REVIEW

LESSONS LEARNED ABOUT OPPORTUNISTIC INFECTIONS IN SOUTHEAST ASIA

Veeranoot Nissapatorn

Department of Parasitology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Abstract. Southeast Asia is a region where the number of people infected with HIV/AIDS is one of the fastest growing in the world. Tuberculosis (TB) has grown along with the HIV epidemic. TB is not only the most common AIDS-defining illness but is also the leading cause of morbidity and mortality in AIDS patients. Cryptococcosis (meningitis or disseminated) is one of the most common opportunistic infections in AIDS patients. Cryptococcal meningitis is the first in the differential diagnosis considered with meningeal irritation. Penicillosis, a unique systemic mycosis, is an important emerging public health problem and has been classified as an AIDS defining illness in endemic areas like Thailand. *Pneumocystis carinii* (*jiroveci*) pneumonia has been one of the most important opportunistic infections in AIDS patients. Among parasitic infections, cryptosporidiosis is the most common intestinal protozoan infection relating to diarrhea in AIDS patients and toxoplasmosis is the only parasitic infection of the nervous system with a substantial incidence, up to 14.8%. Cytomegalovirus (CMV) retinitis has a lower prevalence compared to other opportunistic infections. In the era of highly active antiretroviral therapy (HAART), the incidence of opportunistic infections has significantly reduced in the past few years. Subsequently, the phenomena of immune restoration inflammatory syndrome (IRIS) in AIDS patients has been reported in this region as a result of HAART.

INTRODUCTION

The first patient diagnosed with Acquired Immunodeficiency Syndrome (AIDS) in Thailand was in 1984. Since then, the increasing number of AIDS patients has been directly proportional to the number of HIV infections. Opportunistic infections (OIs) are the most common causes of morbidity and mortality in AIDS patients. The spectrum of OIs affecting HIV-infected individuals is divided into four categories: bacteria, fungi, parasites, and viruses. These OIs are not only associated with symptomatic HIV-infected patients but also are more evident with decreasing immune state (CD4 cell count < 200 cells/mm^3), which constitutes an AIDS-defining illnesses (ADI). The main systemic AIDS-related diseases are tuberculosis (TB) (pulmonary and extrapulmonary), cryptococcal meningitis (CM), *Pneumocystis carinii* (*jiroveci*) pneumonia (PCP), penicilliosis (PM), cryptosporidiosis, toxoplasmosis (TE), and cytomegalovirus (CMV) retinitis. Clinical studies relating to these OIs are mainly from Thailand, followed by Malaysia and Singapore. Recent papers from Cambodia and Vietnam have also been published. This review aims to highlight the important issues pertaining to these opportunistic infections among AIDS patients at present in Southeast Asia. This retrospective

Correspondence: Assoc Prof Dr Veeranoot Nissapatorn, Department of Parasitology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
Tel: 6-03-79676618; Fax: 6-03-79674754
E-mail: nissapat@hotmail.com

also focuses on diverse aspects, such as epidemiology, clinical management in terms of prophylaxis (primary *vs* secondary) as well as the treatment outcomes of patient with OIs in different settings.

OPPORTUNISTIC INFECTIONS DURING THE PRE-HAART ERA

Bacteria: from antiquity to resurgence

Tuberculosis (TB) is the leading opportunistic disease and cause of death among AIDS patients in this region. From 1992 to 2005, pulmonary tuberculosis (PTB) had a high prevalence (up to 85%) in HIV/TB patients and extrapulmonary tuberculosis (ETB) was found in nearly half or more of these patients as shown in Table 1. TB was clinically diagnosed in patients with a high index of suspicion, in confirmed cases, and in hospital admissions (Suwanagool *et al*, 1997; Wannamethee *et al*, 1998; Inverarity *et al*, 2002; Tansuphasawadikul *et al*, 2005). The clinical manifestations of TB in theses patients are usually typical with a higher occurrence of lymphadenopathy. Cavitations are less commonly detected on radiography due to advanced immunosuppression; which is associated with a poor granulomatous response (Putong *et al*, 2002; Tansuphasawadikul *et al*, 2005). Extensive CD4 cell depletion in HIV infection results in impaired immunity against TB, leading to the development of disseminated active TB (Putong *et al*, 2002).

The course of TB treatment depends on its location. The six month regimen is more commonly used in pulmonary TB. Whereas, a longer period is required for extrapulmonary and relapse TB cases. Adjunctive treatment with dexamethasone improves survival in patients over 14 years of age with tuberculous meningitis but probably does not prevent severe disability (Thwaites *et al*, 2004). Non-adherence or non-compliance to anti-tubercular therapy is the biggest problem and is often encountered in clinical practice when managing TB in HIV/AIDS patients. Several contributing factors such as gender (male), racial origin, intravenous drug use, low socioeconomic status, immigrants, denial of HIV status, past history of TB or TB treatment, newly diagnosed with TB, adverse drug reactions, miscommunication between medical personnel and patients, and inadequate knowledge of the disease are commonly identified causes of non-compliance (Hongthiamthong *et al*, 1994a; Tansuphasawadikul *et al*, 1998; Ngamvithayapong *et al*, 2000; Poprawski *et al*, 2000; Nissapatorn *et al*, 2003a, 2005; Rojpibulstit *et al*, 2006).

Non-compliance is more likely to increase the spread of disease, cost of treatment, relapses and drug resistance. This, therefore, calls for directly observed therapy, short course (DOTS) to be strictly implemented with close monitoring of all TB/HIV patients. The drug resistance is an issue of utmost concern and a new challenge in treating TB/HIV patients. From 1994 to 2002, varying prevalence rates from 2% to 26.6% were detected in both newly diagnosed TB and in patients previously treated with antitubercular therapy. The lower rate was found in the former, while the high rate was detected in the latter. Most studies found the resistance to isoniazid (INH) and the combination of INH and rifampicin or streptomycin were the most common causes of individual and combined drug resistances found in TB/HIV patients. HIV positivity, age < 50 years, disseminated TB, a past history of TB or its treatment, treatment in a provincial hospital, suboptimal compliance to INH preventive therapy and mortality are significant contributing factors associated with MDR-TB (Hongthiamthong *et al*, 1994a,b; Riantawan *et al*, 1998; Ruxrungtham and Phanuphak, 2001; Yoshiyama *et al*, 2001; Reechaipichitkul, 2002; Putong *et al*, 2002; Quy *et al*, 2006).

HIV prevalence is high among TB patients and is associated with MDR-TB, including a

Table 1
Summary of studies of tuberculosis in HIV/AIDS patients in Southeast Asia.

Study (Ref)	Country	No. of patients	Overall percentage (%) TB (PTB, PETB, and ETB)	Leading opportunistic infection
Thongchareon, 1992	Thailand	307	31.3; PTB: 5.9; PETB: 8.5; ETB: 16.9	(1)
		79	62.0; PTB: 12.7; PETB: 30.4; ETB: 18.9	(1)
Swasdisevi, 1994	Thailand	52	21.4; PTB; 19.2; ETB: 3.9	(3)
Mootsikapun, 1996	Thailand	88	37.2	(1)
Ruxrungtham *et al*, 1996	Thailand	446	15.0; PTB: 58; PETB: 16; ETB: 26	(1)
Tan *et al*, 1997	Singapore	29	PETB: 27.6	(2)
Suwanagool *et al*, 1997	Thailand	605	1.4; PTB: 19.7; PETB: 5.5; ETB: 17.2	(1)
Cheong *et al*, 1997	Malaysia	66	56.0	(1)
Yoong and Cheong, 1997	Malaysia	49	PTB; 14.3	(1)
Wannamethee *et al*, 1998	Thailand	266	56.4	(1)
Tansuphasawadikul *et al*, 1998	Thailand	200 TB/HIV	PTB; 42: ETB: 58	-
Wood *et al*, 1998	Malaysia	144	40.0	(1)
Amornkul *et al*, 1999	Thailand	2,104	23.3	(2)
Ismail, 2004	Malaysia	170	33.5	(1)
Tansuphasawadikul *et al*, 1999	Thailand	1,553	37.4	(1)
Proprawski *et al*, 2000	Thailand	200 TB/HIV	ETB: 58	-
Pichith *et al*, 2001	Cambodia	356	43.5; PTB: 65.2; ETB: 34.8	(1)
Chariyalertsak *et al*, 2001	Thailand	101,945	28.9	(2)
Inverarity *et al*, 2002	Thailand	229	15.0; PTB: 3; ETB: 12	(3)
Bendick *et al*, 2002	Cambodia	101	18.8	(3)
Putong *et al*, 2002	Thailand	271 TB/HIV	PTB: 35.4; PETB: 45.4; ETB: 19.2	-
Senya *et al*, 2003	Cambodia	381	26.0	(1)
Nissapatorn *et al*, 2003d	Malaysia	282	47.9; PTB: 39.4; PETB: 1.8; ETB: 6.7	(1)
Nissapatorn *et al*, 2003b	Malaysia	123	30.3; PTB: 84.6; PETB: 5.7; ETB: 9.8	(1)
Nissapatorn *et al*, 2003a	Malaysia	290 TB/HIV	PTB: 85.9; PETB: 6.6; ETB: 7.6	-
Anekthananon *et al,* 2004	Thailand	286	29.3	(1)
Bellamy *et al*, 2004	Singapore	1,742	22.7	(2)
Nissapatorn *et al*, 2004	Malaysia	205	45.4; PTB-PETB: 28.4; ETB: 17.1	(1)
Louie *et al*, 2004	Vietnam	100	37.0	(1)
Tansuphasawadikul *et al*, 2005	Thailand	59	44.0; PTB: 16.9; PETB: 27.1	(2)
Nissapatorn *et al*, 2005	Malaysia	252 TB/HIV	PTB: 70.2; PETB: 8.3	-
Kong *et al*, 2007	Cambodia	100	43; PTB: 35; ETB: 42; PETB: 23	(1)

PTB: pulmonary TB; PETB: pulmonary and disseminated TB; ETB: extrapulmonary TB; (1): The most common OI; ETB, was the most common form of TB. ETB: accounted for nearly half or more of PTB cases.

12-times higher risk of MDR-TB (Punnotok *et al*, 2000). Therefore, education of the doctor and structured treatment programs are also required to prevent increases in the prevalence of MDR-TB (Reechaipichitkul, 2002). Sputum culture and drug susceptibility testing for *Mycobacterium* spp should be obtained in all newly diagnosed TB patients who have been previously exposed to anti-tubercular drugs. Surveillance of anti-tubercular drug resistance is an important method of evaluating the quality of tuberculosis control programs and the success of MDR-TB therapy (Anunnatsiri *et al*, 2005). These strategies are urgently needed to further prevent a rise in MDR-TB cases in HIV/AIDS patients. Overall, the HIV epidemic and the emergence of drug resistance are two main contributing factors associated with the increased incidence of TB (Narain and Lo, 2004).

Fungi: from emerging to endemic

Cryptococcal meningitis (CM) is the most common fungal infection of the nervous system in AIDS patients. It is the most common opportunistic infection in northern Thailand. Fever and headache are the most common clinical manifestations of CM, which causes 60% of the mortality rate in AIDS patients (Tansuphasawadikul *et al*, 1999). Headache and neck stiffness are more common in HIV-positive patients and CM should be included in the differential diagnosis among febrile immunocompromised patients with meningeal irritation (Pichith *et al*, 2001; Huynh *et al*, 2003a; Viriyavejakul *et al*, 2004). Extrapulmonary cryptococcosis is more likely to be seen in males age < 33 years with severe immunosuppression who are not injecting drugs, and in HIV-subtype E (Amornkul *et al*, 1999, 2003). The severity of the prognosis is mainly linked to the delay before hospitalization, the possible association with other opportunistic infections, and the availability of appropriate treatment (Huynh *et al*, 2003a).

Due to the high cost of both chemoprophylaxis and treatment for cryptococcal meningitis in AIDS patients, prophylaxis is not widely used. However, prophylaxis is practiced in Thailand due to the availability of a generic drug which is cheap and easily accessible (Ruxrungtham and Phanuphak, 2001). An alternative regimen is needed as is shown in two recent studies indicating the efficacy of the combination of amphotericin B and rifampin for the initial treatment of CM (Srimuang *et al*, 2000; Chotmongkol and Methawasin, 2001). A subsequent study found this combination was not superior to treatment solely with amphotericin B (Chotmongkol *et al*, 2005). High-dose amphotericin B followed by oral azole treatment was not found to be effective in treating CM and early death was associated with a history of weight loss, a Glasgow Coma Score < 13, and hypoalbuminemia, while later mortality was related to delayed CSF yeast clearance and relapse (Pitisuttithum *et al*, 2001).

Posaconazole, an extended-spectrum triazole antifungal agent and an oral medication, has clinical activity against fungal infections of the CNS and may provide a valuable alternative to parenteral therapy in patients failing to respond to existing antifungal agents (Pitisuttithum *et al*, 2005). Prolonged use of posaconazole did not increase the risk of individual adverse events, and no unique adverse effects were observed with longer exposure to this new agent (Raad *et al*, 2006). After acute treatment, relapsed CM was reported in more than 50% of patients who had not received prophylaxis.

Itraconazole, an alternative drug to fluconazole, was an effective suppressive therapy for maintenance in AIDS-related cryptococcal meningitis (Chotmongkol and Sukeepaisarnchareon, 1997). From these comprehensive trial studies, the clinical challenges posed by *Cryptococcal* infection have led researchers to further explore novel antifungal agents in treating this opportunistic disease.

So far, no evidence of drug resistance to CM has been reported (Archibald *et al*, 2004) when compared to other parallel OI, such as tuberculosis, in this region. However, increasing *in vitro* resistance to fluconazole has been reported in Cambodian patients, which appears to be linked to extended maintenance regimens (Sar *et al*, 2004). Further studies are warranted to clarify this finding.

Penicillosis (PM), a unique endemic and systemic mycosis, is an important emerging public health problem, especially among AIDS patients, in Southeast Asia (northern Thailand), China, and India. PM was first detected in HIV-positive patients in 1990 (Supparatpinyo *et al*, 1992a). Since then, penicillosis has been regarded as one of the most common opportunistic infections besides TB, PCP, and CM (Clezy *et al*, 1994). PM is more prevalent in Thailand than in other countries in this region such as Lao PDR (Clyti *et al*, 2006), Malaysia (Rokiah *et al*, 1995; Nissapatorn *et al*, 2003d, 2004), Singapore (Kurup *et al*, 1999), and Vietnam (Huynh *et al*, 2003b; Louie *et al*, 2004).

The incidence of PM has increased markedly over the past several years in direct proportion to the increasing numbers of HIV patients (Sirisanthana, 1997). Due to its significant importance, the Ministry of Public Health, Thailand has identified penicillosis as an AIDS defining illness in addition to the standard classification of the CDC in Atlanta. Interestingly, *Penicillium marneffei* infection is subject to seasonal variation, which may provide valuable information in determining the reservoirs and recent exposure to this organism in the soil that leads to disseminated disease (Chariyalertsak *et al*, 1996, 1997). Another study suggested that transmission may occur from rodents to human or that rodents and humans are co-infected from common environmental sources (Vanittanakom *et al*, 2006).

Disseminated PM has been reported in both children and adult HIV- infected patients. It is consistently found in those with low CD4 cell counts (Supparatpinyo *et al*, 1994; Sirisanthana and Sirisanthana, 1995; Huynh *et al*, 2003b). Pneumonia is one of the most common presentations of disseminated penicillosis (Pothirat *et al*, 1995; Deesomchok and Tanprawate, 2006). Although, the prognosis is generally good, it depends on the ability of the physician to make the diagnosis and start early treatment (Vanittanakom and Sirisanthana, 1997).

The standard regimen used for PM is either amphotericin B alone which is effective but requires a prolonged hospital stay or an alternative regimen of amphotericin B and itraconazole, which has been shown to be effective and safe in treating disseminated PM (Sirisanthana *et al*, 1998). Relapses are quite common in disseminated penicillosis patients (up to 50%) within 6 months after completion of treatment, regardless of the initial antifungal therapy (Supparatpinyo *et al*, 1992b, 1993, 1994, 1998). Itroconazole has been recommended for lifelong secondary prophylaxis or maintenance in HIV-positive patients (Sirisanthana, 1997).

Pneumocystis carinii (*jiroveci*) pneumonia (PCP) has historically been one of the most important opportunistic infections in AIDS patients. It is one of the most common causes of interstitial pneumonitis found in these patients (Tansuphasawadikul *et al*, 2005). Most diagnoses of PCP infection are made on a presumptive basis which may not accurately reflect the true incidence of PCP in many settings. The incidence of PCP remains high probably because of a lack of knowledge regarding HIV infection and its consequences, late presentation to medical care, lack of chemoprophylaxis and inaccessibility to HAART (Kay-Thwe-Han *et al*, 2003; Anekthananon *et al*, 2004). Primary chemoprophylaxis against PCP is generally recommended in asymptomatic HIV positive patients. This was not done in the early decade of HIV infection and many patients still have

not received prophylaxis, particularly in endemic areas like Thailand, Cambodia (Swasdisevi, 1994; Chariyalertsak *et al*, 2001; Senya *et al*, 2003; Anekthananon *et al*, 2004) Vietnam or Indonesia, where the incidence of this OI is unclear. PCP continues to be a major public health problem due to the steadily increasing number of HIV/AIDS patients and drug resistant HIV infections (Morris *et al*, 2004).

CMV: from uncertain to future concern

CMV retinitis is the most important opportunistic viral infection associated with AIDS. Approximately 5.8 million cases have occurred in this region (Linda, 2003). The incidence of CMV is generally reported as low due to poor case detection clinically. It is often only detected in advanced stages of visual impairment. There is also limited access to laboratory tests (Inverarity *et al*, 2002). About 25% of AIDS patients in Singapore have been affected by CMV retinitis. This is the most prevalent ocular infection to cause visual loss. Recognizing the ophthalmic signs in HIV patients could facilitate early diagnosis. Prompt treatment could prevent or delay blindness, which is psychologically and functionally important in these patients (Lim *et al*, 1997). It was also shown to be one of the three most common opportunistic infections relating to the nervous system before and after HAART introduction (Subsai, 2004, 2006). Due to the high cost of both prophylaxis and treatment, most patients are unfortunately left untreated until they are completely blind and die from other HIV-related illnesses (Ruxrungtham and Phanuphak, 2001). With inconsistent HAART distribution, CMV retinitis presents a bleak outcome for these patients.

Parasites: from HIV and AIDS

Parasites are common causes of opportunistic infection in AIDS patients. Cryptosporidiosis, isosporiasis and toxoplasmosis have been categorized by the CDC as AIDS defining illnesses. Diarrhea is a common complaint in HIV/AIDS patients. Diarrhea has been found in 46% to 48% HIV-infected children (Sirisanthana *et al*, 1993; Chearskul *et al*, 1995, 1996). Cryptosporidiosis and isosporiasis are the two most common intestinal protozoan parasites causing diarrhea and pose a public health problem in AIDS patients. The prevalence (≤ 5%) of isosporiasis has decreased over the past few years, due mainly to the sensitivity and efficacy of primary chemoprophylaxis (Cotrimoxazole) against *Pneumocystic carinii* pneumonia (PCP) as shown in Table 2.

The prevalence of cryptosporidiosis, particularly in Thailand and Malaysia, has also decreased, whereas, recent studies from Cambodia still show a very high prevalence (13-40%) (Chin *et al*, 2006; Kong *et al*, 2007). In clinical cryptosporidiosis, chronic diarrhea with watery stools, weight loss and dehydration are the prominent features in symptomatic patients (Moolasart *et al*, 1995; Manatsathit *et al*, 1996). Moreover, cryptosporidiosis occurs in AIDS patients when the CD4 cell count is less than 200 cells/mm^3 (Wiwanitkit, 2001; Nissapatorn *et al*, 2003d; Lim *et al*, 2005). To date, no specific drug has been shown to be effective against this infection. Therefore, it was a breakthrough event when HAART was introduced in HIV/AIDS patients. One recent study found no oocysts of *Cryptosporidium* spp were detected in patient stools who were on antiretroviral therapy (Wiwanitkit and Srisupanant, 2006).

It is important to note the presence of *Microsporidium* spp in symptomatic HIV patients particularly in Thailand, even though it has not been included as an AIDS defining illness. This parasitic infection has the highest prevalence (1.7-33.3%) among related parasites. The prevalence was shown to be higher in children than adult HIV patients due to inconsistency in previous studies which detected this pathogen mainly in HIV-infected children.

Table 2
Summary of studies of GI parasitic infections in HIV/AIDS patients in Southeast Asia.

Study (Ref)	Country	Period	No. patients	Population	Diagnosis	Percent (%)
Thongchareon, 1992	Thailand	1987-1992	307	AIDS	Stool	4.6-*Cryptosporidium*
Shekhar *et al*, 1993	Malaysia	-	Case report	AIDS	Stool	*Isospora*
Kamel *et al*, 1994	Malaysia	1992	100	HIV	Stool	23-*Cryptosporidium*
Moolasart *et al*, 1995	Thailand	1988-1993	250	HIV (A+C)[a]	Stool	8.8-*Cryprosporidium*
Manatsathit *et al*, 1996	Thailand	1995	45	AIDS	Stool, Bx, EGDS	
					Aspirate, colonoscopy	20-*Cryptosporidium*
Punpoowong *et al*, 1998	Thailand	1994-1995	22	HIV	Stool	9-*Cryptosporidium*
						27.3-*Microsporidium*
						4.5-*Isospora*
Uga *et al*, 1998	Thailand	1997	61	HIV (A+C)	Stool	10-*Cryptosporidium*
Wanachiwanawin *et al*, 1998	Thailand	1996-1996	66	HIV (C)	Stool	33.3-*Microsporidium*
Chokephaibulkit *et al*, 2001	Thailand	1997-1998	82	HIV (C)	Stool	6-*Cryptosporidium*
						19.5-*Microsporidium*
						3.6-C+M
Leelayoova *et al*, 2001	Thailand	1999-2000	141	HIV (C)	Stool	7.1-*Cryptosporidium*
						7.1-*Microsporidium*
Waywa *et al*, 2001	Thailand	1999-2000	288	AIDS	Stool	19.2-*Cryptosporidium*
						4.5-*Isospora*
						11-*Microsporidium*
Wiwanitkit, 2001	Thailand	2000	60	HIV	Stool	3-*Cryptosporidium*
						5-*Isospora*
Saksirisampant *et al*, 2002	Thailand	2001	156	HIV(A+C)	Stool	12.8-*Cryptosporidium*
Wanachiwanawin *et al*, 2002	Thailand	1996-2000	95	HIV (C)	Stool	25.3-*Microsporidium*
						12.5-*Cryptosporidium*
Lim *et al*, 2005	Malaysia	2004	66	HIV	Stool	3-*Cryptosporidium*
Wiwanitkit and Srisupanant, 2006	Thailand	2003	40	HIV	Stool	2.5-*Cryptosporidium* without HAART
						Nil with HAART
Chin *et al*, 2006	Cambodia	<2006	40	HIV	Stool/PCR	40-*Cryptosporidium*

[a]HIV (A+C) means children and adult HIV patients

In 1995, the first case of microsporidiosis was reported and found clinically related to acute and chronic diarrhea (Pitisutithum *et al*, 1995; Leelayoova *et al*, 2001). Interestingly, most studies found that *Cryptosporidium* spp was the most common intestinal parasitic co-infection with *Microsporidium* spp (Punpoowong *et al*, 1998; Chokephaibulkit *et al*, 2001; Leelayoova *et al*, 2001; Waywa *et al*, 2001; Wiwanitkit, 2001; Wanachiwanawin *et al*, 2002). However, there is no effective drug to treat this pathogen. Higher prevalences of these opportunistic intestinal parasitic infections are found related to CD4 cell counts of less than 200 cells/mm^3. Primary effectiveness of prevention and control strategies against these parasitic infections should be practically implemented in HIV/AIDS patients particularly in poor resource settings.

An epidemiological study carried out in Malaysia and Thailand on HIV/AIDS patients revealed seroprevalence rates of latent *Toxoplasma* infection as 21% to 53.7% (Wongkamchai *et al*, 1995, 1999; Sukthana *et al*, 2000; Shamilah *et al*, 2001; Wanachiwanawin *et al*, 2001; Nissapatorn *et al*, 2001, 2002, 2003a-e, 2004, 2005a,b, 2007). This is a great help in better understanding *Toxoplasma* infection and its consequences. Hence, screening for *Toxoplasma* serostatus is recommended for all newly diagnosed HIV-infected patients, particularly in this region where *Toxoplasma* prevence is high. Preventive behavioral practices, such as eating well-cooked meat, washing hands after outdoor activities involving soil and cat contact, should also be routinely practiced by these patients to avoid primary *Toxoplasma* infection. Toxoplasmosis is the only parasitic infection and the most common cause of intracerebral lesions found in AIDS patients. The majority of toxoplasmic encephalitis (TE) cases are the result of secondary reactivation of latent *Toxoplasma* infection; few cases are due to primary *Toxoplasma* infection.

In this region, up to 14.8% incidence rate of TE, which is comparatively high (Swasdisevi, 1994; Haniffah *et al*, 1996; Ruxrungtham *et al*, 1996; Chariyalertsak *et al*, 2001; Pichith *et al* 2001; Iverarity *et al*, 2002; Senya *et al*, 2003; Nissapatorn *et al*, 2003c-e, 2004, 2005; Anekthananon *et al*, 2004; Bellamy *et al*, 2004; Subsai *et al*, 2004, 2006) and is directly proportional to the prevalence of *Toxoplasma* infection and the number of AIDS patients. TE is based on the following criteria for presumptive diagnosis: neurological manifestations, such as headache and hemiparesis, which are the most common presentations, a CT scan showing typical single or multiple ring enhancing lesions, a CD4 cell count less than 100 cells/mm^3 with or without evidence of *Toxoplasma* serostatus and responding well to anti-*Toxoplasma* therapy. However, TE is still rarely encountered due to difficulties in diagnosis (Pichith *et al*, 2001) in certain countries. TE is a life-threatening but treatable condition with a high treatment success rate.

Relapse of TE has been reported in AIDS patients (Nissapatorn *et al*, 2003c-d, 2004, 2005; Bellamy *et al*, 2004). This is due mainly to non-compliance with therapy, its side effects and discontinuation of secondary prophylaxis. No specific drug has been proven to target the cystic (tissue cyst) stage of the *Toxoplasma* parasite which causes the relapse of TE.

Opportunistic infections are the major cause of death in HIV/AIDS patients. The severity depends on the type (organism and acute/chronic) and single or multiple episodes of OIs at the time a patient is infected. In general, a presumptive diagnosis has been used to avoid the extensive work-up and perform invasive diagnostic procedures in HIV-infected patients. Frequently, the diagnosis is correct. If it is incorrect, a definite diagnosis might never be made since autopsy on HIV patients is rarely performed (Ruxrungtham and Phanuphak, 2001). Therefore, the official

causes of death in AIDS patients are usually made from medical records, as was shown in one previous study where MAC infection was identified as the most frequent principal cause of death, followed by TB, pneumonia (unknown cause), CM, and PCP. The most frequent causes of death were TB, and systemic CMV disease found among AIDS patients in Singapore (Bellamy *et al*, 2004). Necropsy studies were conducted in clarifying the cause of death in patients in Thailand where a report case of a coinfection with CMV and *Cryptosporidium* was found in an AIDS patient (Viriyavejakul *et al*, 1999). Another study found that cryptococcal meningitis was the most common ADI found in 117 liver specimens, followed by tuberculosis, CMV infection, and penicillosis. It also showed that CM, CMV, PM, and bacterial pneumonia were equally distributed (2 cases for each disease) and 1 case each for cryptosporidiosis and PCP, while the lungs were the most common location for infection, followed by the liver and intestine in 17 HIV-infected patients. Based on these necropsy studies, biopsy and appropriate diagnostic procedures may help in the early diagnosis of opportunistic infections and in early HIV infection. These studies were the first kind of surveillance in Southeast Asia which recommended monitoring of opportunistic infections in HIV/AIDS patients (Viriyavejakul *et al*, 2000, 2002).

PRIMARY CHEMOPROPHYLAXIS *VS* HAART: A DILEMMA IN CLINICAL PRACTICE FROM THE PRE-TO POST-HAART ERA?

An important question is whether primary chemoprophylaxis is still necessary against opportunistic infections in HIV-infected patients in this present situation where antiretroviral therapy is available. In order to answer this question, several factors should be taken into consideration. With tuberculosis, isoniazid (INH) preventive therapy (IPT) was recommended if a tuberculin skin test (TST) positive in HIV-infected patients. It is not feasible to reduce the risk of developing active TB in PPD positive HIV-infected patients (Anonymous, 1999). Recent studies suggested TST screening and HIV testing should be done together to assess the prevalence of latent TB, particularly in areas where HIV infection is endemic, such as in Thailand (Hiransuthikul *et al,* 2005a). However, TST screening is not a predictor of adherence to IPT once therapy began, but was associated with a higher drop-out rate prior to therapy (Hiransuthikul *et al*, 2005a). In this region, such a program is not widely recommended due to the induction of drug-resistant mycobacterium if compliance is suboptimal and there is physician non-adherence to the IPT guidelines which may affect the efficacy and feasibility of tuberculosis chemoprophylaxis (Ruxrungtham and Phanuphak, 2001; Louie *et al*, 2004; Hiransuthikul *et al*, 2005a).

While, standard chemoprophylaxis for PCP, cryptococcal meningitis and penicillosis is recommended due to their high prevalence, low cost and wide availability of generic drugs (Ruxrungtham and Phanuphak, 2001), prophylactic against PCP might confer little effect in a country like Vietnam (Louie *et al*, 2004). In certain opportunistic diseases, such as CMV retinitis and MAC infection, primary chemoprophylaxis is not practical due to its cost, as reported in Thailand (Ruxrungtham and Phanuphak, 2001).

Regarding toxoplasmosis, one study showed the incidence was significantly reduced in patients receiving standard primary chemoprophylaxis when compared to patients without receiving it (Nissapatorn *et al*, 2004). However, the incidence of toxoplasmosis was not different between patients receiving and not receiving chemoprophylaxis, probably due to the low event rate (Anekthananon *et al*, 2004). Another study showed the incidence of TE was not reduced despite the use of

Cotrimoxazole, therefore it was suggested that an optimal regimen for primary chemoprophylaxis for TE should be studied and implemented, particularly in endemic areas for toxoplasmosis (Subsai *et al*, 2004). Primary chemoprophylaxis is still recommended for all HIV-infected patients with low CD4 cell counts (adjusted by clinicians) regardless of *Toxoplasma* serostatus. Prophylaxis against specific OIs may benefit patients who are not ready or able to take HAART or in others who tried HAART regimens but the therapy failed (Anekthananon *et al*, 2004). Primary chemoprophylaxis is continuing to be used and benefits patients who are unable to afford HAART.

The role of HAART is of great interest regarding the life-expectancy of patients living with HIV/AIDS. Recent studies have shown the incidence of opportunistic infections is remarkably reduced in the HAART era (Subsai *et al*, 2006; Wiwanitkit and Srisupanant, 2006; Lian *et al*, 2007). HAART plays an important role in improving immune function and when combined with primary chemoprophylaxis, it drastically reduces morbidity and mortality in HIV-infected patients (Anekthananon *et al*, 2004). Nevertheless the immune restoration disease (IRD) is seen with the commencement of HAART. However, there is very little data regarding this complication reported in this region, due to the fact that the majority of HIV-infected patients are still unable to access HAART.

Recent studies have reported IRD in adult AIDS patients with the common neurological opportunistic infections as being toxoplasmic encephalitis, cryptococcal meningitis, and CMV retinitis (Subsai *et al*, 2006). Other opportunistic infections included tuberculosis (Bonnet *et al*, 2006) with a particularly high proportion of extrapulmonary TB involvement (Manosuthi *et al*, 2006). In children, IRD has been shown to be associated with mycobacterial and nonmycobacterial organisms, varicella zoster, herpes simplex, and cryptococcal meningitis in advanced stages of disease (Puthanakit *et al*, 2005,2006a,b). IRD are more commonly seen relating to AIDS defining illnesses in adult patients and necessary measures should be taken to curb the incidence of IRD in the future where HAART is available on a larger scale for HIV-infected patients.

HAART is the best option for restoring immune status and reducing the incidence of opportunistic infections while improving the quality of life in HIV-infected patients. However, HAART is still too expensive for many HIV/AIDS patients who are largely living in marginalized conditions. More time, decades even, may be needed to solve this problem in Southeast Asia.

CONCLUSION

The following recommendations are proposed to control HIV/AIDS. Primary health promotion and awareness should not be delayed, particularly in endemic countries like Cambodia, Indonesia, Myanmar, Lao PDR, Philippines, and Vietnam and should be consistently implemented in countries like Malaysia, Singapore, and Thailand to further achieve prevention of the spread of HIV infection. More clinical research should be carried out regarding opportunistic infections in HIV/AIDS patients, especially around the Mekong region (Cambodia, Lao PDR, Myanmar, and Vietnam), Indonesia and Philippines where there is little data regarding this problem. Primary chemoprophylaxis is affordable particularly for the main opportunistic infections, such as PCP, cryptococcal meningitis, toxoplasmosis, and penicillosis, which are needed in the majority of HIV/AIDS patients who are poor and do not have access to HAART. AIDS defining illnesses should be classified according to regional variations, due to the fact that certain diseases may not occur in some regions. This would be helpful in managing OIs in these patients. Reference and multicenter studies for major or endemic opportunistic infections, such as

tuberculosis, toxoplasmosis, and others, should be established in this region. This could help to strengthen regional collaborations in terms of infrastructure and provide expertise and funding in specific areas of interest to more limited resource settings. Novel drugs, including herbal medicine, are cheaper and more affordable, and are desperately needed to reduce the cost of treatment, particularly in public hospitals. Lastly, vaccine trials have been carried out since 1994 but, their results have not yet fulfilled the dream of HIV eradication worldwide. It is hoped the trend in new HIV infections will not continue to increase in this region.

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