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/mm³), 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), penicillosis (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
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 these 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.

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Country</th>
<th>No. of patients</th>
<th>Overall percentage (%)</th>
<th>TB (PTB, PETB, and ETB)</th>
<th>Leading opportunistic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thongchareon, 1992</td>
<td>Thailand</td>
<td>307</td>
<td>31.3; PTB: 5.9; PETB: 8.5; ETB: 16.9</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Swasdisevi, 1994</td>
<td>Thailand</td>
<td>79</td>
<td>62.0; PTB: 12.7; PETB: 30.4; ETB: 18.9</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Mootskapun, 1996</td>
<td>Thailand</td>
<td>88</td>
<td>21.4; PTB: 19.2; ETB: 3.9</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Ruxrungtham et al, 1996</td>
<td>Thailand</td>
<td>446</td>
<td>15.0; PTB: 58; PETB: 16; ETB: 26</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Tan et al, 1997</td>
<td>Singapore</td>
<td>29</td>
<td>PETB: 27.6</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Suwanagool et al, 1997</td>
<td>Thailand</td>
<td>605</td>
<td>1.4; PTB: 19.7; PETB: 5.5; ETB: 17.2</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Cheong et al, 1997</td>
<td>Malaysia</td>
<td>66</td>
<td>56.0</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Yoong and Cheong, 1997</td>
<td>Malaysia</td>
<td>49</td>
<td>PTB: 14.3</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Wannamethee et al, 1998</td>
<td>Thailand</td>
<td>266</td>
<td>56.4</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Tansuphasawadikul et al, 1998</td>
<td>Thailand</td>
<td>200 TB/HIV</td>
<td>PTB: 42; ETB: 58</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Wood et al, 1998</td>
<td>Malaysia</td>
<td>144</td>
<td>40.0</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Amomkul et al, 1999</td>
<td>Thailand</td>
<td>2104</td>
<td>23.3</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Ismail, 2004</td>
<td>Malaysia</td>
<td>170</td>
<td>33.5</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Tansuphasawadikul et al, 1999</td>
<td>Thailand</td>
<td>1,553</td>
<td>37.4</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Proprawski et al, 2000</td>
<td>Thailand</td>
<td>200 TB/HIV</td>
<td>ETB: 58</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Pichith et al, 2001</td>
<td>Cambodia</td>
<td>356</td>
<td>43.5; PTB: 65.2; ETB: 34.8</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Charyalentsak et al, 2001</td>
<td>Thailand</td>
<td>101,945</td>
<td>28.9</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Inverarity et al, 2002</td>
<td>Thailand</td>
<td>229</td>
<td>15.0; PTB: 3; ETB: 12</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Bendick et al, 2002</td>
<td>Cambodia</td>
<td>101</td>
<td>18.8</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Putong et al, 2002</td>
<td>Thailand</td>
<td>271 TB/HIV</td>
<td>PTB: 35.4; PETB: 45.4; ETB: 19.2</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Senya et al, 2003</td>
<td>Cambodia</td>
<td>381</td>
<td>26.0</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Nissapatom et al, 2003d</td>
<td>Malaysia</td>
<td>282</td>
<td>47.9; PTB: 39.4; PETB: 1.8; ETB: 6.7</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Nissapatom et al, 2003b</td>
<td>Malaysia</td>
<td>123</td>
<td>30.3; PTB: 84.6; PETB: 5.7; ETB: 9.8</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Nissapatom et al, 2003a</td>
<td>Malaysia</td>
<td>290 TB/HIV</td>
<td>PTB: 85.9; PETB: 6.6; ETB: 7.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anekthananon et al, 2004</td>
<td>Thailand</td>
<td>286</td>
<td>29.3</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Bellamy et al, 2004</td>
<td>Singapore</td>
<td>1,742</td>
<td>22.7</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Nissapatom et al, 2004</td>
<td>Malaysia</td>
<td>205</td>
<td>45.4; PTB-PETB: 28.4; ETB: 17.1</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Louie et al, 2004</td>
<td>Vietnam</td>
<td>100</td>
<td>37.0</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Tansuphasawadikul et al, 2005</td>
<td>Thailand</td>
<td>59</td>
<td>44.0; PTB: 16.9; PETB: 27.1</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Nissapatom et al, 2005</td>
<td>Malaysia</td>
<td>252 TB/HIV</td>
<td>PTB: 70.2; PETB: 8.3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kong et al, 2007</td>
<td>Cambodia</td>
<td>100</td>
<td>43; PTB: 35; ETB: 42; PETB: 23</td>
<td>(1)</td>
<td></td>
</tr>
</tbody>
</table>

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 (Ruxrunghtham 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 Sukkeeponsamchareon, 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 (Sirisantha, 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; Sirisantha and Sirisantha, 1995; Huynh et al, 2003b). Pneumonia is one of the most common presentations of disseminated penicillosis (Pothirat et al, 1995; Deesonomchok 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 Sirisantha, 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 (Sirisantha 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). Itraconazole has been recommended for lifelong secondary prophylaxis or maintenance in HIV-positive patients (Sirisantha, 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 (Ruxruntham 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 Pneumocystis 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<sup>3</sup> (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 Srisupanan, 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.

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Country</th>
<th>Period</th>
<th>No. patients</th>
<th>Population</th>
<th>Diagnosis</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shekhar et al, 1993</td>
<td>Malaysia</td>
<td>-</td>
<td>100</td>
<td>AIDS</td>
<td>Stool</td>
<td>Isospora</td>
</tr>
<tr>
<td>Kamel et al, 1994</td>
<td>Malaysia</td>
<td>1992</td>
<td>100</td>
<td>HIV</td>
<td>Stool</td>
<td>23-Cryptosporidium</td>
</tr>
<tr>
<td>Wanachiwanawin et al, 1998</td>
<td>Thailand</td>
<td>1996-1996</td>
<td>66</td>
<td>HIV (C)</td>
<td>Stool</td>
<td>33.3-Microsporidium</td>
</tr>
<tr>
<td>Chokephaibulkit et al, 2001</td>
<td>Thailand</td>
<td>1997-1998</td>
<td>82</td>
<td>HIV (C)</td>
<td>Stool</td>
<td>6-Cryptosporidium, Microsporidium, 3.6-C+M</td>
</tr>
<tr>
<td>Leelayoova et al, 2001</td>
<td>Thailand</td>
<td>1999-2000</td>
<td>141</td>
<td>HIV (C)</td>
<td>Stool</td>
<td>7.1-Cryptosporidium, Microsporidium</td>
</tr>
<tr>
<td>Wiwanitkit, 2001</td>
<td>Thailand</td>
<td>2000</td>
<td>60</td>
<td>HIV</td>
<td>Stool</td>
<td>4.5-Isospora</td>
</tr>
<tr>
<td>Saksirisampant et al, 2002</td>
<td>Thailand</td>
<td>2001</td>
<td>156</td>
<td>HIV(A+C)</td>
<td>Stool</td>
<td>12.8-Cryptosporidium</td>
</tr>
<tr>
<td>Wanachiwanawin et al, 2002</td>
<td>Thailand</td>
<td>1996-2000</td>
<td>95</td>
<td>HIV (C)</td>
<td>Stool</td>
<td>25.3-Microsporidium</td>
</tr>
<tr>
<td>Lim et al, 2005</td>
<td>Malaysia</td>
<td>2004</td>
<td>66</td>
<td>HIV</td>
<td>Stool</td>
<td>12.5-Cryptosporidium</td>
</tr>
<tr>
<td>Wiwanitkit and Srisupanant, 2006</td>
<td>Thailand</td>
<td>2003</td>
<td>40</td>
<td>HIV</td>
<td>Stool</td>
<td>3-Cryptosporidium</td>
</tr>
<tr>
<td>Chin et al, 2006</td>
<td>Cambodia</td>
<td>&lt;2006</td>
<td>40</td>
<td>HIV</td>
<td>Stool/PCR</td>
<td>2.5-Cryptosporidium without HAART</td>
</tr>
</tbody>
</table>

*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/mm³. 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, 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/mm³ 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 co-infection 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.

ACKNOWLEDGEMENTS

The author would like to thank the University of Malaya for funding this literature review that was presented at the World Aids Day China (WADC) in Tianjin during 1-3 December, 2006.

REFERENCES


Clezy K, Sirisanthana T, Sirisanthana V, Brew B, Cooper DA. Late manifestations of HIV in Asia and the Pacific. AIDS 1994; 8: S35-43


Rojpibulstit M, Kanjanakiritamrong J, Chong-


Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated Penicillium marneffei infections and


Wiwanitkit V. Intestinal parasitic infections in Thai HIV-infected patients with different immunity status. BMC Gastroenterol 2001; 1: 3.


