OUTCOMES IN HIV-INFECTED PATIENTS ON ANTIRETROVIRAL THERAPY WITH TUBERCULOSIS

Somsit Tansuphasawadikul[1], Wakana Saito[2], Jerome Kim[3], Benjaluck Phonrat[2], Jittima Dhitavat[2], Supat Chamnachanan[2] and Punnee Pitisuttithum[2]

[1]Bamrasnaradura Institute, Ministry of Public Health, Nonthaburi; [2]Faculty of Tropical Medicine, Mahidol University, Bangkok, [3]Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand

Abstract. HIV-infected patients with active tuberculosis (TB) having CD4 counts <100/mm^3 and who were antiretroviral therapy (ART) naïve were reviewed retrospectively to determine the outcomes of their tuberculosis infection. All patients received ART at or after receiving anti-TB treatment. Clinical manifestations, treatment regimens and outcomes were analyzed. Of 101 patients, 62 (61.4%) completed TB treatment. Of these, 53.2% were treated with a 6-month standard TB regimen, while the rest were treated with prolonged TB regimens. The median interval between anti-TB treatment and ART was 68 days (range: 0-381). Among the clinically cured patients 66.1% received rifampin concomitantly with nevirapine, and 32.3% received rifampin concomitantly with efavirenz. The treatment success rate was 75.6%, with a mortality rate of 6.1%. The risk factors for death were resistant TB (p=0.03) and poor compliance (p<0.05). Seven point nine percent had multi-drug resistant TB. Possible or probable immune reconstitution inflammatory syndrome (IRIS) was seen in 15 cases (14.9%). No life-threatening IRIS was reported, and it did not affect disease outcome (p=0.5). A shorter time between anti-TB treatment and ART onset was associated with the occurrence of IRIS (31 days *vs* 90 days; p<0.05). Regarding adverse drug effects, 44.6% had side effects due either to anti-TB drugs or ART. Sixty-six point one percent of them occurred within the first 2 months of TB treatment, and 43 (76.8%) had to stop or change either anti-TB treatment or ART. The mortality rate with TB and HIV on ART was low and the occurrence of IRIS did not carry any additional mortality.

INTRODUCTION

Although the mortality rate of Acquired Immune Deficiency Syndrome (AIDS) has dramatically decreased because of the introduction of antiretroviral therapy (ART), opportunistic infections (OIs) continue to threaten Human Immunodeficiency Virus (HIV)-infected patients. Tuberculosis (TB) is one of the most common OIs and one of the major causes of death in AIDS patients, especially in developing countries. It is not recommended to begin both ART and anti-TB treatment at the same time to avoid drug interactions and severe adverse events (Dean *et al*, 2002).

Immune reconstitution inflammatory syndrome (IRIS) with paradoxical worsening of the TB manifestations in HIV-1-infected patients after the initiation of ART (Crump *et al*, 1998; Narita *et al*, 1998) makes the treatment more complicated. Although IRIS is usually mild and self-limited (Wendel *et al*, 2001), it may be severe and require steroid treatment (Buckingham *et al*, 2004). ART initiation with a low CD4 count is a risk factor for IRIS

Correspondence: Prof Punnee Pitisuttithum, Department of Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, 420/6, Ratchawithi Road, Ratchathewi, Bangkok 10400, Thailand.
Tel: +66 (0) 2643-5599, +66 (0)2643-5584; Fax: +66 (0) 2643-5598
E-mail : tmppt@mahidol.ac.th

(Jevtovic *et al*, 2005). It may be better to start ART immediately if anti-TB treatment is tolerable. It is therefore a dilemma for clinicians to decide when to start HAART in advanced HIV-infected TB patients.

Another concern is drug interactions. Because rifampin (RFP) reduces serum levels of some antiretroviral drugs, rifabutin is recommended instead of RFP. However, rifabutin is not available in most developing countries. Among non-nucleoside reverse transcriptase inhibitors (NNRTIs), an increased dose of efavirenz (EFV) is recommended with RFP, and nevirapine (NVP) use is not recommended with RFP. However, NVP is more accessible in many countries due to its lower cost. Clinical data regarding the co-administration of NNRTIs or protease inhibitors with RFP is still scarce.

Hence, this study aimed to determine the clinical outcomes of TB in HIV-infected patients on ART in Bamrasnaradura Institute, Ministry of Public Health, Nonthaburi Province, Thailand. We also investigated the incidence and manifestations of adverse events and IRIS in association with ART initiation.

PATIENTS AND METHODS

The medical records of TB patients who presented to Bamrasnaradura Institute with culture proven TB from any clinical specimen were identified from January 2004 to June 2005 using mycobacterial isolation records from the Microbiology Department. All TB patients with positive HIV results who have available medical records and fulfilled the following criteria were selected: (1) patients who were >15 years old, (2) naïve to ART at the time of TB diagnosis and initiated ART during TB treatment, and (3) a CD4 count <100/mm^3 at TB diagnosis. Information regarding demographic characteristics, anti-TB treatments, TB resistance, CD4 cell counts, ART regimens, clinical course, possibility of IRIS and side effects, body weight (BW), CD4 count and plasma viral load (pVL) were reviewed from their medical charts. Karnofsky's score (O'Dell *et al*, 1995) was abstracted from the medical charts or derived by the researcher and OPD nurse from information at the time of TB diagnosis, at 6 and 12 months after TB diagnosis.

HIV status was determined on one blood sample, on which two serological tests, such as Microparticle Enzyme Immunoassay (Abbott Laboratories, Abbott Park, Illinois, USA) and Serodiagnostic test (Fujirebio, Tokyo, Japan), were performed. Definitive TB was defined as isolation of *Mycobacterium tuberculosis* from any clinical specimens. Anti-TB therapy was considered to be effective if bacteriological failure or relapse could not be documented, if the strains of *M .tuberculosis* were susceptible to anti-TB drugs, and if the patient adhered adequately to anti-TB therapy.

IRIS was defined as "possible" if there was a reappearance of or worsening of the previous TB manifestations or if there was an appearance of new manifestations, despite effective anti-TB therapy, after the exclusion of other diagnose. IRIS was classified as "probable" if there were positive results on direct bacteriological examination, showing the presence of acid-fast bacilli in an organ suspected of exhibiting IRIS, without further positive culture results (Breton *et al*, 2004).

TB treatment outcomes followed the definitions of the World Health Organization and the European Region of the International Union against Tuberculosis and Lung Disease, which are as follows (Veen *et al*, 1998):

(1) Cure refers to the completion of a full course of TB treatment and documented bacterial conversion.

(2) Presumptive cure refers to documented treatment completion, but no documented bacterial conversion.

(3) Treatment failure refers to being culture positive after 5 months of treatment.

(4) Death refers to death due to any

cause before the end of TB treatment.

(5) Treatment interruption refers to discontinuation of TB treatment for 2 consecutive months or more.

(6) Treatment refers to another physician from whom information regarding treatment outcome could not be obtained.

Relapse refers to the circumstance in which a patient either becomes culture positive again or has clinical or radiographic deterioration that is consistent with active TB at any time after completion of treatment (Blumberg *et al*, 2003).

Since the mortality rate of HIV-patients co-infected with TB is about 10% (Dheda *et al*, 2004), using a 5% error allowance and using the formula

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

where (z_α=1.96, p=0.1 and d=0.05), the calculated sample size was 138. The mycobacterial smear tests and cultures were performed at Bamrasnaradura Institute clinical microbiology laboratory. All culture positive specimens were checked for susceptibility by the standard methods. Data were coded and analyzed using Epi Info (Version 6). Continuous data were described by median for non- parametric data. Categorical data were compared using the chi-square test or Fisher's exact test where appropriate, and non-categorical data, such as medians, were compared among groups using the Mann-Whitney test. Mortality was calculated as the proportion of patients who died. A p-value <0.05 was considered statistically significant.

The study was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University and Institutional Review Board of Bamrasnaradura Infectious Disease Institute.

RESULTS

Between January 2004 and June 2005, a total of 459 cases had culture positive *M. tuberculosis*. Due to selection of cases according to our definition, medical records of 101 cases remained eligible, as shown in Fig 1, and the baseline characteristics of these 101 cases are presented in Table 1. Of 101 patients, 62 completed TB treatment. Of

Table 1
Baseline characteristics of HIV/TB co-infected patients.

Characteristics	TB-ART (n=101)
Age (years) median (range)	33 (20-58)
Male/Female	73/28
Baseline BW (kg) median (range)	48.7 (33.0-81.7) (n=94)
History of tuberculosis n (%)	14 (13.9)
HBV+ n (%)	1 (6.7) (n=15)
HCV+ n (%)	9 (60.0) (n=15)
History of OI n (%)	43 (42.6)
Baseline CD4 (/mm^3) median (range)	30 (1-97)
Baseline log pVL median (range)	5.67 (4.6 - >5.87) (n=37)
Duration between TB treatment and ART (days) median (range)	68 (0-381)

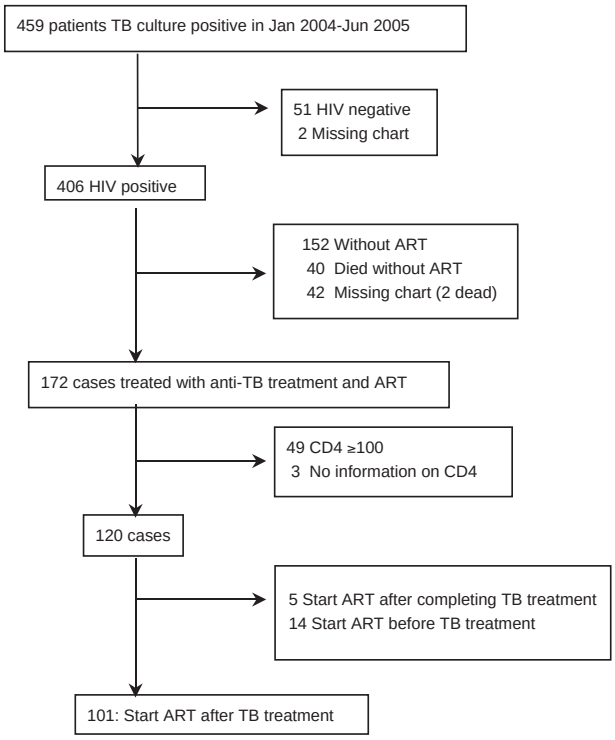

Fig 1–Diagrams for selecting medical records of patients included in this study.

these, 53.2% (33/62) were treated with a 6-month standard regimen. The others were treated with prolonged TB treatment (7-9 months in 38.7%, 10-12 months in 4.8%, 13-18 months in 1.6%, and 19-21 months in 1.6%). Reasons for prolonged TB treatment were *M. tuberculosis* strain resistance and inadequate regimens.

Of 82 cases (19 were still on treatment at the time this paper was written and so they were excluded from the 101 cases in the study), 20 cases (24.4%) were cured. Forty-two cases (51.2%) had a presumptive cure. Treatment failure was observed in 2 cases (2.4%). Five cases (6.1%) died before TB treatment completion. Seven cases (8.5%) interrupted TB treatment due to drop-out. Six cases (7.3%) were referred to another hospital during TB treatment. Only 24 patients had CD4 count results and 12 patients had pVL results available at the time of TB diagnosis, and 6 and 12 months after TB diagnosis. Of those patients, the median CD4 cell counts were 29.0/mm^3, 93.5/mm^3 and 146.5/mm^3 at 0, 6 and 12 months, respectively. The median log pVL decreased from 5.46 to <1.69 and remained <1.69 at 12 months after TB diagnosis.

Table 2 shows the comparison of baseline characteristics between the dead and clinically cured patients. Five cases (6.1%) died before TB treatment completion [222 days (78-441days) after TB diagnosis]. Mortality was not statistically significantly associated with disseminated TB (p=0.19), use of NVP and RFP (p=0.06) or EFV and RFP. There were no deaths among patients who had ART failure or who were treated with EFV and RFP. IRIS did not affect the clinical outcome (p=0.43). The number of cases with poor compliance and MDR-TB were significantly higher in the dead cases. Only one of the dead cases had received either NVP or EFV with RFP. The median duration between initiation of anti-TB treatment and ART was longer in the dead cases, but the difference was not statistically significant (p=0.08).

Forty-five of 101 cases (44.6%) experienced 56 episodes of side effects during TB treatment and 66.1% (37/56) occurred within the first 2 months of treatment. In 12 cases (11.9%), rash occurred during anti-TB treatment. Ten of 12 cases (83.3%) experienced rash within the first 2 months of TB treatment. Seven cases (6.9%) had moderate to severe nausea and most of the cases (85.7%) occurred within the first 2 months of TB treatment. Eighteen cases (17.8%) showed hepatotoxicity during treatment. The majority had jaundice. Of the 18 cases, 12 (66.7%) had hepatotoxicity within the first 2 months of initiating TB treatment and 17 cases (94.4%) had to either stop or change treatment (RFP: 13 cases, RFP+NVP: 3 cases, NVP: 1 case). Ten cases (9.9%) had neuropathy. Six cases were

Table 2
Comparison between deaths and clinically cured cases.

Variables	Death (n=5)	Clinically cured (n=62)	p-value
Age (years) median (range)	38 (28-46)	33 (24-52)	0.31[a]
Gender (% of male)	4 (80.0)	43 (69.4)	1.00[b]
Baseline BW (kg)	48 (39.4-53.0)	48.25 (35.0-76.0) (n=58)	0.58[a]
Karnofsky's score	40 (40-90)	70 (30-90) (n=61)	0.58[a]
Poor compliance n (%)	3 (60.0)	0 (0)	0.05[b]
TB history n (%)	1 (20.0)	7 (11.3)	0.48[b]
Disseminated TB n (%)	1 (20.2)	34 (54.8)	0.19[b]
MDR-TB n (%)	2 (40.0)	2 (3.2)	0.03[b]
Baseline CD4 (/mm^3) median (range)	24 (5-48)	31 (1-87)	0.57[a]
Baseline log pVLA median (range)	5.54 (5.51-5.56) (n=2)	5.69 (4.6 - >5.87) (n=22)	0.53[a]
Concomitant use of NVP+RFP n (%)	1 (20.0%)	41 (66.1%)	0.06[b]
Concomitant use of EFV+RFP n (%)	1 (20.0%)	20 (32.3%)	1.00[b]
Duration between TB treatment and ART (days)	133 (48-381) (n=5)	66 (13-319) (n=62)	0.08[a]

[a]Mann-Whitney test
[b]Fisher's exact test

treated with anti-TB treatment and ART. Four cases had joint pain. PZA was suspected as a causative agent in all cases and stopped in 2 cases.

Fifteen of 101 cases (14.9%) were considered to have IRIS (14 possible IRIS, 1 probable IRIS) (Table 3). IRIS occurred at a median of 14 days (8-69days) after ART initiation. Six cases were treated with 0.25-0.5mg/kg corticosteroid for IRIS. There were no deaths or relapses. The interval duration between the initiation of ART and TB treatment was significantly shorter among cases with IRIS ($p<0.05$). Extra-pulmonary tuberculosis (EPTB) or disseminated TB were not more common with IRIS. NVP or EFV use with RFP was also not related to IRIS.

Nineteen cases had another OI after the initiation of either anti-TB treatment or ART (Cytomegalovirus retinitis in 8 cases, herpes simplex virus infection in 4 cases, cryptococcal meningitis in 4 cases, herpes zoster in 2 cases, and condyloma acuminatum in 1 case). The median duration between OI diagnosis and TB diagnosis was 221 days (34-514 days). Cases that experienced OI after treatment had a statistically significantly longer duration between ART initiation and TB treatment initiation ($p<0.05$). After TB treatment, 54 cases were followed up for a median duration of 8 months (1-16 months). Among these 54 cases, 2 had a relapse of TB, one at 4 months and the other at 8 months after completion of initial anti-TB treatment.

DISCUSSION

The mortality rate in this study (6.1%) was lower than that in a previous report (10%) (Dheda *et al*, 2004). The mortality rate could have been higher because some of the treatment interruption cases or referred cases were assumed to have a poor prognosis. However,

Table 3
Comparison between patients with IRIS and those without IRIS.

Characteristics	Patients with IRIS (n=15)	Patients without IRIS (n=83)	p-value
Age(years) median(range)	35 (25-49)	33 (20-58)	0.63[a]
Gender (% of male)	73.3	72.3	0.97[b]
History of OI n(%)	8 (53.3)	35 (42.2)	0.53[b]
Site of TB n(%)			
Pulmonary	2 (13.3)	17 (20.5)	0.73[c]
Extra pulmonary	13 (86.7)	66 (79.5)	
Disseminated TB n(%)	8 (53.3)	41 (49.4)	0.53[b]
Duration between initiation of ART and TB treatment (days)	31 (13-90)	90 (0-381)	<0.05[a]
ART regimen			
GPOvir	10 (66.7)	66 (79.5)	
D4T+3TC+EFV	4 (26.7)	16 (19.3)	0.29[b]
ABC+3TC+EFV	1 (6.7)	1 (1.2)	
NVP or EFV use with RFP			
None	0 (0)	22 (26.5)	
NVP+RFP	10 (66.7)	43 (51.8)	
EFV+RFP	4 (26.7)	14 (16.9)	
(NVP+RFP)+(EFV+RFP)	1 (6.7)	4 (4.8)	
Baseline BW (kg)	49.0 (38.3-65.0)	48.9 (33.0-81.7) (n=78)	0.77[a]
Baseline CD4 count (/mm^3)	36 (5-87)	30 (1-97)	0.68[a]
Baseline log pVL (log10)	5.76 (5.67-5.87) (n=7)	5.55 (4.6-5.87) (n=28)	0.01[a]

[a] Mann-Whitney test; [b]Chi-square test; [c]Fisher's exact test

there were 42 deaths in 406 HIV/TB co-infected cases (Fig 1; 40 cases died without using ART; 2 cases had missing charts). Most of the dead cases died before starting ART. Several papers have reported improved outcomes in HIV/TB co-infected cases in the era of HAART (Hung *et al*, 2003; Dheda *et al*, 2004). Study on these treated without HAART reported a mortality rate of 13.3% (Putong *et al*, 2002). Only 11.4% were successfully treated and 46.7% were lost to follow-up (Putong *et al*, 2002). Our study had a high rate of treatment interruptions (9.4%) and referred cases (7.3%).

In our study, IRIS occurred in 14.9% of patients. Previous estimates of the incidence of IRIS vary from 9.6% to 43% (Narita *et al*, 1998; Wendel *et al*, 2001; Breton *et al*, 2004; Kumarasamy *et al*, 2004). There are several problems with the diagnosis of IRIS in resource limited settings because of no clear clinical criteria to diagnose IRIS and exclusion of other possible causes is also needed. In most previous studies, IRIS occurred within the first 4 weeks after initiating ART (Narita *et al*, 1998; Wendel *et al*, 2001; Breton *et al*, 2004). In our study, the median time to the diagnosis of IRIS after starting HAART was 14.5 days. IRIS was manageable, and corticosteroid 0.25-0.5mg/kg was used in 6 cases. A shorter duration between the initiation of anti-TB treatment and ART was associated with the occurrence of

IRIS. The same phenomenon was reported in a previous study (Shelaburne *et al*, 2005). Abundant microbial antigen may promote a greater immune response (Shelaburne *et al*, 2005; Lipman and Breen, 2006). Former reports suggested that a large drop in pVL or a large elevation in CD4 count is a risk factor for IRIS (Shelaburne *et al*, 2005; Manosuthi *et al*, 2006). We could not investigate this point. Baseline CD4 count, disseminated TB, extrapulmonary TB and ART regimen were not associated with IRIS. NVP or EFV use with RFP were also not associated with IRIS.

The timing of ART initiation after TB treatment for HIV-associated TB cases remains an important question. In the present study, the median duration from initiation of anti-TB treatment to ART was 68 days, similar to a previous report (Sungkanuparph *et al*, 2006). Shorter duration between initiation of ART and TB treatment is a risk factor for IRIS. However, delay in initiation of ART is a risk factor for additional AIDS-related events and death. Even though there is a risk of IRIS, it is probably better to start ART right away, rather than postpone onset, since in advanced AIDS cases IRIS was manageable.

In the present study, all the patients were treated with a NNRTI based regimen. More than half patients used NVP with RFP concomitantly, and 23.8% of cases were treated with EFV along with RFP. Even though, we had satisfactory CD4 and pVL responses. There are many countries that must use NVP to treat HIV-associated TB patients receiving RFP. One study reported that NVP used with RFP can provide a satisfactory clinical outcome (Jesus *et al*, 2003). Manosuthi *et al* (2005) compared the plasma levels of NVP and virological and immunological outcome between HIV-infected patients receiving and not receiving rifampicin. They reported that although plasma levels of NVP were lower in patients who received NVP with RFP than those who received NVP alone, but the majority of NVP levels were still higher than the recommended level (>3.4mg/l) (Manosuthi *et al*, 2005). In our study, NVP use with RFP was not related to mortality or AIDS-related events with treatment. There was one case of ART failure, but this patient was treated with EFV and RFP. As a nature of a retrospective study, there were several disadvantages due to limited data collection.

In conclusion, this study had demonstrated outcomes of HIV/TB co-infected patients on ART. The TB cure rate was 75.6% and the mortality rate was 6.1%. Poor compliance and anti-TB drug resistance were risk factors for death. Deferral of ART was associated with increased death and AIDS-associated illness. In general, after NVP with RFP treatment, there were successful CD4 and pVL responses. IRIS occurred in 14.9% of the patients. There were no life-threatening IRIS and IRIS did not affect outcome. A short duration between initiation of anti-TB treatment and ART was a risk factor for IRIS. Further studies are needed regarding appropriate timing for initiating ART in advanced HIV-infected TB patients and studies of NNRTI co-administration with RFP are needed.

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