Clinical Manifestations and Antiretroviral Management of HIV/AIDS Patients with Tuberculosis Co-infection in Kramat 128 Hospital

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INTRODUCTION

HIV/AIDS is an emerging health problem worldwide, including in Indonesia. The global number of people living with HIV/AIDS (PLWHA) is estimated to be more than 39.5 (34.1-47.1) million (WHO/UNAIDS estimation, 2006). The exact data on number of PLWHA in Indonesia still vary according to the source, but it is predicted that the prevalence will keep increasing. The prevalence varies between 88.600 to 138.800 (Garnett and Grassly, 2002); 100.000 to 290.000 (UNAIDS/WHO, 2006) and 165.000 to 216.000 (Ministry of Health, 2006). Treatment of HIV/AIDS using antiretroviral combination therapy was successful in significantly reducing morbidity and mortality of HIV/AIDS. However, availability of first-line antiretroviral agent in Indonesia is still limited, such as Lamivudine (3TC), Zidovudine (AZT), Stavudine (d4T), Nevirapine (NVP) and Efavirenz (EFV). This constraint elevates the essential selection of combination among the five antiretrovirals, and the selected antiretroviral regimen should be able to provide higher success rate.

The HIV/AIDS problem in Indonesia is also marked by the high prevalence of pulmonary tuberculosis. Based on the available data, the prevalence ranges between 162 to 379/100.000 population (WHO, 2005). Indonesia together with India, Bangladesh, Vietnam, Cambodia, Thailand, and Myanmar, are enlisted as the 22 countries with high TB burden. More than 80% of all TB cases worldwide are from these countries. It is estimated that TB kills more than 2 million people each year, 26% of all preventable death in developing countries. Pulmonary TB and HIV/AIDS are two disease entities that could increase morbidity and mortality of each other. Besides, combination of antiretroviral and antituberculosis therapy could also result in disadvantageous interaction. Antituberculosis, in this context rifampicin, could decrease serum level of protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI)
antiretroviral agents up to 90% or even more, leaving 
less than 10% serum drug level. On the other hand, PI 
group could increase rifabutin antituberculosis level from 
two- to four-fold, which results in clinical toxicity 
(leukopenia, uveitis, arthralgia, and skin discoloration).6-9

The aim of this study is to provide initial illustration 
on HIV/AIDS and tuberculosis coinfection in Jakarta 
especially in Kramat 128 Hospital, based on the 
immunological and virological status point of view, and 
proper choice of antiretroviral agents.

METHODS

This is a cross-sectional descriptive study performed 
at the Kramat 128 Hospital Jakarta Outpatient Clinic 
throughout June and July 2007. Data were collected 
through direct interview and medical record tracing. The 
inclusion criteria are patients willing to be interviewed 
and considered eligible to answer questions. Exclusion 
criteria include patients with incomplete or lost medical 
record. Sampling method of subjects was consecutive 
sampling, i.e. all HIV-AIDS + TB patients admitted 
during the above period are included as study subjects. 

Confirmation of TB infection in the lungs was done 
through combination of clinical manifestations and chest 
X-ray, and acid-fast staining when performed. Viral Load 
was measured using Polymerase Chain Reaction (PCR) 
method in referral laboratories at Dharmais Hospital or 
Cipto Mangunkusumo Hospital. Measurement of CD4 
level was also performed by the referral laboratories at 
both hospitals using flow cytometry. Virologic failure is 
defined as detection of viral load that persists after 6-
month ARV therapy.

After a patient is diagnosed HIV-positive and 
fulfilled the therapeutic criteria, i.e. AIDS (HIV-
positive with opportunistic infection), CD4 <350 cells/ 
µL or Viral Load >55,000 copies, the patient begins to 
receive antiretroviral (ARV) therapy. The first choice 
for ARV is based on the patient’s clinical status, patient 
usually receive combination of 3TC+AZT+NVP as the 
first regimen. Patients with anemia receive d4T as a 
replacement for AZT, HCV-positive patients are 
considered to receive EFV instead of NVP, and 
pregnant patients do not receive EFV as a part of their 
ARV regimen. The 3TC dose is 2 x 150 mg with brand 
name Hiviral or Duviral (in combination with AZT 300 
mg). Dosage for AZT is 2 x 300 mg with brand name 
Duviral (in combination with 3TC 150 mg). Dosage for 
d4T is 2 x 30 mg with brand name Stavir. Dosage for 
Nevirapin is 2 x 200 mg with brand name Neviral, and 
for Efavirenz is 1 x 600 mg with brand name Stocrin, 
Efavir and Aviranz.

In patients with TB coinfection, treatment should be 
started with antituberculous drugs according to DOTS 
regimen before initiation of ARV. Antituberculous drugs 
should be given during the first two weeks, then followed 
by simultaneous ARV administration.

Data were then collected and tabulated using SPSS 
program version 14. Statistical analysis was also 
performed with the said program using non-parametric 
test, i.e. Chi Square, that was chosen due to abnormal 
data distribution of proportional data.

RESULTS

There were 130 patients who participated in this study, 
and the gender distribution was 26 females (20%) and 
104 males (80%). In general we found intravenous drug 
 injection 51.5% (n=67) and sexual intercourse 46.9% 
(n=61) as the main factors for transmission in these 
patients. Transmission in female was mainly through 
sexual intercourse (88.5%), while in male through 
intravenous drug injection (61.5%). The mean age of 
patients in this study was 32.30 years, the youngest 
patient was 22 years old and the oldest 56 years old. In 
patients younger than 30 years of age (n=69/130), the 
most common way of transmission was through 
intravenous drug injection (72.5%). On the other hand, 
the most common way of transmission in patients above 
30 years of age (n=61/130) was through sexual 
intercourse (70.7%).

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<th>Table 1. Characteristics of study population</th>
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The most common opportunistic infection found in 
this study was pulmonary TB 66.9% (87/130), followed 
by oral candidosis 36.9% (48/130), Toxoplasma
encephalitis 16.2% (21/130) and recurrent pneumonia 10.8% (14/130). As for the incidence of toxoplasma encephalitis, the diagnostic criteria being used in this study were by CT scan, thus the prevalence could not be exactly measured because some of the patients could not afford the cost of examination.

The most common clinical manifestation in this study was weight loss (76.9%), cough that lasted for at least one month (76.2%), prolonged fever (58.5%), chronic diarrhea (43.8%), aphthae and pain in swallowing (43.1%), and dyspnea (36.9%). Patients with pulmonary TB co-infection presented with more severe clinical manifestations compared to patients without co-infection. (Table 2) Patients with TB co-infection usually present with 3 to 4 clinical manifestations (mean=3.8; 95% CI 3.52-4.09) compared to patients without co-infection, i.e. 2 to 3 clinical manifestations (mean=2.74; 95% CI 2.35-3.14; p<0.001). Patients with pulmonary TB also need more frequent hospitalization compared to patients without pulmonary TB: 44.8% vs. 11.6% (39/87 vs 5/43, p=0.003). Patients with TB co-infection, considering that they have more clinical manifestations and need for hospitalization, seemed to show worse general condition compared to patients without co-infection.

The choice of ARV regimen in this study was a combination of 3 from 5 ARV: 3TC, AZT, d4T, NVP, and EFV. Distribution of regimen choice was as follows: 56.2% 3TC+AZT+NVP (73/123), 13.1% 3TC + AZT + EFV (17/123), 11.5% 3TC + d4T + EFV (15/123), and 10.8% 3TC + d4T + NVP (14/123). Duration of therapy was between 1 to 80 months, with mean 20.5 months. Temporary drug withdrawal was found in 7 patients and ranged between 1 to 25 months with mean 10.8 months. Therapeutic success that shows undetected viral load was found in 67.7% (44/65) of patients, while therapeutic failure was found in 37.7% (21/65) of patients. Therapeutic success in patients with 3TC + d4T + EFV regimen was up to 83.3% (5/6), with 3TC + AZT + EFV was up to 80% (8/10), with 3TC + AZT + NVP up to 71.7% (38/53) and with 3TC + d4T + NVP regimen reached 60% (3/5), none of them showed significant difference with p=0.632.

Anemia after antiretroviral therapy was found in 41.5% (51/123) of patients, with the lowest Hb level 3.5 g/dL and the highest 12.8 g/dL, and mean Hb level 9.95 g/dL (95% CI 9.25-10.64). Liver function test in 31 patients found elevated ALT and AST level to more than twice normal value in 21 subjects (67.7%) for AST and 12 subjects (38.7%) for ALT, with mean increase of 42.9 points for AST and 26.5 points for ALT.

In this study patients were admitted with mean CD4 level 156.39 cells/µL. The other 66.2% (86/118) presented with serum CD4 level below 200 cells/µL (low), 13.1% (17/118) between 200-350 cells/µL and 11.5% (15/118) above 350 cells/µL (high). Mean elevation of CD4 after 6-month ARV therapy was 132.70 cells/µL. Mean elevation of CD4 in patients with virologic failure (VL still detected) showed lower score compared to successful patients, 82.3 cells/µL vs. 156.7 cells/µL (95% CI 24.9-139.7 vs. 116.7-196.7; p=0.005). Choice of ARV also contributes to the elevation of CD4 level, and choosing AZT + 3TC + EFV showed mean elevation of CD4 level 215.5 cells/µL (95% CI 124.3-306.7), d4T + 3TC + NVP showed 146.4 cells/µL (95% CI 80.7-212.1) and AZT+3TC+NVP showed 134.2 cells/µL (95% CI 101.5-166.9). Choosing d4T + 3TC + NVP as ARV regimen seemed to result in the lowest elevation of CD4 level after 6-month therapy, with mean 62.00 cells/µL (95% CI -308.0-237.2; p=0.045).

Patients with pulmonary TB presented with lower mean CD4 level compared to patients without pulmonary TB, 126.49 cells/µL vs. 240.68 cells/µL (95%
Patients with pulmonary TB also presented with lower CD4 count, 64.6% (51/79) of patients with pulmonary TB presented with CD4 <100 cells/µL compared to only 25.6% (10/39) patients without pulmonary TB (p<0.001).

After 6 month ARV therapy, the mean CD4 cell count in patients with pulmonary TB is also lower compared to patients without pulmonary TB: 257.13 cells/µL vs. 394.04 cells/µL (95% CI 206.07-308.19 vs. 280.34-507.34; p=0.015), with the mean elevation 128.58 cells/µL vs. 138.04 cells/µL.

Patients with pulmonary TB also demonstrated higher virologic failure, 38% (19/50) of patients with pulmonary TB showed positive viral load after 6-month therapy compared to 12.5% (3/24) in patients without pulmonary TB (p=0.030). Therapeutic failure in these patients with TB is thought to be caused by administration of NVP-based regimen together with antituberculous drugs. In this case, TB patients treated with NVP-based ARV regimen demonstrated higher therapeutic failure compared to EFV-based ARV regimen, i.e. 37.8% vs. 6.3% (14/37 vs. 1/16, p=0.019).

**DISCUSSION**

Distribution of HIV/AIDS between male (80%) and female (20%) patients in this study is similar to the epidemiological data issued by WHO in 2006, i.e. 82% in male and 18% in female. These data shows increasing percentage of women infected with HIV/AIDS in the last few years compared to the 1980s when HIV/AIDS is still dominated by the homosexuals (74.5%) and male intravenous drug users (14.2%). The increased percentage in female patients might be caused by increased number of female IDUs, and unprotected sexual activity with HIV-positive patients.

Risk factors for HIV/AIDS transmission in Indonesia are mainly needle injection and sexual intercourse. Our study data showed 51.5% from needle transmission and 46.9% from sexual intercourse. This is similar to the data issued by WHO on 2006, which predicted 51.27% of infection transmitted through intravenous drug injection and 48.12% from sexual intercourse. From this study we found that male subjects below 30 years of age which was also an intravenous drug user have a high risk for HIV/AIDS, although the extent of risk still have to be further studied. However in male subjects over 30 years old, the most common way of transmission was through unprotected sexual intercourse (70.7%, p<0.001). This tendency indicates the need of counseling and testing (VCT) for the two groups mentioned above, so that recommendations for HIV screening in the two groups could be established.

In our study data TB seems to be the most common opportunistic infection, which affected around 66.9% of patients. Several studies on prevalence of HIV/AIDS in patients with TB in Asian countries show considerably high prevalence. Studies in Asia found prevalence between 9.4-40%, New Delhi (India) 9.4%, Mumbai (India) 30%, and North Thailand 40%. In Indonesia, to the author’s knowledge, there is currently no definite prevalence of HIV/AIDS in patients with TB. Proposed data by Corbett et al. in 2003 estimated the prevalence of co-infection around 0.2% from overall TB cases in
Indonesia. However, these data should be carefully interpreted, because HIV/AIDS serology screening in TB patients has not been established as a policy in Indonesia.\textsuperscript{10,14}

Patients with TB were also the main emphasis in this study due to the high incidence of TB infection in our study population (66.9\%), and also due to the extent of problem associated with TB co-infection. Patients with TB co-infection presented with worse general condition compared to patients without co-infection. This could be observed from the higher number of clinical manifestations (mean 3.8 vs. mean 2.74; \(p<0.001\)) and higher possibility of hospitalization (44.8\% vs. 11.6\%; \(p=0.003\)) compared to patients without TB. This result is similar to a number of previous studies that relate clinical progression of HIV/AIDS with TB. A study in India revealed that the chance of clinical TB in patients with HIV(+) after exposure was 5-10\% annually, compared to 5-10\% for a lifetime in patients without HIV infection.\textsuperscript{13,14} The higher prevalence of TB in HIV/AIDS patients is due to the similarity in the pathogenesis of Cell-Mediated Immunity, especially the CD4 cell. Suppression of CD4 cell by HIV will compromise the mechanism that controls \textit{M.tuberculosis} infection, which results in easier invasion and dissemination of disease. This similarity of pathogenesis also complicates the TB course, because CD4 suppression lowers the incidence of caseous necrosis essential to expose \textit{M. tuberculosis} to the outside environment. This low exposure causes difficulties in establishing TB diagnosis using acid-fast staining, and will further complicate TB diagnosis in HIV/AIDS patients.\textsuperscript{17,20}

Tuberculosis also has a large impact on HIV/AIDS, approximately 40\% of mortality in HIV/AIDS worldwide is due to TB, with four-fold mortality rate compared to HIV/AIDS patients without TB. Degree of immune system destruction in HIV/AIDS patients is closely related to mortality. Tuberculosis further suppresses the low CD4 level, causing increased mortality. A study by Schluger in 2001 shows that for every predetermined CD4 level, patients with HIV/AIDS-TB co-infection demonstrate higher mortality compared to the ones without co-infection. The above data show that TB and HIV/AIDS co-infection is a problem that necessitates comprehensive management.\textsuperscript{13,23}

This study, which was commenced in Jakarta, showed that patients with pulmonary TB co-infection presented with lower immunological status on admission, with mean CD4 level 126.49 cells/µL and 64.6\% of patients with TB co-infection presented with CD4 level below 100 cells/µL. Patients with TB-HIV/AIDS co-infection who required ARV also had lower CD4 increase (128.58 cells/µL vs. 138.04 cells/µL) with higher therapeutic failure (38\% vs 12.5\%) compared to patients without co-infection. TB could accelerate the course of HIV disease through several mechanisms, such as cellular activation mechanism which at the end will increase HIV viral load. TB onset in HIV/AIDS patients could elevate plasma viremia level between 5 to 160 times (Schluger, 2001).\textsuperscript{13,23}

Higher therapeutic failure in patients with TB-HIV/AIDS co-infection, 38\% vs. 12.5\% \((p=0.030)\), is a serious problem. Patients with TB-HIV/AIDS co-infection are faced with a complicated drug interaction problem. Rifampicin as a standard regimen for TB management in Indonesia has a strong interaction with NNRTI (NVP and EFV) and PI group. Indonesia itself still relies on NNRTI group as the first line for antiretroviral therapy, while the availability of PI group is still limited and being used as second-line therapy. Rifampicin induces cytochrome P450-3A, which results in enhanced metabolism to PI and NNRTI group, thus reducing the serum drug level up to 90\% or above. However, a study in Bangkok, Thailand about the efficacy of Nevirapine and Rifampicin when administrated together, found that addition of Rifampicin to Nevirapine regimen did not seem to demonstrate significant difference in efficacy. In this Thailand study, after 24-week ARV therapy, 88\% of patients receiving both Rifampicin and Nevirapine reached viral load lower than 400 copies/ml. This result is also supported by a study in Spain, with lower success rate 74\%.\textsuperscript{24,25} In Indonesia, we also have some limitations in choosing ARV, since we still have to rely on NVP and EFV (NNRTI group) as one of the main choices for HIV/AIDS therapy. Based on the Thailand study and other studies, it seems that nevirapine could be maintained as the first-line therapy in HIV/AIDS patients, although its administration should be monitored through routine liver function test and viral load test to evaluate the therapeutic success.

In this study 67\% of patients received NVP-based regimen as the first-line therapy, and 24.6\% received EFV as a basis. This study demonstrates that the therapeutic failure in TB-HIV patients receiving NVP-based regimen was 38\%, compared to only 6.3\% \((p=0.019)\) in patients receiving EFV. The result is similar to a study by Nachega et al in southern part of Africa, where virologic failure could be minimized to 0\% in patients receiving EFV compared to 69\% with NVP. Nachega stated that one of the possible causes is interaction between NVP and rifampicin commonly used for tuberculosis therapy in their population. However, considering that different situations in each country will result in different therapeutic success with NNRTI group.
and Rifampicin, further study is still needed based on the result of current study showing EFV superior to NVP when being used together with Rifampicin. Further randomized clinical trial study is expected to be able to provide clear illustration on EFV, NVP, and Rifampicin interaction in HIV/AIDS-TB co-infected patients in Indonesia.7-9,26

Rifabutin, an example of rifamisn group, is the best choice in the management of patient with TB-HIV co-infection. This happens because rifabutin results in weaker induction of CYP3A, compared with rifampin (rifampicin) that is currently available in Indonesia. Thus the low ARV level could be managed by adjusting the ARV dose. By increasing available rifabutin and ARV dosage, we could obtain similar therapeutic efficacy and suppression of relapse episodes compared to rifampin (rifampicin). Based on the above analysis, Rifabutin should be considered as a therapy for patients with HIV/ AIDS-TB co-infection. As an alternative, although with higher risk of adverse effects with consideration to individual variability of CYP3A, rifampicin could be used with Efavirenz-based ARV regimen. The increasing dose of EFV in this context up to 800 mg/day to compensate for increased drug metabolism by CYP3A enzyme, as recommended by some other studies, does not seem to be necessary. Standard-dose Efavirenz, i.e. 600 mg/day, is still effective in the management of patients with HIV/ AIDS-TB co-infection in Jakarta. This recommendation is in line with our study, where patients with EFV dose demonstrate higher therapeutic success up to 93.8%, compared to only 62.2% (p=0.019) in patients with NVP.7-9,27,28

CONCLUSION

We can conclude from this study that TB is an opportunistic infection often found in HIV/AIDS patients in Jakarta. Tuberculosis co-infection in these patients result in more severe clinical manifestation and higher possibility of hospitalization. Patients with TB co-infection also present with more complicated problem during management of their immunological and virological status. Therapeutic failure in this group of patients, both virological failure and failure to improve their immunological status, complicates the management of these patients. Choice of ARV in this group of patients is also faced with possibilities of therapeutic failure using combination of NVP and Rifampicin. Solution for this problem could be through administration of EFV-based regimen 600 mg daily. Nevirapine could still be used for first-line therapy as long as it is routinely monitored.

REFERENCES


