Prolonged Fever due to *Mycobacterium Avium* Complex (MAC) Disease in Advanced HIV Infection: A Public Health Concern

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Abstract

From March 1997 to June 1998, infectious etiologies of prolonged fever was prospectively investigated in 104 advanced human immunodeficiency virus (HIV) infected patients admitted to Siriraj Hospital. The etiology could be identified in 91 cases (87.5%). Of these, blood cultures from 68 patients yielded mycobacteria and fungi. *Mycobacterium avium* complex was the most common blood isolate in 24 per cent of the patients; followed by *Mycobacterium tuberculosis* in 20.2 per cent, *Cryptococcus neoformans* in 5.8 per cent, *Penicillium marneffei* in 5.8 per cent. During the course of febrile illness, 79 of the 91 patients (86.8%) exhibited focal lesions. Weight loss, elevated serum alkaline phosphatase were often found to be significantly more associated with MAC bacteremia ($P < 0.05$). Pulmonary involvement significantly correlated more with *M.tuberculosis* bacteremia than MAC bacteremia ($P < 0.05$). No cause could be identified in 13 cases. Mycobacterium blood culture alone established the etiologies in 68 cases (65.4%). Of the 25 patients with disseminated MAC (DMAC) infection, nine patients died during hospitalization. Another three cases died within a few months of appropriate anti-MAC chemotherapy. We concluded that the risk of DMAC infection in advanced AIDS patients in Thailand is high when low CD_4 lymphocyte count is established. The prolonged fever resulted from DMAC in advanced HIV infection is warrant to be public health concern. Mycobacterium blood culture is a most valuable tool contributing to the diagnosis of infectious agents in this condition. The guidelines of 1997 USPHS/IDSA should be followed to give chemoprophylaxis against DMAC disease in patients with advanced HIV infection and a CD_4 count less than 50 cells/mm^3.

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Fever is a common complaint among patients with advanced human immunodeficiency virus (HIV) infection. Long-lasting fever without a recognizable source is frequently encountered which poses a diagnosis and therapeutic challenge to the clinician. Sepkowitz et al[1] described causes of fever in an outpatient cohort of predominant homosexual males with advanced HIV disease. Approximately one-third of AIDS-defining illness is caused by *Mycobacterium avium* complex (MAC) infection. Miralles et al[2] assessed 50 patients with fever of uncertain origin in an advanced stage of HIV infection and found that tuberculosis (42%) and disseminated MAC (14%) were the most frequent diagnoses. In Thailand, a study of the prevalence of disseminated MAC infection (DMAC) was conducted from 1995 to1996 among Thai AIDS patients from four hospitals who had prolonged fever for at least two weeks without an obvious site of infection. The overall prevalence of DMAC was calculated to be 14 per cent[3].

We present herewith data from a prospective study of etiologies of prolonged fever among advanced HIV-infected patients admitted to Siriraj Hospital, Bangkok. Our purpose was to assess the frequency, clinical manifestations, laboratory data related to the causes of prolonged fever especially due to DMAC and *M.tuberculosis* among these patients.

MATERIAL AND METHOD

This prospective study was conducted in the in-patient medical service admitted to Siriraj Hospital from March 1997 through June 1998. Our study population was primarily of low socioeconomic status living in the Bangkok metropolitan area or provinces of central Thailand. Presence of HIV infection was documented by HIV-1 seropositivity while a diagnosis of AIDS was made on the basis of the 1993 criteria of the Ministry of Public Health, Thailand and the Centers for Disease Control and Prevention, U.S.A.[4,5]. Patients were included if they had a history of prolonged fever for at least two weeks and had an oral temperature of $\geq$ 38.2°C during the first three days of observation. A final selection criteria was the inconclusive etiology after seven days of investigation despite appropriate procedure being performed which included complete blood cell count, liver function test, blood and urine cultures, chest radiography, tissue biopsy if focal infection was suspected or found. After one week as such and the diagnosis was still indeterminate, then blood culture for mycobacteria with Bactec 9240 media was done in which 1-2 blood samples were obtained from each patient. If disseminated mycobacterial disease was highly suspected on the first day, the blood culture with Bactec 9240 media was done immediately. Blood cultures were processed according to the manufacturer's manual and identification was confirmed with DNA probe.

Demographic information, medical history, physical examination, results of laboratory testing and outcome of therapy were collected and recorded on case record forms by one of the authors and the medical housestaff. The diagnosis of infection was based on microbiological or histologic confirmation. The association between symptoms, signs, and laboratory parameters was assessed by Chi square test or Fisher's exact test, as appropriate and continuous variables were compared by student *t*-test and Wilcoxon test.

RESULTS

From March 1997 through June 1998, three hundred and forty-two patients with AIDS sought medication at Siriraj Hospital. One hundred and four patients (30.4%) fulfilled the criteria for prolonged fever and recruited in the study. Eighty-eight (84.6%) were men and 16 (15.4%) were women. The mean ($\pm$ S.D.) age was 32 $\pm$ 5 years (range 21-47 years). Risk factors for HIV infection included heterosexual contact found in 99 patients (95.2%), homosexual or bisexuality in three patients (2.9%) and intravenous drug users in two patients (1.9%). The cause of fever was determined on the basis of a clinical diagnosis and proven by microbiological identification or a probable diagnosis was reached if no microbiological test could confirm the likely diagnosis. Some patients had more than one infectious agent.

All 104 patients were in stage IV HIV disease according to criteria laid down by Centers for Disease Control and Prevention (CDC), U.S.A. and Ministry of Public Health (MOPH), Thailand[4,5]. The median CD_4 cell count for this group of patients was 13.5 cells/mm^3 (range: 1-182 cells/mm^3, mean $\pm$ S.D.: 27 $\pm$ 36.4 cells/mm^3). Etiology of fever was identified in 91 (87.5%) of the total 104 patients (Table 1). Of these, 72 pathogens were isolated in 68 patients (74.7%) by blood culture with Bactec 9240 and the results of culture

Table 1. Cause of prolonged fever and systemic involvement among 104 advance HIV-infected patients*.

Cause	Number (%) of patients					
	Total	Systemic involvement				
		R.S.	G.I.	L.N.	Skin	Hemato
Mycobacterium avium complex	25 (24.0%)	5	19	-	-	24
Mycobacterium tuberculosis	21 (20.2%)	14	9	3	-	14
Multi drug resistance (MDR) tuberculosis**	1 (1.0%)	1	-	-	-	1
Mycobacterium of unspecified type	2 (1.9%)	1	2	-	-	1
Suspected *Mycobacterium tuberculosis****	16 (15.4%)	14	11	3	-	9
Cryptococcus neoformans	6 (5.8%)	1	1	-	-	4
Penicillium marneffei	6 (5.8%)	3	5	-	2	5
Histoplasma capsulatum	2 (1.9%)	-	2	-	-	2
Cytomegalovirus	6 (5.8%)	1	2	-	-	2
Salmonella infection	7 (6.7%)	-	2	-	-	2
Klebseilla spp.	2 (1.9%)	1	1	-	-	2
Streptococcus pneumoniae	1 (1.0%)	-	-	-	-	-
Unidentified	13 (12.5%)	2	5	-	-	1
Total	104 (100%)					

* The table includes the agent most likely to be responsible for the prolonged fever, more than one infectious agent was identified in four patients.

** Sputum culture: *Mycobacterium tuberculosis* resistant to INH, rifampicin

*** Clinical, radiographic finding suspected *Mycobacterium tuberculosis* infection and or AFB smear positive and 12 patients were given empiric antimycobacterial therapy, of whom 10 patients had a favorable response, 2 patients were lost follow-up

Abbreviation are as follows:
R.S. = coughing, sputum AFB+ve, abnormal chest X-ray finding : infiltration, adenopathy, effusion,
G.I. = diarrhea, abdominal pain, hepatomegaly, splenomegaly, high alkaline phosphatase,
L.N. = solitary lymphadenopathy, Skin = pustule, Hemato = anemia (Hemoglobin < 10 g/dL), leukopenia (<4,000 x 10^9/L)

were available in 28 ± 5 days (mean ± S.D.) after phlebotomy (Table 1). Blood isolates included *Mycobacterium avium* complex in 25 cases, *Mycobacterium tuberculosis* in 21 cases, mycobacteria of unspecified type in 2 cases, *Cryptococcus neoformans* in 6 cases, *Penicillium marneffei* in 6 cases, *Histoplasma capsulatum* in 2 cases, *Salmonella* spp. in 7 cases, klebsiella in two cases, *S.pneumoniae* in one case. Four patients with dual infectious agents included salmonella and *Mycobacterium avium* complex (3 cases), salmonella and *Histoplasma capsulatum* (1 case). The remaining 36 patients for whom a diagnosis of prolonged fever was made included one patient with isoniazid and rifampicin-resistant *Mycobacterium tuberculosis*. Tuberculosis was likely in other 16 cases (17.6%) who had focal findings which included abnormal chest roentgenogram (infiltration, adenopathy or effusion) in ten cases and/or positive smear for acid-fast bacilli in eight cases, solitary adenopathy in three cases, gastrointestinal symptom (diarrhea, abdominal pain, hepatomegaly, splenomegaly) in eleven cases. Among these 16 patients, four cases died during hospitalization. Twelve patients were given therapeutic diagnosis with empiric antimycobacterial therapy and ten cases had a favorable response. The other two patients were lost to follow-up. The disseminated cytomegalovirus infection was diagnosed on clinical grounds in six patients in whom during the evaluation, a localized lesion was found which was compatible with cytomegalovirus infection such as retinitis in four patients and cytomegalovirus colitis in two patients proven by colonic biopsy and histopathology. Because there are several limitations to this study, extensive work up such as lymph node, bone marrow, lung, liver, gastrointestinal biopsy and cultures to enable the diagnosis were performed only in a certain number of patients. For thirteen patients with prolonged fever in whom the etiology could not be determined pre-

cisely, duration of fever ranged from 20-58 days (mean 23 ± 5.7 days). All had symptoms of asthenia, wasting, weight loss and low CD_4^+ cell counts (mean = 12 cells/mm^3). Five patients died while having a febrile episode during hospitalization. Fever in the remaining four patients was self-limiting within few weeks of hospitalization and required no antimicrobial therapy. Two patients were referred to their home province and the other two patients were lost to follow-up. The other work up that should be mentioned in this study included serum cryptococcal antigen (performed in six patients), serum toxoplasma antibody-IgG (performed in three patients).

Of the 104 cases, twenty-five patients (24 per cent) had no focal symptoms or signs of diseases. The remaining seventy-nine patients (76 %) presented with or during the course of the febrile illness had focal lesions, conditions, symptoms and signs (Table 1). The focal lesion and findings as shown in Table 1 included the following: solitary adenopathy, pustule, cough, productive sputum and positive smear for acid-fast bacilli, abnormal chest roentgenogram finding (infiltration, adenopathy, effusion), abdominal pain, diarrhea, hepatomegaly, splenomegaly, high serum alkaline phosphatase, anemia, leukopenia. The number of patients per diagnosis category who had these focal conditions are shown in Table 1 and serveral patients had more than one focal finding.

Mycobacterium avium complex (MAC) bacteremia was found in 25 cases. It is the most frequent cause (36.8%) of prolonged fever among the 68 patients with positive blood culture. A detailed description of the characteristics of 25 patients with *Mycobacterium avium* complex bacteremia is shown in Table 2. Of these 25 patients, nine patients died during hospitalization before the diagnosis was confirmed. Anti-MAC chemotherapy (clarithromycin, ethambutol) was started in eleven patients within 30 ± 6 days after diagnosis. Three patients (12%) had poor clinical evolution and died within a few months of therapy. Eight patients (32%) had good clinical evolution and presently receive follow-up care in the HIV clinic. The remaining three patients (12%) were referred to physicians in their home provinces for further management. Two patients (8%) were lost to follow-up. For the 21 patients with *Mycobacterium tuberculosis* bacteremia, three patients died during hospitalization, eleven patients had a good clinical evolution within two months of follow-up, four patients were referred to their home provincial hospitals for further management and three patients were lost to follow-up. Thus, if adding together, twenty-one patients (55.3%) of thirty-eight patients with prolonged fever and a diagnosis of tuberculosis (Table 1) had *M.tuberculosis* bacteremia.

The patients with *Mycobacterium tuberculosis* (T.B.) and *Mycobacterium avium* complex (MAC) bacteremia shared few similar symptoms and physical findings. The frequency of symptoms, signs related to mycobacteremia and pertinent laboratory data are comparable as shown in Table 3. Prolonged fever, weight loss, abdominal pain, hepatomegaly, splenomegaly and diarrhea were examples. In our study, anemia (hemoglobin < 10 g/dL) was almost universal. The leukopenia (white blood cells < 4,000 x 10^9/L) was significantly lower in those with MAC bacteremia ($P < 0.001$), Elevated serum alkaline phosphatase level (more than three times the upper normal limit) were found in the majority of patients. However, alkaline phosphatase levels were found to be significantly higher in cases with MAC bacteremia ($P = 0.002$). Weight loss of more than ten per cent of body weight within three months was found to be significantly higher in cases with MAC bacteremia ($P = 0.003$). Moreover, in patients with *Mycobacterium tuberculosis* bacteremia, there was a significant correlation between pulmonary involvement more than with MAC bacteremia ($P = 0.009$). Pulmonary parenchyma involvement was found in thirteen of twenty-one patients (61.9%) with *Mycobacterium tuberculosis* bacteremia. By contrast MAC bacteremia was found in five of twenty-five patients (20%) ($P = 0.009$). Positive sputum smear results for acid-fast bacilli were found in seven patients with TB bacteremia and only in one patient with MAC bacteremia. The abnormal roentgenographic finding was found in nine patients with *Mycobacterium tuberculosis* bacteremia and four patients with MAC bacteremia respectively. Regarding the number of previous AIDS-defining illnesses, there were twelve AIDS-defining illnesses (48%) in cases of MAC bacteremia and four (19%) in cases of *Mycobacterium tuberculosis* bacteremia ($P = 0.08$). Regarding a past history of *Pneumocystis carinii* pneumonia (PCP), PCP occurred in seven patients (28%) with MAC bacteremia and in only one patient (4.8%) with *Mycobacterium tubercu-*

Table 2. Summary of clinical features of *Mycobacterium avium* complex bacteremia in twenty-five patients with advanced HIV infection.

Case No.	Age Yr/Sex	CD4 cell count x10^6/L	Month, Year presentation	Prior opportunistic infection, months	Clinical presentation, duration, days	Associated illness	Chest radiographic findings	Antiretroviral therapy	Outcome
1	35/M	10	Mar, 97	Pulmonary TB, 12 mos	Fever, 28 d, wt loss, anemia abdominal pain, hepatomegaly	Oral candidiasis, PPE	nL	No	Improved
2	46/M	52	Mar, 97	-	Fever, 35 d, wt loss, anemia, diarrhea, 14 d	Oral candidiasis, Sinusitis	nL	No	Improved
3	27/M	3	Jul, 97	Cryptococcal meningitis, 2 mos, HZV, 6 mos	Fever, 21 d, wt loss, anemia	Oral candidiasis, PPE, Herpes labialis, Seborrheic dermatitis	nL	AZT, 3TC, crixivan	Improved
4	20/M	18	Aug, 97	-	Fever, 90 d, wt loss, anemia, diarrhea, 10 d	Oral candidiasis, Salmonella gr D Bacteremia, stool AFB+	nL	No	Improved
5	32/F	6	Aug, 97	PCP, 8 mos	Fever, 28 d, anemia, hepatomegaly	OHL	nL	DDI	Improved
6	26/M	1	Sept, 97	PCP, 24 mos	Fever, 28 d, anemia, diarrhea, 7 d	Oral candidiasis, Seborrheic dermatitis, PPE, Salmonella gr B Gastroenteritis, stool AFB+	nL	No	Improved
7	34/M	7	Oct, 97	PCP, 12 mos	Fever, 42 d, anemia, wt loss, diarrhea, 20 d, abdominal pain, 7 d	Oral candidiasis, OHL, PPE	nL	No	Died
8	39/F	6	Nov, 97	PCP, 12 mos	Fever, 90 d, wt loss, diarrhea, 18 d abdominal pain, hepatomegaly	Oral candidiasis	nL	AZT, DDC DDI, D4T	Improved
9	38/M	15	Dec, 97	-	Fever, 90 d, anemia, wt loss	Oral candidiasis, PPE	nL	No	Died
10	28/M	NA	Dec, 97	-	Fever, 84 d, wt loss, anemia	OHL, Oral candidiasis	nL	No	Died
11	23/M	13	Dec, 97	-	Fever, 56 d, wt loss, anemia, diarrhea	Oral candidiasis	nL	No	Improved
12	41/M	16	Jan, 98	PCP, HZV	Fever, 28 d, cough, wt loss, anemia diarrhea, 15 d, hepatomegaly	PPE, stool AFB+	abn	No	Died
13	32/M	4	Jan, 98	-	Fever, 21 d, wt loss, anemia, diarrhea	Oral candidiasis, Salmonella gr B bacteremia, stool AFB+	nL	AZT, DDI	Improved

Table 2. Summary of clinical features of *Mycobacterium avium* complex bacteremia in twenty-five patients with advanced HIV infection.

Case No.	Age Yr/Sex	CD4 cell count x10^6/L	Month, Year presentation	Prior opportunistic infection, months	Clinical presentation, duration, day	Associated illness	Chest radiographic	Antiretroviral therapy	Outcome
14	40/M	11	Jan, 97	-	Fever, 28 d	Oral candidiasis	nL	AZT, D4T, DDI	Improved
15	43/M	12	Feb, 97	HZV, 24 mos	Fever, 35 d, wt loss, diarrhea, 28 d abdominal pain	OHL, PPE	nL	AZT, DDI	Died
16	33/M	2	Feb, 97	Disseminated penicilliosis, 9 mos	Fever, 56 d, wt loss	Oral candidiasis	abn	No	Died
17	26/F	6	Feb, 97	PCP, 12 mos	Fever, 35 d, wt loss, diarrhea, 21 d, anemia	Oral candidiasis, PPE, Herpes labialis	abn	No	Improved
18	33/M	1	Mar, 98	-	Fever, 35 d, wt loss, anemia, hepatomegaly	OHL, PPE, Sinusitis, Liver biopsy AFB+	abn	No	Improved
19	25/M	5	Mar, 98	-	Fever, 21 d, wt loss, cough, abdominal pain, diarrhea, 14 d, hepatosplenomegaly	Oral candidiasis, Stool AFB+, Skin: pustule AFB+, pleural fluid AFB+, Alcoholism	abn	No	Improved
20	31/M	1	Apr, 98	-	Fever, 30 d, wt loss, diarrhea, 21 d, cough, anemia, hepatosplenomegaly	OHL, Oral candidiasis, Salmonella gr D bacteremia stool AFB+, Sputum: AFB+, HBsAg+	nL	No	Improved
21	27/M	13	Apr, 98	-	Fever, 60 d, wt loss, abdominal pain, hepatosplenomegaly	PPE, Diarrhea: Shigella spp. Liver biopsy AFB+	nL	AZT, DDI	Improved
22	31/M	NA	Apr, 98	PCP, 16 mos	Fever, 35 d, wt loss, abdominal pain, diarrhea, 14 d, anemia	PPE, Erythrema multiforme	nL	No	Died
23	19/M	12	May, 98	-	Fever, 21 d, wt loss, diarrhea, 14 d, anemia	Oral candidiasis, PPE	nL	No	Died
24	21/ M	5	May, 98	-	Fever, 28 d, anemia, hepatosplenomegaly	Oral candidiasis, OHL, PPE	nL	No	Died
25	44/M	119	June, 98	TB colon, 48 mos	Fever, 28 d, wt loss		nL	No	Improved

Abbreviation are as follows: NA = not available, T.B. = tuberculosis, PCP = *Pneumocystis carinii* pneumonia, HZV = *Herpes zoster* virus, PPE = papulo pruritic eruption, OHL = oral hairly leukoplakia, d = days, mos = months, wt = weight, nL = normal, abn = abnormal

Table. 3. Demographics, previous AIDS defining illness, clinical and laboratory characteristics of causes at time of *Mycobacterium avium* complex (MAC) bacteremia and *Mycobacterium tuberculosis* (TB) bacteremia*.

Characteristic	MAC with Bacteremia (n = 25)	TB with Bacteremia (n = 21)	P. value
Age (mean, years)	31.8 ± 7.7	33 ± 9.8	0.632
Sex, No. (%)			
Male	21 (84)	19 (90.5)	0.428
Female	4 (16)	2 (9.5)	
HIV risk factor, No. (%)			
Heterosexual contact	24 (96)	18 (85.7)	
Homo/Bisexual male	1 (4)	-	
Injecting drug use	-	3 (14.3)	
Unknown	-	-	
Previous AIDS-defining illness			
Yes, No (%)	12 (48)	4 (19.0)	0.08
Mean (±S.D.) time, months	10.5 ± 5.6	7 ± 4.2	0.22
Previous *Pneumocystis carinii* pneumonia, No. (%)	7 (28)	1 (4.8)	0.054
Clinical manifestations, No. (%)			
Weight (kg), mean ± S.D.	48.3 ± 5.7	53.1 ± 8.2	0.38
Weight loss > 10% body weight/3 months	20 (80)	7 (33.3)	0.003
Mean (±S.D.) time of symptoms, days	40.9 ± 20.9	30.73 ± 20.1	0.113
Only fever (≥38°C)	3 (12)	5 (23.8)	1
Fever plus abdominal pain	7 (28)	4 (19.0)	0.71
Fever plus diarrhea	14 (56)	6 (28.6)	0.116
Fever plus hepatomegaly or splenomegaly	6 (24)	4 (19.0)	0.73
Fever plus hepatospenomegaly	6 (24)	1 (4.8)	0.1
Fever plus pulmonary involvement**	5 (20)	13 (61.9)	0.009
Laboratory data:			
CD_4^+ cell count (/mm^3)			
range	1-119	8-88	
mean ± S.D.	15.1 ± 25.5	54.7 ± 23.8	<0.001
median	8.5	28	
Hemoglobin (g/dL), mean ± S.D.	7.9 ± 1.6	8.6 ± 2.3	0.258
White blood cells (x10^9/L), mean ± S.D.	2937.5 ± 989.7	6010 ± 2633.8	<0.001
SGOT (U/L), mean ± S.D.	86.0 ± 54.6	54.8 ± 35.9	0.021
SGPT (U/L), mean ± S.D.	82.9 ± 57.4	42.4 ± 17.1	0.004
Alkaline phosphatase (U/L), mean ± S.D.	437.2 ± 342.5	214.6 ± 159.1	0.002
Chest X-ray findings			
Normal, No. (%)	20 (80)	10 (47.6)	
Abnormal (infiltration, adenopathy, pleural effusion), No. (%)	5 (20)	11 (52.4)	0.047
Outcome			
Improved, No. (%)	16 (64)	18 (85.7)	
Died, No. (%)	9 (36)	3 (14.3)	0.29

* one patient may have more than one organ involvement

** pulmonary involvement = coughing, sputum AFB smear +ve, abnormal chest X-ray finding

losis bacteremia (P = 0.05). All six patients with *Cryptococcus neoformans* bacteremia had no clinical evidence of meningitis. All had positive serum cryptococcal antigen, four cases of cryptococcal bacteremia were successfully treated. *Penicillium marneffei* bacteremia was found in six patients. Two patients died within one week of admission. The other four patients responded well to amphotericin B treatment and are still regularly followed-up and on a maintenance therapy with itraconazole. This fungus is known to be endemic and highly prevalent in Thai AIDS patients who live in the upper northern provinces of Thailand, the majority of cases have skin manifestations[6] which were found only in one of our six patients.

Overall, thirty-four of one hundred and four patients with prolonged fever (32.7%) died during the study period.

DISCUSSION

Our study shows that prolonged fever occurs frequently in patients with advanced HIV infection similar to other reports and infections are frequently identified as the cause of fever[1,2,7-10]. Of 342 AIDS patients admitted to Siriraj Hospital during the 15 months period, 104 cases (30.4%) had prolonged fever. Siriraj Hospital of Mahidol University in Bangkok is the largest general hospital in Thailand with approximately 200 beds belonging to the medical service. Each day there are 3-8 adult AIDS patients in the emergency room waiting for admission. Only 15-20 per cent are ultimately admitted for care. The limitation on AIDS admission is primarily due to the need to offer a range of care covering the full spectrum of infectious diseases, non-infectious diseases as well as other conditions in this university hospital[11,12].

The cause of fever could be detected in 91 (87.5%) of the total 104 patients with findings similar to other studies[1,2,7]. Of these, the causes of prolonged fever in 68 patients (65.4%) were identified by blood culture for mycobacteria and fungus with Bactec 9240. The etiology could not be determined in 13 hospitalized AIDS patients (12.5%). This range of unidentifiable etiology is comparable to that reported in the literature[2,7,10]. AIDS-defining illnesses accounted for 85 (78.7%) of the diagnoses. Mycobacterial infections which are the leading cause cited in most reports[1,2,7,9] accounted for two-thirds of 104 cases. *Mycobacterium avium* complex (MAC) and tuberculosis were the etiologic agents in 24 per cent and 20.2 per cent of the cultures as the confirmed cause of bacteremia respectively. It should be noted that 55.3 per cent of the patients with tuberculosis in our study had bacteremia. The high yield of mycobacterial tuberculosis culture in this study may be related to the high prevalence of tuberculosis in our geographic area. However, the cause may differ in other areas, where different infections may be endemic. For example, visceral leishmaniasis has also been a frequent cause in areas where such infection is prevalent[13]. In a report by Sepkowitz[1] from the United States assessing the cause of fever longer than 14 days in an out-patient setting, the etiologic agents were mostly MAC, *P.carinii* and non-Hodgkin's lymphoma. When the result of our report and those other series[1,2,7] are combined the most frequent causes of prolonged fever are *Mycobacterium avium* complex infection and tuberculosis.

Our study demonstrated that mycobacteremia is a frequent event in prolonged fever among patients with advanced HIV infection and or suspected disseminated mycobacterial disease. With the epidemic of AIDS, mycobacteremia has been increasingly documented. In addition, *Mycobacterium tuberculosis* bacteremia has also been increasingly reported,[14-22] although less frequently than MAC[14,15,23-29]. Thus, mycobacterium blood culture has become a valuable tool for detection of mycobacteremia and is the only method used to confirm the diagnosis of disseminated MAC[27-34]. The detection of mycobacteremia in 48 of 104 cases (46.2%) suggests that mycobacterium blood culture should be a routine tool to confirm the diagnosis, particularly in patients suspected of having disseminated mycobacterial disease. The diagnosis may also be of additional help in identifying fungemia (histoplasmosis, penicillosis, cryptococcosis) as shown in this study (Table 1) and thereby, prolonging survival and quality of life once the appropriate therapy is begun.

In Thailand, one million people are estimated to be infected with human immunodeficiency virus and a cumulative total of 90,637 AIDS patients have been reported to Ministry of Public Health, Thailand from 1984 through June 1998. Of these, 24,667 have died. Approximately one-fifth of AIDS patients live in Bangkok and near-by provinces[35,36]. Between November 1995 and October 1996, the first multicenter cooperative studies were conducted to determine the prevalence of disseminated *Mycobacterium avium* complex (DMAC) in Thai AIDS patients who had prolonged fever for at least two weeks without an obvious site of infection among four hospitals in Thailand. The overall prevalence of DMAC is 14 per cent (65 /449 cases). These data alert us to the fact that disseminated MAC is not uncommon and should be considered in AIDS patients with prolonged fever. Our current study shows a rising trend. Twenty-four per cent of the patients had MAC bacteremia or disseminated MAC (DMAC) which is the most frequent bacteremia among the bacteremic patients with prolonged fever and advanced HIV infection. It was associated with high mortality and accounted for 25 cases of 342 hospitalized adult AIDS patients (7.3%). *Mycobac-*

terium avium complex (MAC) was recognized early in the AIDS pandemic as a cause of serious disseminated infection[37,38] and now, as an AIDS-defining illness, is the most common bacterial infection among advanced AIDS patients[23,24, 39,40]. It has been estimated that up to one-fourth of all AIDS patients will experience this infection during their life time[25]. In AIDS patients, bacteremia is the most common syndrome of MAC disease and with high grade bacteremia, frequently there is widespread dissemination often to the liver, spleen, bone marrow, lymph node and the patients usually have prolonged fever, weight loss, abdominal pain, diarrhea, anemia, leukopenia and elevated alkaline phosphatase[26,40]. The studies by Gordin et al[41] found that fever, weight loss, anemia suggest early manifestation of MAC disease. Pulmonary parenchymal disease in the setting of disseminated MAC occurs infrequently (< 5 per cent of cases)[40,42]. As previously mentioned, when the clinical syndrome is suggestive, a mycobacterial blood culture should be performed. However, tissue such as bone marrow and liver may be infected before bacteremia is established. Thus, if there is no limitation of work-up, and if clinically is indicated, the biopsy of tissue with acid fast bacilli staining and culture may detect disseminated MAC before the blood culture result[30,31].

Although MAC is ubiquitous and can be recovered from water, soil, food and animals, it is not clear which environment/source is responsible for human infection[43-45]. Therefore, specific recommendations for avoiding exposure are not supported at this time[46]. Interestingly, disseminated MAC is rare in Africa even though MAC was prevalent in soil and water samples from this area of the world[47,48]. There are several risk factors for development of disseminated MAC including prior *Pneumocystis carinii* pneumonia (PCP) and severe anemia[49]. By far, the most important risk factor is a low CD4 lymphocyte count[50-52]. In previous epidemiological studies when disseminated MAC was diagnosed, the median CD_4 cell counts were consistently less than 50 cells/mm^3[27,52]. The substantial morbidity and mortality are known to be associated with disseminated MAC in spite of early diagnosis and treatment. Therefore the current recommendations for treatment of disseminated MAC should include oral clarithromycin (prefered as the first agent), azithromycin (as an alternative first agent) and ethambutol, which seems to be the most rational choice for a second drug[53].

Several studies have demonstrated that the risk of disseminated MAC in patients with advanced HIV infection is high in relation to low CD_4 lymphocyte count[50-52] and disseminated MAC is a contributing factor to morbidity and mortality in the late stage of the disease[25,28,40,43]. Consequently, controlled trials have demonstrated that primary chemoprophylaxis for MAC infection can substantially decrease the incidence of disease and can prolong survival[52,54,55]. The United States Public Health Service (USPHS) and Infectious Disease Society of America (IDSA) 1997 guidelines recommended chemoprophylaxis for MAC infection as a standard of care in adult and adolescent HIV-infected patients with CD_4 cell count less than 50 cells/mm^3. Either clarithromycin or azithromycin is the preferred therapy rather than rifabutin (which is now recommended as an alternative) and found a significant reduction in the incidence of MAC bacteremia and death in the treated group[46,52,54,55]. Disseminated MAC should be ruled out by clinical assessment which included a negative blood culture before initiating a prophylactic regimen. In addition to their preventive activity for MAC disease, clarithromycin and azithromycin also confer protection against respiratory bacterial infection[46]. Whether routine MAC prophylaxis in Thailand is cost-effective as recommended by 1997 USPHS/IDSA still needs further study. More information on the incidence of MAC infection among HIV-infected patients with different CD_4 cells count in all parts of Thailand is needed.

In summary we conclude that prolonged fever in our Thai patients with advanced HIV infection (mean CD_4 cell count 27 $\pm$ 36.4 cells/mm^3, median, 13.5 cells/mm^3) is common and the two most common causes are *Mycobacterium avium* complex (MAC) and tuberculosis. Mycobacterium blood culture is a valuable tool to confirm the diagnosis of DMAC infection and disseminated tuberculosis as well as fungemia due to cryptococcosis, penicilliosis and histoplasmosis. The majority of our hospitalized AIDS patients belong to low socioeconomic status groups and have a median CD_4 count of 43.5 cells/mm^3[12] and rarely have been on antiretroviral therapy. Since

the incidence of disseminated MAC in AIDS patients is proportional to the severity of immunodeficiency status and, in our study, the median CD_4 lymphocyte counts at the time of MAC bacteremia was 8.5 cells/mm^3, thus, clinicians should be familiar with the clinical syndrome of DMAC infection which is similar to *M. tuberculosis* bacteremia to promptly initiate appropriate therapy. From a viewpoint of public health concern, a survival advantage with MAC chemoprophylaxis(54,55) should be seriously considered due to the high mortality of DMAC in spite of appropriate chemotherapy and its rising trend as showed in our study. In clinical practice we suggest following the guidelines of the 1997 USPHS/IDSA that adults and adolescents infected with HIV should receive chemoprophylaxis against disseminated MAC disease if they have CD_4 lymphocyte counts of <50 cells/mm^3(46). An oral azithromycin weekly which is affordable for Thai AIDS patients may be considered. Further study in Thailand is needed to determine the cost-effectiveness of preventing MAC disease and the usefulness of prophylactic treatment for MAC as a guide for public health measures or a national policy.

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ไข้เรื้อรังจากการติดเชื้อ *Mycobacterium avium* complex (MAC) ในผู้ป่วยติดเชื้อเอชไอวี: ปัญหาสาธารณสุขที่น่ากังวล

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ระหว่างเดือนมีนาคม 2540 ถึงเดือนมิถุนายน 2541 ผู้รายงานและคณะ ได้ศึกษาสาเหตุของไข้เรื้อรังนานกว่า 2 สัปดาห์ ในผู้ป่วยเอดส์ 104 ราย และพบสาเหตุของไข้ 91 ราย (87.5%) การเพาะเชื้อจากเลือดโดยใช้อาหารพิเศษ (Bactec media) ช่วยวินิจฉัยสาเหตุของไข้ได้ 68 ราย (65.4%) สาเหตุของไข้เกิดจาก *Mycobacterium avium* complex (MAC) bacteremia 25 ราย (24%), *Mycobacterium tuberculosis* bacteremia 21 ราย (20.2%), Cryptococcosis 6 ราย (5.8%), Penicilliosis 6 ราย (5.8%), ผู้ป่วย 25 รายที่เป็น disseminated MAC, 9 รายเสียชีวิตระหว่างรักษาในโรงพยาบาล, 3 รายเสียชีวิตใน 2–3 เดือน ขณะได้รับยาที่ถูกต้อง ลักษณะทางคลินิกของ MAC bacteremia คล้ายกับ *M. tuberculosis* bacteremia แต่พบว่าผู้ป่วยที่เป็น MAC bacteremia มีน้ำหนักลด, เม็ดเลือดขาวต่ำ, และระดับของ alkaline phosphatase สูง, อย่างมีนัยสำคัญกว่าผู้ป่วย *M. tuberculosis* bacteremia ($P < 0.05$) ในขณะที่ *M.tuberculosis* bacteremia พบความผิดปกติของระบบทางเดินหายใจมากกว่า ($P < 0.05$) เนื่องจากการเกิด disseminated MAC มีอัตราตายสูงแม้จะได้ยาต้านจุลชีพที่เหมาะสม, จึงสรุปว่า ไข้เรื้อรังจากการติดเชื้อ MAC ในผู้ป่วยเอดส์เป็นปัญหาสาธารณสุขที่น่ากังวลปัญหาหนึ่ง ผู้รายงานจึงแนะนำให้ใช้แนวทางปฏิบัติของ USPHS/IDSA, สหรัฐอเมริกา ในปี พ.ศ.2540 ที่แนะนำให้ยาป้องกันแบบปฐมภูมิแก่ผู้ติดเชื้อเอชไอวีทุกรายที่ระดับของ CD_4 lymphocyte น้อยกว่า 50 เซลล์/ลบ.มม.

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