Outcomes of Antituberculosis Treatments at 18 Months Follow-Up in TB-HIV Co-Infected Patients on ART: A Retrospective Review of 166 Cases

Pongsak Chunpongthong MD*,
Zin Zin Win Ko Ko MBBS**, Chuenrutai Yeekian MNS*,
Viravarn Luvira MD**, Punnee Pitisuttithum MBBS, DTM&H, FRCPT**

** Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand*
*** Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand*

Objectives: *To study the outcomes of antituberculosis treatment in HIV/AIDS patients on antiretroviral therapy (ART).*
Material and Method: *This retrospective cohort study was performed by reviewing medical records of 166 patients co-infected with tuberculosis (TB) and HIV in a hospital in Thailand seen between January 2005 and February 2008. These patients were treated with both antituberculosis (antiTB) and antiretroviral drugs (ART) and were followed for 18 months after the beginning of antiTB.*
Results: *Total 166 HIV patients with TB on ART and anti tuberculosis drugs were analyzed. The median age of patients was 36 years (20-72). Sixty-nine (41.6%) patients had pulmonary TB and 97 (58.4%) disseminated TB. Among them, 127 (76.5%) were cured and 15 (9.0%) had unsuccessful treatment. Median time for successful treatment was 10.8 months (6-32) during 18 months follow-up. There was no statistically significant difference in outcome of tuberculosis between the NVP and EFV base regimens in combination with rifampicin (5.4% vs. 10.8%, p = 0.751).*
Conclusion: *Majority of HIV patients on ART with tuberculosis were successfully treated with antiTB drugs with median time of 10.8 months and no significant difference of adverse events reported between NVP and EFV.*

Keywords: *TB-HIV/AIDS patients, Treatment outcome, Anti retroviral therapy*

J Med Assoc Thai 2011; 94 (6): 664-70
Full text. e-Journal: *http://www.mat.or.th/journal*

Tuberculosis is also one of the most common opportunistic infections and of the leading causes of death in HIV infected persons[1]. The risk of developing TB rises sharply with worsening immune status. By the end of 2000, 11.5 millions HIV infected patients worldwide were co-infected with *Mycobacterium tuberculosis* and 2,269,000 patients were in South East Asia. HIV infection on lifetime risk of an *M. tuberculosis*-infected individual developing TB is 10 times increasing compared with an individual who is not infected with HIV[2]. In Thailand, the most common opportunistic infection in HIV/AIDS patients are Tuberculosis (emaciation, slim disease) 69,037 cases (20.58%), Pneumocystis pneumonia 67,856 cases (20.23%), Cryptococcosis 40,034 cases (14.32%) and Candidiasis cases 16,849 cases (5.02%)[3].

HIV not only increases the number of TB cases, but also alters the clinical course of TB disease. As HIV-related immunosuppression increases, the clinical pattern of TB disease changes, with increasing numbers of smear-negative pulmonary TB and extra-pulmonary TB cases. TB is more likely to be disseminated and more difficult to diagnose as immunosuppression progresses[4]. Concomitant administration of both HIV and TB treatment is sometimes difficult because of drug interactions, overlapping toxicity, immune reconstitution syndrome and pill burden, although there are effective therapies for both HIV and TB. Several studies have now showed that ART reduces the likelihood of death during TB treatment of HIV infected TB patients. In population-based prospective study from a rural province in northeastern Thailand, a high rate of death in HIV-infected TB patients and a substantial reduction in the

Correspondence to:
Pitisuttithum P, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Rd, Bangkok 10400, Thailand.
Phone: 0-2643-5599, Fax: 0-2643-5598
E-mail: tmppt@mahidol.ac.th

risk of death during TB treatment was documented in patients receiving Antiretroviral therapy (ART)[5].

There is no recommendation for optimal time to start HAART in TB/HIV patients. Delay of highly active antiretroviral therapy (HAART) increases the significant risk of death and new AIDS defining illness[6]. Beginning of both ART and anti-TB treatment at the same time can also cause discontinuation of both treatment because of toxicities, side effects, paradoxical reactions or drug/drug interactions. Therefore, the present study was aimed to assess medium term outcomes of antituberculous drugs in HIV patients who received ART.

Material and Method

The present retrospective study was conducted at Queen Savang Vadhana Memorial Hospital, Chonburi Province, Thailand from January 2005 to 2008 to determine the outcome of tuberculosis in HIV/AIDS patients treated with antiretroviral therapy and anti TB drugs during 18 months of follow-up.

The inclusion criteria are both sexes, age 12 years and above, diagnosed as HIV/AIDS by ELISA and Tuberculosis infection as documented by clinician's diagnosis and/or Acid Fast Bacilli (AFB) smear and/or radiological evidence and on first-line anti-tuberculosis drugs. The present study excluded patients with less than two months duration of follow-up period or death within the first two months and referral patients who have no available baseline data.

The operational definition for sputum-positive cured case, relapse, treatment after failure, treatment after default, treatment failure, transfer out, and treatment completed are taken from treatment of tuberculosis guidelines for national programs[7]. For the AFB smear negative TB cases, the case definition of cure was defined as a smear negative case with treatment completed and negative smear result at the end of treatment and by clinical judgement of the physician in charge[8]. Two hundred eighteen cases fulfilled the criteria for ART and fifty-two patients were excluded because of their missing chart within two months after starting anti TB drugs. Clinical information on demographic characteristics, baseline CD4 counts at start of ART, ART regimen, anti-TB treatment and TB resistance were collected. Clinical course, side effects also body weight, CD4 counts, liver function tests and necessary investigation results were abstracted from medical charts during follow-up period. All patients were treated with first line drugs initially and changed if medically indicated. Recommended doses of Nevirapine (NVP) and Efavirenz (EFV) were 400 mg/day and 600 mg/day respectively.

Statistical analysis

Data are summarized by descriptive statistics. A χ^2 test was used to assess associations between variables with significance level of $p < 0.05$ by using SPSS software version 16.

Results

Baseline characteristic of patients

Of 166 patients with TB and HIV in the study cohort studied the majority were male patients (71.1%) and mostly (56.6%) in the age group of 31-40 years with the median age of 36 years. The baseline demographic data of the patients in the present study is shown in Table 1.

Among the patients of 166, only 11 (6.6%) of cases had underlying diseases and four (38.5%) of them had a history of hypertension. A few cases (n = 29) had a history of TB, which included TB lymphadenitis (40.7%), TB meningitis (3.7%), and TB pleural effusion (3.7%) respectively. Fifteen (55.6%) patients with a history of TB were reported to be successfully treated. 57 (34.3%) of the cases received ART before TB diagnosis, mostly (75.4%) EFV based regimen and 26.4% received NVP based regimen. Seven patients who received ART had stopped the drugs prior to the

Table 1. Clinical and laboratory profile of TB-HIV patients (n = 166)

Characteristics	n (%)
Median age, years (range)	36 (20-72)
Sex, male (%)	118 (71.1)
Median baseline body weight, kg (range)	53 (31-91)
History of underlying disease	11 (6.6)
Past history of TB	29 (17.5)
Treatment status of TB in the past (n = 29)	
Success	17 (58.6)
Duration of HIV positivity	
Less than or equal 5 years	149 (89.8)
More than 5 years	17 (10.2)
History of receiving ART in the past	57 (34.3)
Baseline CD4 at the time of diagnosis of TB (cells/mm^3)	
< 100	107 (66.5)
100-200	24 (14.9)
> 200	30 (18.6)

diagnosis of TB (6 cases were lost to follow-up and 1 case was transferred out). Baseline CD4 counts were recorded in 161 (97.0%) cases. Of these, 66.5% had CD4 cell count less than 100 cells/mm^3, 14.9% had CD4 100-200, and 18.6% had CD4 cell count more than 200 cells/ mm^3 with median CD4 count of 58 (1-800) cells/mm^3. At the end of 18 months follow-up, the median CD4 was increased to 285 (1-1085) cells/mm^3. At the time of TB diagnosis, most of the 131 patients (81.4%) had a low CD4 count of less than 200 cells/mm^3.

More than half (75.3%) of the cases were in stage IV of WHO HIV classification and some (24.7%) were in stage III at the time of TB diagnosis as shown in Table 2. Extra pulmonary TB was found in 58 cases (34.9%). Among them, some patients had TB more than one site, 10 cases had pleural effusion, 38 cases had TB Lymphadenitis, two cases had TB meningitis, 11 cases had TB abdomen and eight cases had joint or bone TB. History of opportunistic infections (OI) other than TB was reported in more than half (64.3%). The most common opportunistic infection in patients was PCP (12.0%). Fourteen point one percent reported other OIs like wasting syndrome, toxoplasmosis, MAC, herpes, 7.8% and 6% had a previous history of cryptococcosis and candidiasis respectively.

Only a small portion of patients can be diagnosed by the presence of AFB either in sputum or in biopsy or via haemoculture, 115 patients show x-ray features of TB.

Use of anti-tuberculous and anti-retroviral drugs

All 166 cases were started with first line anti-tuberculosis drug. During the period of 18 months, 28.9% were changed from the first line to second line drugs due to adverse reactions. In 73 (44%) of the 166 patients, anti TB drugs were started within seven days of initiation of ART whereas ART was started 8-60 days after Anti TB in 79 (47.6%) of the patients and was started later than 60 days in 14 (8.4%) of the patients. Fifty-four (32.5%), 30 (18.1%), 37 (22.3%), and 45 (27.1%) cases were treated with a six month standard regimen, 6-9 month regimen, 10-12 month regimen, and more than one year regimen respectively. EFV based ART regimen was administered in 101 (60.8%), 57 (34.3%) received NVP based regimen and PI or boosted PI in eight (4.8%). Median duration time between Anti TB and ART in the present study was 53.5 days (range 0-605). Among 166 cases, 54 cases had severe adverse effects from anti tuberculosis treatment during 18 months. The most common side effect of anti-tuberculous drugs was hepatitis (35.2%), hypersensitivity reaction (59.3%) and anemia (1.9%) (No data presented).

Seventeen (10.2%) cases on ART developed adverse effects, five cases received NVP based regimen while 12 cases were on EFV based regimen and none were treated with PI based regimen as shown in Table 3.

Table 2. Characteristics of the HIV positive patients at the initiation of antiTB treatment

Characteristics	n (%)
Median baseline CD4 count, cells/mm^3 (range)	58 (1-800)
WHO classification of HIV (%)	
Stage III	41 (24.7)
Stage IV	125 (75.3)
Opportunistic infections (%)	
Yes	70 (42.2)
No	96 (57.8)
Site of TB (%)	
Pulmonary TB	69 (41.6)
Extra Pulmonary TB	58 (34.9)
Disseminated TB	39 (23.5)
Specimen for AFB smear (n = 114)	
Sputum	
AFB positive (%)	23 (20.2)
Lymph node biopsy and hemoculture	
Positive (%)	6 (5.3)
X-ray finding (n = 115)	
Infiltration $\pm$ cavitations (%)	108 (93.9)
Pleural effusion (%)	6 (5.2)
Miliary TB (%)	1 (0.6)

Table 3. Adverse events due to anti TB and ART reported among study patients

Characteristics	n (%)
AntiTB drug reaction (n = 54)	
Hepatotoxicity	19 (35.2)
Hypersensitivity	32 (59.3)
Both	3 (5.5)
ART adverse event	17 (10.2)
Hypersensitivity	16 (94.1)
IRS	1 (5.9)
ART adverse events according to regimens (n = 17)	
NVP base	5 (29.4)
EFV base	12 (70.6)

Outcome of TB in HIV/AIDS patients with anti-retroviral therapy

One hundred twenty seven cases (76.5%) of 166 patients receiving anti-tuberculous drug and ART had treatment success at end of 18 months of follow-up (Table 4, Fig. 1). Fifteen patients were considered to have unsuccessful treatment. Of which, six (40.0%) cases died. Relapse was reported in five (33.3%) and four (26.7%) had treatment failure with no report of relapse. Seventeen (70.8%) were lost to follow-up and seven (29.2%) were transferred out. Median time for death and loss to treatment follow-up were 6.5 (3-18) and 6.0 (3-12) months respectively. Median time for successful treatment was 10.8 (6-32) months among those followed for 18 months.

Twelve (7.2%) of 166 patients developed anti TB drug resistance to a single drug. Five (3.0%) patients developed multi AntiTB drug resistance during the follow-up period and eight of 166 (4.8%) patients receiving the treatment developed resistance to ART (No data presented).

When the ART treatment regimens among these groups were further analyzed by classifying into NVP base regimen and EFV base regimen, treatment was unsuccessful in 5.4% in NVP, 10.8% in EFV and 12.5% in PI based regimen as shown in Fig. 2 and there was no statistically significant difference in outcome of tuberculosis between the NVP base and EFV base in combination with rifampicin treated patients ($p = 0.751$). But on finding association between these two groups of treatment (NVP + Rifampicin and EFV + Rifampicin) with unsuccessful outcomes or adverse events, significant association was found in NVP and Rifampicin group with hepatitis ($p = 0.05$). In EFV and Rifampicin group, significant association was found with rash (0.028) and hepatitis (0.000).

Discussion

The present study shows over representation of young males in the age group of 30-40 years, which lead to the assumption that a major fraction of the population constitutes young industrial male workers.

In the present study, an overall TB treatment success rate of 76.5%, was similar to those of previous studies in Thailand[9,10] although under a different setting. In another study[5] the median time between both was 93 days revealing a different practice in prescription of drugs, which might be due to perception of the physician about pill burden, drug–drug interaction and IRIS. Most of the cases in the present study could be diagnosed by routine sputum AFB but needed culture or x-ray results, which are sometimes not feasible in some settings in developing countries.

The median interval for treatment success was as long as 10.8 months in the present study, which could be due to prolonged clinical recovery in already

Table 4. AntiTB treatment outcomes in HIV/AIDS patients treated with ART (n = 166)

Characteristics	n (%)
Overall outcome	
Treatment success	127 (76.5)
Treatment not success	15 (9)
Others	24 (14.5)
Treatment success (n = 127)	
Cure	120 (94.5)
Complete	7 (5.5)
Treatment not success (n = 15)	
Dead	6 (40)
Relapse	5 (33.3)
Incomplete	4 (26.7)
Others (n = 24)	
Loss to follow-up	17 (70.8)
Transfer out	7 (29.2)
Median time for treatment successful in months (range) (n = 127)	10.8 (6-32)
Median time for treatment not successful in months (range) (n = 15)	17.7 (6-47)
Median loss to follow-up time in months (range) (n = 17)	6.0 (3-12)
Median time to death in months (range) (n = 6)	6.5 (3-18)

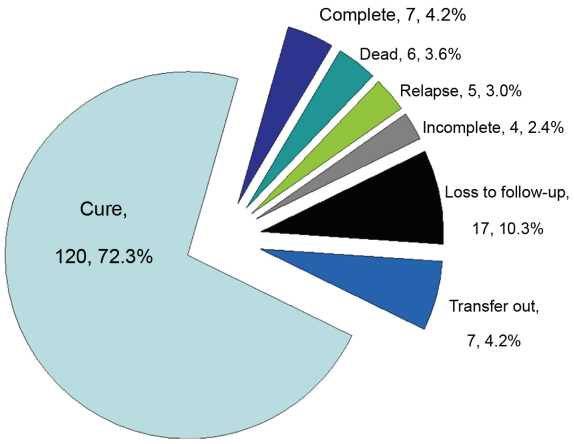

Fig. 1 Outcomes of patients continuing anti TB and ART at 18 months follow-up

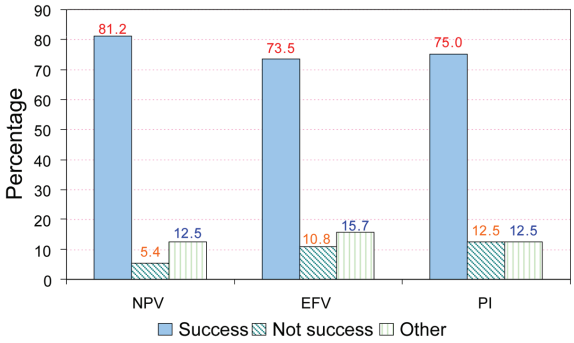

Fig. 2 Outcome of TB among ART regimens at 18 months follow-up

smear negative patients under ART and other reasons include drug to drug interactions between anti TB drugs and ARTs, side effect of the drugs or IRIS due to ART.

Mortality rates during TB treatment were reported to be high for HIV-Infected TB patients as most patients had marked immune suppression[11]. The mortality rate of TB-HIV/AIDS patients in the present study was low 3.6% when compared to the study by S Akksilp et al reporting mortality to be 7%[5] and 6.1% in another study[9]. However most of the deaths in those studies occurred before initiation of ART. ART at the time of recruitment and could account for the lower rate in the present study as well as in other studies[6,10,11]. This underlines the importance of early ART co-treatment in improving the outcomes in HIV/TB co-infected patients.

General reasons for loss to follow-up of cases (8.4%) in the present study could be attributed to stigma and fear of losing their job and lack of health insurance coverage. Those factory workers were less likely to be lost to follow-up than other groups might be explained by their stable workplace situation and social insurance coverage and higher income.

The majority (67.5%) of the patients received prolonged treatment regimen while more than half (53.2%) of the patients were treated with standard 6 months duration in another study[11]. This might be due to a higher number of smear negative, extra-pulmonary, greater immunesuppression, resistance, or drug-drug interactions in the present study patients. Thirty-two percent of the present study patients developed adverse reactions to anti TB drugs. The most common were hypersensitivity and hepatitis and 10.2% developing hypersensitivity to ART regimen. However, 44.6% developed reaction to either TB or ART drugs in another study[11].

In the present study, there was no significant difference in outcome of TB when treated with anti TB drugs containing RFP and in combination with different ART regimens, especially in respect of NVP and RFP interactions; this was in line with the results of previous studies[10].

In general, IRIS in present study was seen only in one patient whereas 14.9% developed IRIS in another study[11] with median duration of 14 days after ART initiation. Though the details on onset of IRIS were not available in the present study, the reason for such a low occurrence of IRIS can be due to the short interval (< 2 months) between initiation of Anti TB and ART in the majority of the patients. However, IRIS is known to be manageable and does not affect the outcome of TB in advanced HIV infected patients[9] that is the reason IRIS was not emphasized in the present study.

The timing of ART in TB treatment remains an important question. In the present study, the median time of initiation of ART after TB treatment was 53.5 (0-605) days. The median time difference in the present study was the same as shown in a previous study suggesting that starting HAART early in severely immunosuppressed HIV patients presenting with TB is associated with decreased mortality and a lowering of the rates of progression[15].

The limitations of the present study were similar to other retrospective studies that it was difficult to get patients with properly defined criteria of diagnosis throughout the series of studied cases and

consequently increased the chances of selection bias. Furthermore, some outcome variables such as clinical findings and radiological findings were not assessed objectively in a prespecified time-frame. The magnitude of confounding due to missing data and variation in prescribing habits of physicians in the present study cannot be estimated.

In conclusion, the antiTB of HIV/AIDS patients concurrently receiving ART were successful in 76.5%. ART is crucial in the successful management of HIV-TB co infection. Concomitant use of NVP and RFP containing first line TB drugs did not significantly differ when compared to EFV. NVP can be used together with TB treatment by close monitoring. The present research would hopefully be useful in future especially in developing and resource limited countries, where advanced stage of tuberculosis remains a significant problem and will lead to better management of HIV-TB co infected patients.

Acknowledgements

The authors wish to thank the study patients and the staff of Queen Savang Vadhana Memorial Hospital, Chonburi Province, Thailand for their support.

Potential conflicts of interest

This research was partly funded by the Faculty of Tropical Medicine, Mahidol University as part of a Masters Research program.

References

1. Getahun H, van Gorkom J, Harries A, Harrington M, Nunn P, Perriens J, et al. The TB/HIV policy writing committee. Interim policy on collaborative TB/HIV activities. Geneva: World Health Organization; 2004.
2. Harries A, Maher D, Graham S. TB/HIV: a clinical manual. 2nd ed. Geneva: World Health Organization; 2004.
3. Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand. The case study of HIV/AIDS cases. Bangkok: Bureau of Epidemiology; 2008.
4. Hargreaves N, Scano F. Guidelines for implementing collaborative TB and HIV programme activities. Geneva: World Health Organization; 2003.
5. Akksilp S, Karnkawinpong O, Wattanaamornkiat W, Viriyakitja D, Monkongdee P, Sitti W, et al. Antiretroviral therapy during tuberculosis treatment and marked reduction in death rate of HIV-infected patients, Thailand. Emerg Infect Dis 2007; 13: 1001-7.
6. Dheda K, Lampe FC, Johnson MA, Lipman MC. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. J Infect Dis 2004; 190: 1670-6.
7. World Health Organization. Treatment of tuberculosis: guidelines for national programs. 3rd ed. Geneva: WHO; 2003.
8. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003; 167: 603-62.
9. Tansuphasawadikul S, Saito W, Kim J, Phonrat B, Dhitavat J, Chamnachanan S, et al. Outcomes in HIV-infected patients on antiretroviral therapy with tuberculosis. Southeast Asian J Trop Med Public Health 2007; 38: 1053-60.
10. Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. J Acquir Immune Defic Syndr 2006; 43: 42-6.
11. Sanguanwongse N, Cain KP, Suriya P, Nateniyom S, Yamada N, Wattanaamornkiat W, et al. Antiretroviral therapy for HIV-infected tuberculosis patients saves lives but needs to be used more frequently in Thailand. J Acquir Immune Defic Syndr 2008; 48: 181-9.
12. Pozniak AL, Miller RF, Lipman MC, Freedman AR, Ormerod LP, Johnson MA, et al. BHIVA treatment guidelines for tuberculosis (TB)/HIV infection 2005. HIV Med 2005; 6 (Suppl 2): 62-83.
13. Victoria M. Antiretroviral treatment in the context of TB/HIV coinfection. Geneva: World Health Organization; 2005.
14. Manosuthi W, Mankatitham W, Lueangniyomkul A, Chimsuntorn S, Sungkanuparph S. Standard-dose efavirenz vs. standard-dose nevirapine in antiretroviral regimens among HIV-1 and tuberculosis co-infected patients who received rifampicin. HIV Med 2008; 9: 294-9.
15. Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS 2002; 16: 75-83.

ผลการรักษาวัณโรคในผู้ป่วยที่ติดเชื้อไวรัสเอดส์ที่ได้รับยาต้านไวรัส

พงษ์ศักดิ์ ชุนพงษ์ทอง, Zin Zin Win Ko Ko, **ชื่นฤทัย ยี่เคียน**, **วีรวรรณ ลุวีระ**, **พรรณี ปิติสุทธิธรรม**

วัตถุประสงค์: *เพื่อศึกษาผลการรักษาวัณโรคในผู้ป่วยที่ติดเชื้อไวรัสเอดส์ที่ได้รับยาต้านไวรัส*

วัสดุและวิธีการ: *การศึกษาแบบย้อนหลังในผู้ป่วยที่มารับการรักษาที่โรงพยาบาลในประเทศไทยระหว่างเดือนมกราคม พ.ศ. 2548 ถึงเดือนกุมภาพันธ์ พ.ศ. 2551 เพื่อประเมินผลการรักษาวัณโรคในผู้ป่วยที่ติดเชื้อไวรัสเอดส์ ที่ได้รับยาต้านไวรัส*

ผลการศึกษา: *ผู้ป่วยวัณโรคที่ติดเชื้อไวรัสเอดส์ที่ได้รับยาต้านไวรัส 166 คน ส่วนใหญ่มีอายุ 36 ปี (ช่วง 20-72 ปี) เป็นวัณโรคปอด 69 คน (41.6%) และเป็นวัณโรคแพร่กระจาย 97 คน (58.4%) ในจำนวนนี้รักษาหาย 127 คน (76.5%) และรักษาไม่หาย 15 คน (9.0%) ระยะเวลากลางในการรักษาหาย (Median time) เป็นเวลา 10.8 เดือน (ช่วง 6-32 เดือน) โดยติดตามผลการรักษาเป็นเวลา 18 เดือน ผลของการรักษาวัณโรคในผู้ป่วยที่ติดเชื้อไวรัสเอดส์ระหว่างกลุ่มที่ได้รับยาต้านไวรัสหลักเป็น NVP และกลุ่มที่ได้ยาหลักเป็น EFV ร่วมกับ rifampicin ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ (5.4% กับ 10.8%, p = 0.751)*

สรุป: *ผู้ป่วยวัณโรคที่ติดเชื้อไวรัสเอดส์ที่ได้รับยาต้านไวรัสส่วนใหญ่ (76.5%) รักษาหายด้วยยารักษาวัณโรค โดยมีระยะเวลากลาง 10.8 เดือน และไม่มีความแตกต่างกันระหว่างผู้ป่วยที่ได้รับยาต้านไวรัสหลักเป็น NVP และ EFV ร่วมกับ rifampicin*