly (Gonzalez-Montaner, 1994 and McGregor et al., 1996)

When a TB patient receiving rifampicin needs to be started on a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor that is compatible with the use of rifabutin, rifampicin should be changed to rifabutin 2 weeks prior to the start of antiretroviral therapy to allow reduction of the enzyme inducing activity of rifampicin (Blumberg et al., 2003).

Rifampicin with NRTI

Rifampicin can be used with nucleoside reverse transcriptase inhibitors (NRTI) without dose adjustments, but it somewhat decreases levels of zidovudine and possibly of abacavir. Therefore, some experts do not agree on its use in combination with the triple nucleoside therapy zidovudine-lamivudine-abacavir (Barnes, 2002).

Rifampicin with NNRTI

Rifampicin can be combined with efavirenz, and some experts recommend increasing the dose from 600 to 800 mg to compensate for a slight decrease in serum efavirenz concentration (CDC, 2000). Rifampicin reduces nevirapine levels by 31%, although the levels still appear adequate without dose adjustments owing to nevirapine's high therapeutic index (Ribera, 2001). However, there is theoretical concern about combined hepatotoxicity of nevirapine and tuberculosis medications (WHO, 2002).

Rifampicin with PI

Rifampicin decreases levels of saquinavir, indinavir, nelfinavir, amprenavir, and lopinavir by >75% (Barnes, 2002). Rifampicin can be administered with full-dose ritonavir (400–600 mg twice daily), and limited data support using low-dose ritonavir "boosting" in combination with saquinavir in patients taking rifampicin (Veldkamp et al 1999). Similarly, a study in healthy volunteers indicated that increased doses of lopinavir/ritonavir (i.e., from the usual 400/100 mg to 400/400 mg and possibly 800/200 mg, twice daily), in conjunction with therapeutic drug monitoring, may allow for concomitant use of rifampin 600 mg once daily (Cvetkovic, 2003). Ritonavir in this role counteracts the hepatic cytochrome P450 isoenzyme CYP3A effects of rifampicin, which makes it a theoretically appealing combination with other protease inhibitors as well. Unfortunately, the effect is not consistent with different protease inhibitors, and the level of, for instance, indinavir is still lowered by almost 90% in the presence of ritonavir and rifampicin (Andrade, 2003).

Interactions of Rifabutin with anti retroviral drugs

This drug is not generally available in resource-limited settings, is much easier to administer in combination with anti retroviral drugs, as it is a much less potent inducer of the cytochrome P450 system. (De Jong et al 2004)

Rifabutin does not interact significantly with nucleoside reverse transcriptase inhibitors (NRTI). But with NNRTI, efavirenz reduces levels of rifabutin by almost 40%, and the dose of rifabutin should be increased to 450–600 mg/day (Lopez-Cortes2002). Nevirapine and rifabutin can be co-administered at normal doses. Protease inhibitors increase rifabutin levels, resulting in higher rates of adverse effects including arthralgias, uveitis, and leukopenia. With most protease inhibitors, rifabutin dose should be lowered to 150 mg/day or even to 150 mg three times weekly when using atazanavir or lopinavir/ritonavir and 150 mg twice weekly when combined with full-dose ritonavir (Cvetkovic 2003 and Pham, 2003).

Interactions with drugs used for Prophylaxis for Other Opportunistic Infections

Rifampicin decreases levels of cotrimoxazole, which is the most widely used prophylaxis in HIV-infected patients for the prevention of both *P. carinii* pneumonia and toxoplasmosis (Ribera, 2001). At lower dosing levels of cotimaxazole, this interaction was found to reduce its efficacy in preventing toxoplasmic encephalitis (Ribera, 1999). It is probably reasonable to give double-strength cotrimoxazole once daily as opposed to three times a week, when it is combined with rifampicin.

The combination of rifabutin and daily azithromycin did not result in significant drug interactions, but it was associated with high rates of neutropenia and gastrointestinal side effects. It is unknown whether weekly azithromycin in combination with rifabutin has the same effect. Rifampicin can dramatically decrease levels of azoles such as itraconazole and ketoconazole. (De Jong et al., 2004)

Immune Reconstitution Syndrome

Patients being treated for tuberculosis may experience a temporary worsening of symptoms or development of new signs or symptoms of tuberculosis. This phenomenon is known as immune reconstitution syndrome or a paradoxical reaction. Immune reconstitution syndrome is thought to represent an enhanced immunologic response to mycobacterial antigens during the course of treatment, resulting in a stronger inflammatory response at sites of tuberculosis infection. It is not associated with changes in *M. tuberculosis* bacteriology (i.e., no change from negative to positive cultures). Immune reconstitution syndrome can occur in HIV-uninfected tuberculosis patients but is probably more common in co-infected patients. It typically appears about 6 weeks after the initiation of antiretroviral therapy in a patient receiving concurrent treatment for active tuberculosis (Orlovic, 2001).

In a prospective study, immune reconstitution syndrome occurred in 36% of patients receiving antiretroviral therapy, compared with 7% in HIV infected patients not receiving antiretroviral therapy and 2% in HIV-uninfected patients (Narita, 1998). Common symptoms and signs of immune reconstitution syndrome include high fevers, lymph adenopathy, worsening of chest radiographic findings, and worsening of original tuberculosis lesions. Less frequent manifestations include pleural effusions, psoas abscesses, central nervous system tuberculomas, and epididymitis and orchitis.

The initiation of antiretroviral therapy can also unmask previously undiagnosed infections by augmenting the inflammatory response. Thus, the diagnosis of immune reconstitution syndrome should be made only after a thorough evaluation has excluded other etiologies. (De Jong et al., 2004)

Immune reconstitution syndrome can be brief or prolonged, with multiple recurrences, but no deaths have been clearly associated with it (Wendell, 2001). In general, antiretroviral therapy should not be interrupted if immune reconstitution syndrome occurs. Non-steroidal inflammatory drugs may provide some relief, but some patients have required the use of corticosteroids (in addition to tuberculosis treatment) to treat these reactions. Indications for use of concomitant corticosteroids for immune reconstitution syndrome include severe hypoxemia, airway obstruction, neurological impairment, or possibly enlarged painful lymph nodes. The ATS/CDC/IDSA guidelines recommend use of prednisone at 1 mg/kg per day with a gradual reduction after 1–2 weeks (Blumberg , 2003).

Treatment consideration in particular patients

Active TB and liver disease

A study of tuberculosis patients with hepatitis C or HIV infection demonstrated a relative risk of hepatotoxicity of five- and fourfold, respectively, for patients with either hepatitis C or HIV. In contrast, those infected with both hepatitis C and HIV faced a 14-fold increase in risk of hepatoxicity. Possible “liver sparing” regimens have been described for use in patients with overt liver failure. These exclude isoniazid, rifampicin, and pyrazinamide and typically include a fluoroquinolone, ethambutol, streptomycin, and cycloserine, and they last for a minimum of 18 months (Blumberg, 2003). Such a regimen can also be used in the patient who develops severe hepatotoxicity on standard tuberculosis drugs (Salomon, 1994). However, there are limited data on these regimens. Patients with underlying liver disease can often be started on the usual four drugs with close laboratory and clinical follow-up. However, these patients have an increased rate of drug-induced hepatitis, and therapy should be held or changed to another regimen if serum aminotransferase levels rise above five times the upper limit of normal, or three times the upper limit of normal in the presence of symptoms. (De Jong et al., 2003)

Patients with Underlying Neuropathy

Neuropathy is very common in people living with HIV. Distal symmetrical polyneuropathy is more common as HIV disease progresses (Wulff, 2000). Data on the effect of isoniazid on HIV-infected patients with pre-existing neuropathy are limited. A retrospective review of patients who had used anti-retroviral drugs with and without isoniazid found higher rates of neuropathy in those on stavudine and isoniazid than in those taking stavudine alone (55% v.s 11%). Pyridoxine intake was not mentioned in this report (Breen, 2000). Patients at risk for neuropathy should preferably still receive isoniazid, with 25 mg of pyridoxine.

Antituberculous Medications in Pregnancy

In HIV-infected pregnant mothers, the incidence of drug-induced hepatitis, especially with isoniazid, is increased during and immediately after pregnancy. Thus, close monitoring of liver function is recommended. Streptomycin should not be used in pregnancy because of the potential for ototoxicity in the fetus (Bothamley, 2001). The benefits of pyrazinamide outweigh the risks, although it should probably not be given during the first trimester unless drug resistance to isoniazid or rifampicin is strongly suspected (Fujiwara, 1999). Pyrazinamide is recommended in WHO guidelines but not in U.S guidelines. ((Bartlett and Gallant, 2004)

Monitoring Anti TB treatment response

Bacteriological evaluation is the preferred method of monitoring the response to treatment for TB. Patients with pulmonary TB should have monthly sputum examination until cultures become negative. With the recommended regime, >80% patients have negative sputum culture at the end of second month of treatment. In some patients especially with extensive cavity disease and large number of bacilli, AFB smear conversion may follow culture conversion, presumably due to expectoration and microscopic visualization of dead bacilli. When patient's sputum cultures remain positive at ≥ 3 months, treatment failure and drug resistant should be suspected. If Mycobacterial cultures not practical, monitoring by sputum smear should be undertaken at 2,5 and 6 months. Smear positive after 5 months are indicative of treatment failure. Bacteriological monitoring of patients with extra-pulmonary TB is

more difficult and often not feasible. In these cases, the response to treatment must be assessed clinically. (Raviglionone and O'Brian, 2005)

Treatment outcomes

Published information on the clinical outcome of concurrent treatment for HIV and tuberculosis is limited. A retrospective study in Thailand showed that initiation of ART with NNRTI based regimes at 4 to 12 weeks of anti-TB treatment in advanced AIDS was safe and effective. Initiation of nevirapine based HAART and non-rifampicin containing maintenance phase after completion 2 months of intensive phase was an alternative for advanced HIV infected patients. Cure rate for pulmonary TB was 90%.and 65.5% and 75.9% of patients achieved undetectable HIVRNA (<50 copies/ml) at 24 and 48 weeks respectively. (Sungkanuparph et al., 2005) A prospective study from Taiwan indicated that virologic, immunologic, and clinical responses to HAART and prognosis of HIV-1 infected TB patients who were concurrently treated with anti TB treatment and HAART were similar to those of non TB patients. (Hung, 2003)

A prospective study from India compared HIV-infected patients with and without TB, who were all started on efavirenz. The CD4 response to antiretroviral therapy was at least as good in the tuberculosis patients, but 8%of them developed paradoxical worsening and 10% hepatotoxicity (Patel, 2003). In a study from Brazil, the success rate of tuberculosis treatment in patients receiving antiretroviral therapy was 84% at 24 months, and 2 of 49 patients relapsed. Paradoxical worsening was observed in 12% (Pedral-Sampaio, 2003). These studies suggest that efavirenz at the normal dose of 600 mg is efficient when given concomitantly with rifampicin. Another study of 188 patients, 45% of whom commenced antiretroviral therapy during tuberculosis treatment, found significant reductions in viral load, AIDS-defining illnesses, and mortality. Adverse events occurred in 54% of patients on treatment for both HIV and tuberculosis, one third of whom changed or interrupted their treatment regimens. The major side effects were peripheral neuropathy (21%), rash (17%), and gastrointestinal upset (10%), the majority of which occurred in the first 2 months. Only 5% experienced a paradoxical reaction (Dean, 2002).

CHAPTER IV
MATERIALS AND METHODS

Materials

Study Site

This study was carried out at Bamrasnaradura Institute, Nonthaburi, Thailand.

Study design and Data collection Period

This study was retrospective, descriptive type to evaluate the outcomes of TB treatment among HIV and TB co infected patients who received both anti TB and antiretroviral treatment. Data collection period will be from November 14, 2005 to January 9, 2006.

Study subjects

All HIV/AIDS patients with TB who are of age 15 years and older, both registered as out-patients or in-patients as Bamrasnaradura Institute during 2 year period beginning from January 1, 2003 to December 31, 2004 were included in this study.

Diagnosis and classification of Tuberculosis was defined according to Bamrasnaradura Institute criteria. The HIV status, if unknown, was determined on one blood sample, on which two serological tests are performed. In cases where HIV status was known by previous tests at any hospital, this history with documentation is taken by hospital doctors as proven HIV infection.

Selection of Cases

Inclusion criteria

1. Age 15 year old and above
2. Diagnosed as Pulmonary Tuberculosis (See Appendix A)
3. Diagnosed as HIV Infection (See Appendix B)
4. Received anti TB treatment and

5. Received NNRTI based antiretroviral treatment

Exclusion Criteria

1. Patients who received ART after completion of anti TB treatment

Sample Size estimation

The main objective of this study was to assess the outcome of anti TB treatment in HIV and TB co-infected patients who received both Anti TB and antiretroviral treatment. The outcome is mainly measured by cure rate. In Thailand, the cure rate in HIV and TB co-infected patients who received both anti TB and antiretroviral treatment had been evaluated by a retrospective from Ramathibodi hospital where the cure rate for pulmonary TB was found to be 90%.(Sungkanuparph et al., 2005) Therefore, the result of Ramathibodi hospital has been taken as reference in order to estimate cure rate for sample size calculation.

$$n = \frac{z^2 \times p \times (1-p)}{d^2}$$

Where

n =calculated sample size

z =1.96 (ά = 0.05)

p = proportion of cured patients

d = error allowance i.e. 5%

$$n = \frac{(1.96)^2 \times 0.9 \times (1 - 0.9)}{(0.05)^2}$$

$$= 138$$

Therefore the number of study subject should be 138.

Methods

1. A list of patients with positive results of culture for *Mycobacterium tuberculosis*, started from January 1, 2003 to December 31, 2004 was obtained from the microbiology lab at Bamrasnaradura Institute.
2. That list was cross-matched with the case file to meet inclusion criteria.
3. In order to pursuit for clinical response and outcome, information of the clinical presentation and associated illness and relevant investigation results were obtained from OPD and IPD case notes and Laboratory records.
4. In case, where death occurred, clinical notes and death certificate were searched and information pertinent to the cause of death was obtained.
5. All these data were entered in the standardized case record form.

Data Analysis

All information collected in the case record forms during the study was coded and entered into computer statistical package. For descriptive parts, frequency and percent calculation were performed along with median (Range).Categorical data were analyzed by $\chi 2$ test. Statistical significance in all tests will be determined at 2 tail p-value of less than 0.05.

CHAPTER V

RESULTS

Background

In a period of two years from January 1, 2003 to December 31, 2004, there were 248 medical records of sputum and Trans-tracheal aspirate culture positive for *Mycobacterium tuberculosis*, at the Microbiology Lab of Bamrasnaradura Institute. A total of 65 patients who fulfilled the inclusion criteria were identified and analyzed. The study profile has been summarized in figure 1.

Demographic Data

The median age of the study population was 32 years with a range of 20 to 58 years, out of which thirty four cases (52.3 %) were between 30-39 years (Figure 2). Forty seven cases (72.3 %) were male and eighteen cases (27.3 %) were female. Concerning with marital status, singles were the majority, twenty six cases (40%). Patients with employment, forty seven cases (72.3 %) were more the patients without unemployment, eighteen cases (27.7 %). Fifteen cases (23 %) had previous history of TB, five cases (7.7%) had HIV positive patients in their family i.e., their spouses and two cases (3.1 %) had TB patients in their family. Among the study subjects, eight patients (12.3%) were IVDU. The median duration between the HIV infection and the diagnosis of TB was 2 years (range, 0-12) (Table 1).

Laboratory Data

Baseline CD4 count were available in fifty three patients. The median CD4 count was 33 cells/ µL (2- 342) and thirty nine patients (73.6%) had CD4 count less 100 cells/ µL and fourteen patients (21.5%) had more than or equal to 100cells/µL. Only seventeen patients had baseline plasma viral load and five patients (29.4%) had plasma viral load of less than or equal 100,000 copies/ml and twelve patients (70.6%) had more than 100,000 copies/ml (Table1).

Since this study focused on pulmonary TB, only sputum and TTA culture positive cases were included in the study and 57 patients (87.7%) had sputum culture positive and 8 patients (12.3%) had TTA culture positive. AFB smear scales were graded as 1+, 2+ and 3+ and the percentage of the scales were 41.5 %, 18.5 % and 30.8 % respectively.

The median base line body weight was 50.3 kg (range, 28.3 – 70.5, N= 56) and the median oral temperature was 38.1˚C (36- 40, n= 60). The base line median value for AST, ALT and alkaline phosphatase were 50 U/L (range 15-257, N=39), 29 U/L (range 6-132, N= 30) and 131 U/L (range 44- 638, N= 27) respectively. Other lab data are mentioned in Table 2.

Clinical Presentation

Most of the patients' complaint of fever (90.8%) and cough (81.5%). The other complaints were tiredness (32.3%), chest pain (16.9 %), anorexia (13.8%), diarrhea (10.8%), headache (7.7%), nausea (6.2 %), hemoptysis (3.1%) and Insomnia (1.5%). Fifteen patients (23.1 %) of patients had cervical and supraclavicular lymph adenopathy (Table 3).

Chest X ray Finding

Chest X ray findings were classified as classical and atypical pattern according to WHO criteria (TB/HIV a clinical manual, 2nd edition, 2004). Baseline Chest X rays was available in only fifty-eight cases. Among these cases, classical patterns were seen in thirty-five patients (60.34%) and atypical were twenty-three patients (39.66%). Upper lobes infiltrates were the most common classical pattern and seen in twenty-three patients (39.66%). Cavitations were seen in five patients (8.62%). Interstitial infiltrates especially in lower zones were the common atypical pattern and seen in eleven patients (18.97%). Chest X ray with no abnormalities were seen in five patients (8.62%) (Table 4).

Opportunistic infections

Opportunistic infections were observed in 44 patients (67.7%) of the 65 study subjects prior to ART. The most common infection was, oral candidiasis;

seen in 28 patients, 43% of the study subjects. Other opportunistic infections included PCP in 7 patients (10.8%) Cytomegalovirus (CMV) retinitis in 5 patients (7.7%), Cryptococcal meningitis in 3 patients (4.6%) and herpes infection in 3 patients (4.6%) (Figure 3).

After ART was started, opportunistic infections were observed only in 4 patients (6.15%). One patient suffered from cryptococcal meningitis, 8 weeks after the initiating of ART. The other 3 patients had CMV retinitis (Table 11). In 3 patients, ART was initiated during TB treatment and in one patient; ART was initiated 6 weeks before TB treatment.

Prophylactic medication

Sixty-two patients (95.38%) received prophylactic medication. Most of the patients (70.78%) received cotrimoxazole and fluconazole. Some patients received dapsone instead of cotrimoxazole because of adverse reactions of cotrimoxazole. Three patients who had CD4 count more than 200/μL for 6 months did not receive prophylactic medication during the course of TB treatment (Table 10).

Anti TB regime

Anti TB regimes were divided into 2 groups i.e. regimes that consist of HRZE for at least 2 months in the initial phase and regimes that do not consist of HRZE for at lease 2 months in the initial phase. Fifty patients (76.92%) received HRZE for at least 2 months in the initial phase and fifteen patients (23.08%) did not received HRZE for at least 2 months in the initial phase. But, there is no association between pulmonary TB treatment outcomes and these two groups of regimes ($p = 0.598$). Details of anti TB treatment regimes are shown in Table 5. Rifampicin resistance was noted in 6 patients (9.23%) and isoniazid resistance was seen in 5 patients (7.69%) (Table 8).

ART regime

ART was initiated during anti TB treatment in 51 patients (78.46%) and ART and anti TB treatment were started at the same time in 6 patients (9.23%). 8 patients (12.31%) already had ART before the diagnosis of TB. There is significant association

between TB treatment outcomes and schedule of initiating ART (p = 0.000). There was no non-cure case in patients who already received ART before TB diagnosis. Apart from those who already received ART, it was initiated at median of 12 weeks (range 0-52) of TB treatment.

All patients in this study received NNRTI based regimes. Forty-three patients (66.15%) received NVP based regimes and 22 patients received EFV based regimes. Among NVP based regime GPO vir was the most commonly used drugs and 41 patients (63.08%) received GPO vir. Among the patients received EFV regime, 17 patients (26.15%) received D4T, 3TC, EFV regime and 5 patients received AZT, 3TC, and EFV regime. NVP was started on 200 me daily for 2 weeks then escalated to 200mg twice a day. EFV was given 600 mg a day. Three patients who received GPO vir for one to two weeks developed skin rash and needed to change NVP based regime to EFV based regime. Thirty-six patients (55.4%) concurrently received NVP and RFP and the median overlapping days was 115 days (range 5-395).

There is no association between pulmonary TB treatment outcomes and ART regime (p = 0.269) and concurrent use of NVP and RFP (p = 0.095).

Drug toxicity

Drug toxicities were observed in 26 patients (40%). Sixteen patients (24.6%) had adverse reactions before staring ART, .i.e., the toxicities were mainly due to anti TB drugs. The most common implicated drug was rifampicin. Its toxicities were observed in 12 patients (18.5%). Skin rash (15.4%) and jaundice (4.6%) were the common events of drug toxicities. A case of Stevens Johnson syndrome was noted in a patient who received nevirapine. Two cases of neuropathy were due to stavudine. Drug toxicities occurred at a median of 4 weeks (range 1-40) after starting TB treatment Details of drugs toxicities were mention in Table 13, 14 and 15.

There were no significant associations between drug toxicity and anti TB regime (p= 0.058), ART regime (p=0.707), concurrent use of NVP-RFP (p=0.139) and schedule of initiating ART (p=0.568) (Table 16).

Immune reconstitution syndrome (IRIS)

It was seen only in 5 patients (7.69%) out of 65 study subjects. Two patients had fever, 2 patients had fever and lymph adenopathy and one patient had lymphadenoapthy and increased infiltration in chest X ray with negative sputum culture. All cases occurred after initiating of ART. IRIS occurred at a median of 12 weeks (range1-20) of TB treatment and at a median of 2 weeks (range 1-9) of ART. (Table 17)

Outcomes

Of 65 study subjects, 33 patients (50.77%) were clinically cured at a median of 10 months (range 6-21) after TB treatment and 20 patients (30.77%) were cured at median of 6 months (range 3-24) of TB treatment. Clinically cured patients completed treatment and improved clinically, but there was no proof of bacteria conversion.

Five patients (7.69%) were transferred out to other hospitals, and their final outcomes were not traced. Three patients (4.62%) who lost to follow up at 2, 4 and 8 months of TB treatment were treatment interrupted. 3 patients died during the time of TB treatment and the cause of death was due to disseminated TB. Two of these patients had history of previous TB infection. Two patients had rifampicin or isoniazid resistance and one patient suffered from rifampicin toxicity. Treatment failure was observed in only one patient (1.54%). This patient had previous history of TB and rifampicin resistance (Table18).

To show the association between pulmonary TB treatment outcomes and different variables, outcomes are divided into two groups i.e. cure and non cure. Cure group consist of cured patients and clinically cured patients and non cure group consist of treatment failure and death cases. Treatment interrupted cases and transferred out cases were not included in the analysis.

There were no significant associations between outcomes and previous TB history ($p = 0.402$), chest X ray findings at the time of TB diagnosis ($p= 0.865$), anti TB regime ($p = 0.598$), ART regime ($p= 0.269$), concurrent use of NVP-RFP ($p = 0.095$), drug resistance ($p = 0.144$), and drug toxicity ($p = 0.735$). But, there was significant association between outcomes and schedule of initiating of ART

($p < 0.001$). All patients who received already ART before TB diagnosis were cured (Table 19).

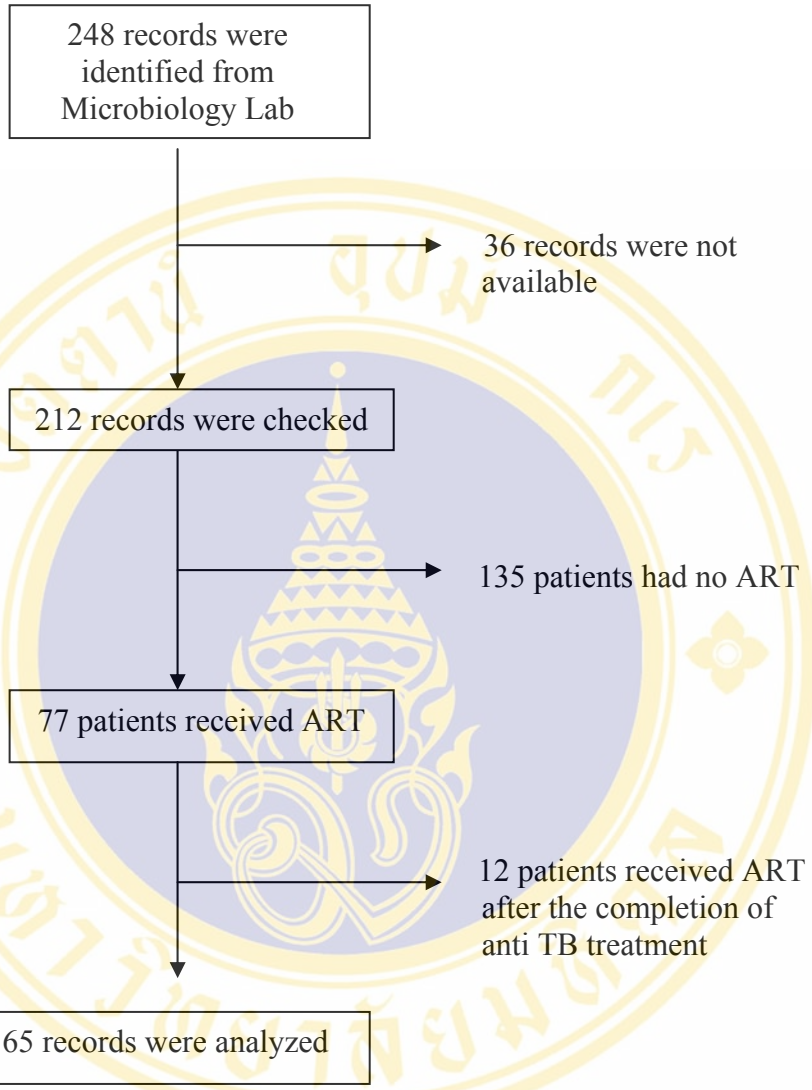

Figure 1. Study profile of the 65 study subjects

Table 1. Baseline characteristics of the 65 study subjects (1)

	N	No. of Patients (%)	Median (range)
Personal Data			
Age(Years)	65		32 (20-58)
Gender	65		
Male		47 (72.3)	
Female		18 (27.7)	
Marital Status	65		
Single		26 (40.0)	
Married		27 (41.5)	
Widowed		8 (12.3)	
Separated		1 (1.5)	
Unknown		3 (4.6)	
Employment	65		
Employed		47 (72.3)	
Unemployed		18 (27.7)	
Previous History of TB	65		
Yes		15 (23.1)	
No		50 (76.9)	
HIV (+) patients in family	65		
Yes		5 (7.7)	
No		60 (92.3)	
TB patients in family	65		
Yes		2 (3.1)	
No		63 (96.9)	
IVDU	65		
Yes		8 (12.3)	
No		57 (87.7)	
Duration between HIV and TB diagnosis (Yr)	59		2 (0-12)
HIV infection			
CD4 T cell count	53		33 (2 - 342)
CD4 <100		39 (73.6)	
CD4 ≥ 100		14(21.5)	
Plasma viral load(copies/ml)	17		
pVL≤100,000		5 (29.4)	
pVL >100,000		12 (70.6)	
TB infection			
Culture	65		
Sputum		57 (87.7)	
TTA		8 (12.3)	
AFB smear scale	59		
1+		27 (41.5)	
2+		12 (18.5)	
3+		20 (30.8)	

Table 2. Baseline characteristics of the 65 study subjects (2)

	N	Median (range)
oral temperature (˚C)	56	38.1 (36.0- 40.0)
body weight (kg)	60	50.3 (28.3 - 70.5)
laboratory data		
Hct (%)	51	31 (15-47)
Hemoglobin (g/dL)	51	10.2 (5.18 - 16.40)
WBC (cells×10^3/mm^3)	49	6.64 (1.85 - 22.7)
Platelet (cells/mm^3)	49	270,000 (68,000-639,000)
Neutrophil (%)	49	72.0 (15-99)
Eosinophil(%)	49	1 (0-18)
lymphocyte(%)	49	14 (0- 57)
monocyte(%)	49	5 (0-17)
Alkaline phosphatase (U/L)	27	131 (44-638)
ALT (U/L)	30	29 (6-132)
AST (U/L)	39	50 (15-257)
Total Bilirubin (mg/dL)	28	0.66 (0.3-2.71)
Direct bilirubin (mg/dL)	9	0.15 (0.04-1.61)
BUN (mg/dL)	18	15.3 (5-31.6)
Creatinine (mg/dL)	25	0.87 (0.33-2.25)
Na (mEq/L)	16	132.5 (125-145)
K (mEq/L)	16	3.9 (3.5-5.2)
Cl (mEq/L)	16	98.5 (92-109)
HCO_3 (mEq/L)	16	24.5 (15.32)
Choloesterol (mg/dL)	9	164 (124-238)

Table 3. Clinical presentation at the time of TB diagnosis

	N=65 Frequency	Percentage
Fever	59	90.8
Cough	53	81.5
Tiredness	22	32.3
Weight loss	21	23.1
Lymphadenopathy (cevical and supraclavicular)	15	23.1
Chest pain	11	16.9
Anorexia	9	13.8
Diarrhea	7	10.8
Headache	5	7.7
Nausea	4	6.2
Hemoptysis	2	3.1
Insomnia	1	1.5

Table 4. Chest X ray pattern at the time of TB diagnosis

	N=58 Frequency	Percent
Classical pattern	**35**	**60.34**
Upper lobe infiltrates	23	39.66
Bilateral infiltrate	7	12.07
Cavitations	5	8.62
Atypical pattern	**23**	**39.66**
Interstitial infiltrate (especially lower zones)	11	18.97
Intrathoracic lymphadenopathy	7	12.07
No abnormalities	5	8.62

Table 5. Anti TB treatment Regime

	N=65	
	Frequency	Percent
Regimes consist of HRZE for at least	**50**	**76.92**
2 months in the initial phase		
2HRZE/4HR	10	15.38
2HRZE/ 6-9 HR	8	12.31
3-8 HRZE	8	12.31
4HRZE/2HR	6	9.23
2HRZE / 15-16 HZEO	2	3.08
4HRZE/ 10-12 HR	2	3.08
5HRZE/4 HZE	1	1.54
3 HRZEOS/ 9 HRZEO	1	1.54
2HRZE/3HRZES/3HR	1	1.54
2HRZE/7HRE	1	1.54
2HRZE/3HR/12 REO	1	1.54
4HRZE/ 17 HZE	1	1.54
4HRZEOK/6HR/3KEO	1	1.54
1HRZES/3HRZE/3HR	1	1.54
3HRZE/3HRZES/5REZ	1	1.54
4HRZE/12 HE	1	1.54
2HRZE/2HESO/14 HEO	1	1.54
4HRZE/7HRE/3HRZS/3HR	1	1.54
2HRZE/16 HEO	1	1.54
4HRZE/1HR/2HOZS/1HZO	1	1.54
Regimes that do not consist of HRZE for		
2 months in the initial phase	**15**	**23.08**
1HRZE/12-19 HZE	4	6.15
1/2 HRZE/3HREO/4HR	1	1.54
1/4 HRZE/4 HEO /17 HE	1	1.54
1HRZE/3HRE/2HR	1	1.54
1/4HRZE/1HZEO/7HZE	1	1.54
1HRZE/2HZE/1HZES/4HZEO/6 HZE	1	1.54
1HRZE/2HZE/9 HEO	1	1.54
1HRZEO/1HRZEOS/1HRZE/9 HEZ	1	1.54
1/4 HRZE/1HEZS/4HES/1ZEO/9 RZEO	1	1.54
1HRZE/3HRE/4HR	1	1.54
1/4 HRZE/ 14 HEO	1	1.54
1HRZEO/1HEO	1	1.54

H= Isoniazid, R= Rifampicin, Z= Pyrazinamide, E= Ethambutol, O= Ofloxacin, S= Streptomycin, K= Kanamycin

Table 6. Schedule of initiating ART

	N=65 Frequency	Percent
Start ART during TB treatment	51	78.46
Start ART before TB diagnosis	8	12.31
start ART and anti TB treatment at the same time	6	9.23
		median (range)
Time of Initiating ART in weeks		12 (0- 52)

Table 7. ART regime

	N=65 Frequency	Percent
NVP based regime	**43**	**66.15**
GPO vir	41	63.08
D4T, 3TC,NVP	1	1.54
AZT, 3TC,NVP	1	1.54
EFV based regime	**22**	**33.85**
D4T, 3TC,EFV	17	26.15
AZT, 3TC,EFV	5	7.69

Table 8. Anti TB drug resistance during treatment

	n=65 Frequency	Percent
No	54	83.08
Rifampicin	6	9.23
Isoniazid	5	7.69

Table 9. Concurrent use of NVP-RFP

	N=65 Frequency	Percent	Overlapping days Median (range)
Yes	36	55.38	115 (5-394)
No	29	44.62	

Table 10. Prophylactic medication among 65 study subjects

	N=65 Frequency	Percent
Yes*	**62**	**95.38**
Cotrimoxazole + Fluconazole	46	70.77
Cotrimoxazole	11	16.92
Dapsone+ Fluconazole	5	7.69
No	**3**	**4.62**

* Include both primary and secondary prophylaxis

Table 11. Occurrence of Opportunistic infections in 4 patients after ART

Patient	Type of OI	Duration of occurrence after ART	ART	Anti-TB regime	Outcome of TB
1	Cryptococcal meningitis †	8 weeks	D4T, 3TC,EFV	Non standard	Clinical Cure
2	CMV retinitis	1 week	GPO vir*	Non standard	Death
3	CMV retinitis	4 weeks	GPO vir *	Standard	Cure
4	CMV retinitis	32 weeks	GPO vir*	Standard	Clinical Cure

†Patient did not received primary prophylaxis but received secondary prophylaxis with Fluconazole after Amphotericin treatment

*NVP-RFP overlapping present.

Table12. Occurrence of drug toxicity in 65 study subjects

	N= 65		
	Frequency	Percent	Time of occurrence after TB treatment in weeks Median (range)
Toxicity	26	40.00	4 (1-40)
No toxicity	39	60.00	

Table13. Schedule of initiating ART and Drug toxicity

	N=65 Frequency	Percent
Start ART during anti TB treatment	**22**	**33.8**
Toxicities before ART	16	24.6
Toxicities after ART	6	9.2
Start ART before TB diagnosis	**2**	**3.08**
Start ART and anti TB treatment at the same time	**2**	**3.08**

Table 14. Drugs implicated in toxicities

	N=65 Frequency	Percent
Anti TB drugs	**15**	**23.1**
Rifampicin	12	18.5
Pyrazinamide	3	4.6
ARV drugs	**6**	**9.2**
Nevirapine	4	6.1
Stavudine	2	3.1
TB + ARV		
Rifampicin + Nevirapine	**2**	**3.1**
Cotrimoxazole	**2**	**3.1**
TB + Fluconazole	**1**	**1.5**

Table 15. Events of anti TB and ARV drugs toxicity

	Drug implicated N=65			
	Anti TB drugs	ARV drugs	TB + ARV	Total
skin rash	6 (9.2%)	3 (4.6%)	1 (1.5%)	10 (15.4%)
skin rash+ facial edema	1 (1.5%)			1 (1.5%)
joint pain + increased uric acid	2 (3.1%)			2 (3.1%)
neuropathy		2(3.1%)		2 (3.1%)
jaundice	2 (3.1%)		1 (1.5%)	3 (4.6%)
Steven Johnson Syndrome		1(1.5 %)		1 (1.5%)
increased liver enzyme	2 (3.1%)			2 (3.1%)
skin rash + jaundice	1 (1.5%) *			1 (1.5%)
skin rash +jaundice+ increased liver enzyme	2 (3.1%)			2 (3.1%)

* Fluconazole is also implicated in this event

Table 16. Association of Drug toxicity and anti TB regime, ART regime, concurrent use of NVP-RFP and time of initiating ART

		Drug toxicity		
	N	Toxicity	No toxicity	p- value
anti TB regime†	65			0.058
Regime(A)		15 (57.7%)	26(83.9%)	
Regime(B)		11(42.3%)	5(16.1%)	
ART regime	65			0.707
NVP based		16 (61.5%)	27 (69.3%)	
EFV based		10 (38.5 %)	12 (30.8%)	
Concurrent NVP-RFP	65			0.139
Yes		11 (42.3%)	25 (64.1%)	
No		15 (57.7%)	14 (35.9%)	
Schedule of initiating ART	65			0.586
Start ART before TB diagnosis		2(7.7%)	6(15.4%)	
Start ART during TB treatment		22(84.6%)	29(74.7%)	
Start ART and anti TB at the same time		2(7.7%)	4 (10.3%)	

†Regime (A) consist of HRZE for at least 2 months in initial phase
Regime (B) do not consist of HRZE for at least 2 months in initial phase

Table 17. Immune Reconstitution Syndrome(IRIS)

	N = 65		duration of occurrence in weeks	
	Frequency	Percent	**After Anti TB**	**After ART**
			median (Range)	median (Range)
Yes*	5	7.69	12 (1-20)	2 (1-9)
symptoms of IRIS				
fever	2	3.08	4.5 (1-8)	1.5 (1-2)
Fever + lymphadenopathy	2	3.08	16.5 (13-20)	1.5 (1-2)
Lymphadenopathy + increased infiltration in CXR	1	1.54	12	2
No	**60**	**92.31**		

* All cases occurred after ART had started

Table 18. Outcomes of pulmonary TB in HIV patients on ART

	N=65		
	Frequency	Percent	Time in months Median (range)
Clinical Cure	33	50.77	10 (6 -21)
Cure	20	30.77	6 (3-22)
Transfer out	5	7.69	4 (1-9)
treatment interrupted	3	4.62	4 (2-8)
death	3	4.62	11 (2-12)
treatment failure	1	1.54	5

Table 19. Associations of Outcomes and different variables

	N	Outcomes				
		Cure		Non cure		p- value
		Cured	Clinical cure	Treatment failure	Death	
Previous history of TB	57					
Present		10(18.9%)		2(50%)		0.402
Absent		43(81.3%)		2 (50%)		
Chest X ray finding	53					
Classical		29(59.2%)		2(50%)		0.865
Atypical		20(40.8%)		2 (50%)		
Anti TB regime†	57					
Regime (A)		39(73.6%)		3(75%)		0.598
Regime (B)		14(24.6%)		1(25%)		
ART regime	57					
NVP based		35(66%)		1(25%)		0.269
EFV based		18(34%)		3(75%)		
Concurrent Use of NVP-RFP	57					
Yes		30(56.6%)		0		0.095
No		23(43.4%)		4(100%)		
Drug resistance	57					
No resistance		46(86.8%)		2(50%)		0.144
Rifampicin		4(7.5%)		1(25%)		
Isoniazid		3(5.7)		1(25%)		
Drug Toxicity	57					
Toxicity		25(47.2%)		1(25%)		0.735
No toxicity		28(52.8%)		3(75%)		
Schedule of Initiating ART	57					
ART before TB diagnosis		6(11.3%)		0		<0.001*
ART during TB treatment		45(84.9%)		1(25%)		
ART and TB treatment at the same time		2(3.8%)		3(75%)		

†Regime (A) consist of HRZE for at least 2 months in initial phase
Regime (B) do not consist of HRZE for at least 2 months in initial phase

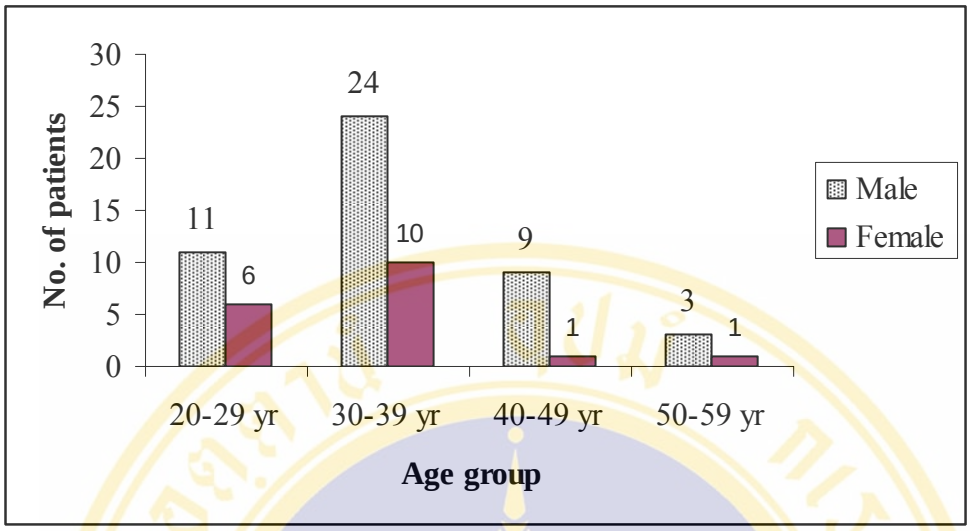

Figure 2. Distribution of age group and gender among 65 study subjects

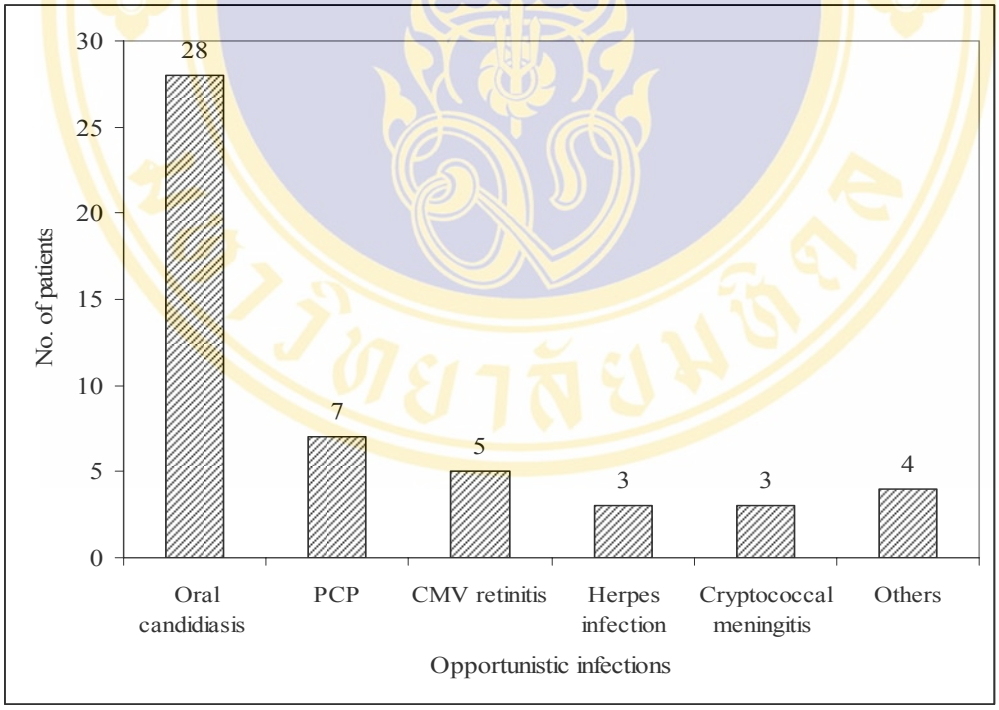

Figure 3. Opportunistic infections prior to ART among 65 study subjects

Others include Oral hairy leukoplakia, Toxoplasmosis, Strongyloidiasis

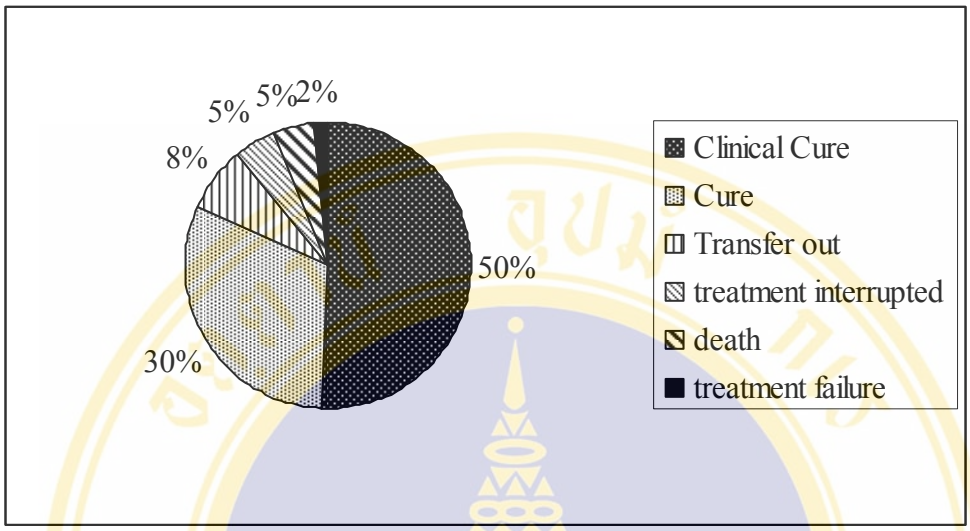

Figure 4: Distribution of outcomes in 65 study subjects

CHAPTER VI
DISCUSSION

There were 248 patients with active pulmonary TB (culture positive cases) in Bamrasnaradura Institute for the period January 2003 to December 2004. During that period, only a small number of patients received ART during the course of TB treatment. Therefore, only 65 cases were available to study the outcomes of pulmonary TB treatment in HIV infected patients on ART.

In the demographic data of the study, men were more prevalent than the women and the male to female ratio was about 3: 1. Over 50 percent of the patients were between the ages of 30 to 39 years. These figures were similar to a previous study done in Bamrasnaradura Institute. (Arain, 2001). This similarity suggests that HIV and TB co-infection is prevalent among socially and sexually active male population. Since over 70 percent of the patients had employment and this factor may be related to the patients' adherence to treatment. Among the 27 married patients in this study, the spouses of 5 patients also had HIV infection. The spouses of remaining 22 patients had no evidence of HIV infection. It is important to stop HIV infection in these couples and health education about transmission of HIV should be given to them.

In this study, TB infection and HIV status were detected at the same time in one third of the patients. This may reflect that these patients were unaware of their HIV infection and were subsequently detected HIV infection. This emphasizes the necessary of screening for HIV infection in patients presented with TB especially in the area of high prevalence of HIV infection.

Clinical presentations at the time of diagnosis were very typical for pulmonary TB. Over 80 percent of the patients presented with fever and cough. The

median oral temperature was 38.1˚C. Only 2 patients had history of hemoptysis. The presentations were similar to previous studies done at Bamrasnaradura Institute. (Arain, 2001).

Various chest X ray patterns were seen at the time of TB diagnosis. Generally classical pattern is more common in HIV negative patients and the atypical pattern in HIV positive patients. But, in this study, classical pattern such as upper lobe infiltrate, bilateral infiltrates and cavitations were seen in 60 percent of the patients. It may be due to the mild immuno suppression in some patients who already received ART and this study included patients with relatively high CD4 Count. Normal looking chest radiographs were seen in 9 percent of the patients although *Mycobacterium tuberculosis* was isolated from the sputum. This finding is similar to that of other studies done 10 years ago. (Greenberg et al., 1994 and Perlman et al., 1997). Therefore, it can be concluded that no chest X ray pattern is absolutely typically for pulmonary TB with underlying HIV infection.

Apart from TB and oral candidiasis, PCP, CMV retinitis, herpes infection and cryptococcal meningitis were common opportunistic infections before the initiation of ART. These findings were similar to previous studies. (Arain, 2001 and Getahun, 2005) After Starting ART, appearances of opportunistic infections were seen in 4 patients, 6.15% of study subjects. It is a small number and lower than that of previous study.(Getuhun, 2005). It may due to the fact that 62 patients (95.38%) of the study population received primary or secondary prophylactic medications such as cotrimazole and fluconazole and also due to effectiveness of ART regime.

Although 6 month standard anti TB regime is recommended for the treatment of TB in HIV infected patients, it was not prescribed in every patients in this study because 15 patients (23.1%) had previous history of TB, 26 patients (40%) had drug toxicities and 6 patients (9.23%) had rifampicin resistance and 5 patients (7.69%) had isoniazid resistance. In this study, 50 patients (76.92%) received HRZE for at least 2 months in the initial phase and 15 patients (23.08%) did not received HRZE for at least 2 months in the initial phase. Some patients received anti TB

treatment for prolong period up to nearly 2 years. But, there is no significant association between outcomes and the anti TB regimes.

Drug toxicities were common in this study, observed in 40% of patients. Most cases had toxicities before the initiation of ART. The toxicities were mainly due to rifampicin. This condition led to the prescription of rifampicin free regimes and the longer duration of treatment. Drug toxicities occurred at a median of 4 weeks (range 1-40) after starting TB treatment. So, if possible, it is better to initiate ART after 4 weeks of TB treatment to avoid complication of drug toxicities from TB and ARV drugs. Although toxicities were common during TB treatment, there were no significant associations between drug toxicity and anti TB regime, ART regime and concurrent use of NVP- RFP and schedule of initiating ART.

In this study, ART was initiated at the same time with TB treatment or during TB treatment over 90 percent of cases. Other cases already received ART before TB diagnosis. Over 60 percent received NVP based regime, mainly GPO vir. ART was initiated at a median of 12 weeks of TB treatment. One study from Ramathibodi Hospital mentioned that initiating of ART with NNRTI based regime at 4-12 weeks of TB treatment was safe and effective. (Sungkanuparh, 2005).

Although ATS and WHO recommended not to use NVP and RFP together (Bartlett and Gallant, 2004), 36 patients (55.4%) in this study received NVP and rifampicin concurrently and the median of overlapping days was 115 days. A study from Bamrasnaradura Institute stated that there was no difference of ALT level and short term virological and immunological outcomes of NVP based ART between patients receiving and not receiving rifampicin. (Manosuthi, 2005) In this study, NVP-RFP overlapping was not significantly associated with drug toxicities and did not change the TB treatment outcome. Among 36 patients who received NVP-RFP concurrently, only three patients (8.3%) had opportunistic infections after ART. Therefore, we can consider NVP based ART as an option for HIV infected patients who receive RFP.

After initiating ART, opportunistic infections were seen in 4 patients after ART. Most of the opportunistic infections were CMV retinitis. Since over 95 percent of patients received cotrimoxazole, there was no case of PCP. Appearance of opportunistic infections in small number of patients after ART may reflect the promising efficacy of NNRTI based ART.

Immune reconstitution syndrome (IRIS) was observed in only 5 patients (7.7%) after ART and antiretroviral therapies were not interrupted because of this. The incidence of IRIS in this study was lower than that of other studies (Narita, 1998 and Padral-Sampaio, 2003). In these studies, incidences were 36% and 12 % respectively. The incidence of IRIS in this study is similar to a study from India, where incidence was 8%. (Patal, 2003) In making a diagnosis of IRIS in our patients, we totally based on the judgment of the physicians who had seen the patients. A number of differential diagnoses were excluded. There included progressive disease due to non adherence with treatment, drug resistance to Mycobacterial infection, adverse drug reaction (such as hypersensitivity pneumonitis) and concurrent opportunistic infections.

The outcomes of pulmonary TB were satisfactory, in this study, compare to a previous study where mortality was 10 percent and over half of the patients lost to follow up within a year. (Arain, 2001). In this study, over 80 percent were cured or clinically cured. But compare to a study from Ramathibodi hospital (Sungkanuparph, 2005), the cure rate of this study was lower. In the study from Ramadibodi Hospital, cure rate was 90%. The patients in that study were treated in a medical school hospital where HIV and TB were cared in the same clinic and the sample size was very small (of 20 patients pulmonary TB, 18 were cured).

Therefore, the integrated care of TB and HIV can result in substantial benefits to patients. These benefits include efficient concomitant TB and HIV management, decreased risk of drug interactions, patients' convenience and cost effective health care budget especially in the developing countries where TB and HIV are highly associated.

In this study, treatment interrupted cases and death cases were only 4.6 percent. Treatment failure was seen in only one patient. The present study mainly focused on patients with pulmonary TB and received ART during TB treatment and some patients had relatively high CD4 count at the time of TB diagnosis. Patients' compliance was also said to be acceptable. HIV and TB were managed in the same clinic. These factors may explain our favorable pulmonary TB treatment outcomes in HIV infected patients.

Although outcome is not associated with previous history TB, Anti TB regimes, ART, Drug toxicity and drug resistance, it has significant association with schedule of initiating ART. There was no non cure case in patients who already received ART before TB diagnosis. Therefore HIV infected patients should receive ART earlier before they get TB infection especially in the area where TB is prevalent.

Finally, 55.4 % of the patients in this study received RFP and NVP concomitantly but the outcome of pulmonary TB treatment was good. It showed that efficacy of RFP was not considerably reduced. Occurrence of Opportunistic infections in only 4 patients after ART indicated that efficacy of NVP was acceptable. Incidence of IRIS was low and drug toxicities were due to RFP alone rather than due to RFP and NVP combination. Therefore concurrent use of RFP and NVP is acceptable in HIV and TB co-infected patients.

CHAPTER VII
CONCLUSION

Pulmonary TB and HIV co infection is common in male middle age married man aged 30-39 years. HIV infected patients usually get TB at a median of 2 years after HIV infection. Unlike other opportunistic infections, active TB develops even in relatively high CD+ T cell count. Nearly one fourth of TB-HIV co infected patients had previous history of TB but it does not affect the outcome significantly. Chest X ray findings are nonspecific. Normal chest X ray can be seen even though there is evidence of sputum culture positive.

ART was initiated at a median of 12 weeks (range 0-52) of TB treatment. 8 patients (12.3%) already received ART before TB diagnosis. Forty three patients (66.1%) received NVP based regime and 22 patients (33.9%) received EFV based regime. 36 patients (55.4%) received NVP and rifampicin concurrently and the median of overlapping days was 115 days (range 5-394).

Drug toxicities occurred at a median of 4 weeks (range 1-40) after starting TB treatment and observed in 26 patients (40%). Sixteen cases occurred before the initiation of ART. Toxicities due to rifampicin were seen in 18.5% of patients. There were no significant associations between drug toxicity and anti TB regime ($p= 0.058$), ART regime ($p=0.707$), concurrent use of NVP-RFP ($p=0.139$) and schedule of initiating ART ($p=0.568$). IRIS occurred in 5 patients (7.7%) and opportunistic infections occurred in 4 patients (6.2%) after ART had started

Out of 65 patients, 33 patients (50.8%) were clinically cured, 20 patients (30.8%) were cured, 5 patients (7.7%) were transferred out, 3 patients (4.6%)

were treatment interrupted, 3 patients (4.6%) died and treatment failure was noted in one patient. Over 80 percent of patients got cured or clinically cured.

Excluding treatment interrupted and transfer out cases, treatment outcome (i.e. cure or non cure) is not associated with previous history TB ($p = 0.402$), chest X ray findings at the time of TB diagnosis ($p= 0.865$), anti TB regime ($p = 0.598$), ART regime ($p = 0.269$), concurrent use of NVP-RFP ($p = 0.095$), drug resistance ($p = 0.144$), and drug toxicity ($p = 0.735$). But, there is significant association between outcome and schedule of initiating of ART ($p <0.001$). All patients who were already on ART before TB infection were cured.

As a nature of a retrospective study, there were limitations in this study. We had small sample size and data such as CD4 count and viral load in series were not available in each case. Comparative analysis of treatment outcomes among different timing of ART initiation such as 4, 8 or 12 weeks not feasible.

In conclusion, initiation of ART in the early course of HIV infection, before TB infection, yields a favorable pulmonary TB treatment outcome. NVP based ART may be an option for HIV infected patients who receive RFP. Further prospective studies for the optimal timing of ART initiation in TB patients and studies of long term virological and immunological outcomes are needed for concurrent use of NVP and RFP.

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APPENDIX

APPENDIX A

Laboratory diagnosis for *Mycobacterium tuberculosis* in Bamrasnaradura Institute

Method of AFB smear: Ziehl-Nelson Staining Method

AFB smear scale

(Public health service, National Tuberculosis reference Laboratory and national laboratory network; IUATLD 1998)

0 = negative

1+ = 10-99cells/ 100 OIF

2+ = 1-10 cells / 1 OIF

3+ = >10 cells/ 1 OIF

OIF = Oil Immersion Field

Method of Culture

Method of decontamination: By Petroff method with 4% NaOH

Modified Ogawa medium (Kudo method)

Method of sensitivity: Indirect absolute concentration method in Lowenstein-Jensen medium

APPENDIX B

Tests for HIV at Bamrasnaradura hospital

Screening: 1. Micro particle Enzyme Immunoassay (MEIA), Axysm, Abbot

2. Particle agglutination test (Serodiagnostic test- Fujirebio, Japan)

3. Immuno chromatography, (Abbot)

Second blood is requested after first blood have reactive results of 3 screening anti HIV test. If these tests are concordance, the result will be concluded.

APPENDIX C

TB treatment outcomes*

1. Cure = complete course of TB treatment and documented bacteria conversion
2. Treatment completed† = documented treatment completion and but no documented bacteria conversion
3. Treatment failure= culture or smear positive at 5 month of treatment
4. Treatment interrupted = off TB treatment for 2 consecutive months or more
5. Relapse= patients who has been cure but sputum turns to be positive after cessation treatment
6. Transfer out= refer to another physician whom information on treatment outcome cannot be obtained
7. Death= death with any cause before end of TB treatment

*Based on definitions from WHO and the International Union against Tuberculosis and Lung Disease (IUATLD)

† In this study, treatment completed was mentioned as clinical cure as these patients improved clinically though there were no documented proof of bacteria conversion.

APPENDIX D

CASE RECORD FORM

Part Identification Data

No	
HN No.	

Part 2 Personal Data

Age	_____ Yr		
Gender	**M / F**		
Marital Status	1Married / 2Single / 3Divorce / 4Seperated / 5Widowed/ 9Unknown		
Education	0. No Education/1Primary/ 2Secondary/ 3University/ 9Unknown		
Occupation	1Unemployed /2 Employed Specify_____		
TB in family	**Y / N**	**HBV**	**Y / N**
HIV(+) in family	**Y / N**	**HCV**	**Y / N**
prev H/O TB	**Y / N**	**Diabetes**	**Y / N**
IVDU	**Y / N**		

Part 3 Associated O I **Y / N**

	Treatment	**Date Start**	**Date Stop**
1			
2			
3			
4			

Part 4 Prophylatic medication **Y / N**

	Dosage	**Date Start**	**Date Stop**
1. co-trimaxole			
2. Fluconazole			
3			
4			

Part 5 HIV & TB status

Date of diagnosis of HIV infection		_____/_____/_____	
Date of diagnosis of TB infection		_____/_____/_____	
AFB smear	0 1+ 2+ 3+		
Culture	sputum	TTA	
Date			

Part 6 Antiretroviral Treatment

Name of Drug	Dosage	Date Started	Date Stopped	Remark
GPOvir				
d4T				
3TC				
NVP				
EFV				
AZT(ZDV)				
IDV				

Part 7 Tuberculosis Treatment

Name of Drug	Dosage	Date Started	Date Stopped	Remark
Isoniazaid				
Rifampicin				
Pyrazinamide				
Ethambutol				
Streptomycin				
Ofloxacin				

Part 8 Drug Toxicity

Nature of event	Date of event	Action Taken	Drug implicated	Remark
Jaundice				
skin rash				
Dizziness				
nausea				
vomitting				
diarrhea				
Neuropathy				

Part 9 Clinical findings and Follow Up

SYMPTOMS	**Baseline**	**1 mo**	**2 mo**	**4 mo**	**6 mo**	**8 mo**	**12 mo**	**16 mo**	**20 mo**	**24 mo**
		±2 wk	± 2 wk	±2 wk	±4 wk	±6 wk	±6 wk	±6 wk	±6 wk	±6 wk
Fever										
Cough										
Hemoptysis										
Dyspnoea										
Night sweats										
Weight loss										
SIGNS										
Temperatrure										
Body weight										
Lymphadenopathy										

Part 10 Investigation

Hct										
Hemoglobin										
platelets										
Total WBC										
Neutrophil %										
Eosinophil %										
Lymphocyte %										
Monocyte%										

Part 10 Investigation

	baseline	**1 mo**	**2 mo**	**4 mo**	**6 mo**	**8 mo**	**12 mo**	**16 mo**	**20 mo**	**24 mo**
		±2 wk	± 2 wk	±2 wk	±4 wk	±6 wk	±6 wk	±6 wk	±6 wk	±6 wk
CD4 Count(cell/µL)										
CD8 Count(cell/µL)										
Viral Load(copies/ml)										
Na										
K										
Cl										
HCO_3										
Urea										
Creatinine										
Total Cholestorol										
Total Bilirubin										
Conjugated Bilirubin										
Alkaline Phosphate										
AST										
ALT										
BloodSuger(Fast/Rand)										
AFB smear										
Sputum Culture AFB										
Blood Culture AFB										
CXR finding										

Part 11 Immune Reconstitution Syndrome Y / N

Problems	Date	Management	Remark
1.Fever			
2.Lymphadenopathy			
3.Pleural effusion			
4.New infiltration in CXR			
5			
6			

Part 12 Outcome of TB

	Date	Remark
1.Cure		
2.Treatment Completed		
3.Treatment Failure		
4.Treatment Interrupted		
5.Relapse		
6.Transfer Out		
7.Death		

BIOGRAPHY

NAME Aung Kay Tu

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INSTITUTION ATTENDED

1991-1993: Institute of Medicine (1), Yangon, Myanmar
1993-1999: Institute of Medicine, Mandalay, Myanmar
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2002-2005: Graduate school of Counseling Psychology,
Assumption University, Thailand
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