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Regional Differences in the Prevalence of Major Opportunistic Infections among Antiretroviral-Naïve Human Immunodeficiency Virus Patients in Japan, Northern Thailand, Northern Vietnam, and the Philippines

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Abstract. To identify regional differences in the distribution of opportunistic infections (OIs) among human immunodeficiency virus (HIV)-infected patients in Asia, the medical records of antiretroviral therapy (ART)-naïve patients who attended the following tertiary hospitals from 2003 to 2011 were reviewed: Nagoya Medical Center (NMC, Nagoya, Japan), Lampang Hospital (LPH, Lampang, northern Thailand), Bach Mai Hospital (BMH, Hanoi, northern Vietnam), and Philippine General Hospital (PGH, Manila, Philippines). Logistic regression analyses were performed to identify associations between country of origin and risk of major OIs. In total, 1,505 patients were included: NMC, $N = 365$; LPH, $N = 442$; BMH, $N = 384$; and PGH, $N = 314$. The median age was 32 years, and 73.3% of all patients were male. The median CD4 count was 200 cells/μL. Most patients at NMC and PGH were men who have sex with men. Injection drug users were most common at BMH (35.7%). *Mycobacterium tuberculosis* (TB) was most common at PGH ($N = 75$) but was rare at NMC ($N = 4$). *Pneumocystis* pneumonia (PCP) prevalence was highest at NMC ($N = 74$) and lowest at BMH ($N = 13$). Multivariable logistic regression showed increased odds of TB at PGH (adjusted odds ratio [aOR] = 42.2, 95% confidence interval [CI] = 14.6–122.1), BMH (aOR = 12.6, CI = 3.9–40.3), and LPH (aOR = 6.6, CI = 2.1–21.1) but decreased odds of PCP at BMH (aOR = 0.1, CI = 0.04–0.2) and LPH (aOR = 0.2, CI = 0.1–0.4) compared with those at NMC. The cryptococcosis risk was increased at LPH (aOR = 6.2, CI = 0.9–41.0) compared with that at NMC. Cytomegalovirus (CMV) retinitis prevalences were similar in all countries. OI prevalence remained high among ART-naïve patients in our cohort. The risks of TB, PCP, and cryptococcosis, but not CMV retinitis, differed between countries. Improved early HIV detection is warranted.

INTRODUCTION

The clinical characteristics of human immunodeficiency virus (HIV)-infected patients before initiating antiretroviral therapy (ART) vary between developed and developing countries and are influenced by sociodemographic factors, geographic distribution of pathogens,[1,2] access to health care,[3] host genetic factors,[4] and virus subtypes.[5]

A range of HIV-associated risk groups has previously been identified in Asia; these groups include men who have sex with men (MSM) in Japan and the Philippines, injection drug users (IDUs) in Vietnam and southern China, and female sex workers and their clients in other Asian countries.[6] Among newly diagnosed HIV-infected patients, the prevalence of acquired immune deficiency syndrome (AIDS) also varies widely from 10% in Taiwan[7] to 30% in Japan[8] and New Zealand[9] and 53% in Bangkok, Thailand.[10] A study in Cambodia reported that 100% of newly diagnosed HIV-infected patients had AIDS.[11]

The major opportunistic infections (OIs) in Asia are extrapulmonary *Mycobacterium tuberculosis* (TB), cryptococcosis, and *Pneumocystis* pneumonia (PCP).[6,12] The predominant AIDS-defining illnesses in Thailand are TB, PCP, and cryptococcosis,[13] whereas those in Japan are PCP, cytomegalovirus (CMV) infection, and candidiasis according to a recent report from the Japanese Ministry of Health, Labor and Welfare.[14] In two different HIV care facilities in Ho Chi Minh City, Vietnam, oral candidiasis and TB were reported to be major OIs, but PCP was reported to be uncommon.[15,16] Disseminated *Penicillium marneffei* infection, that is, penicilliosis, is another well-known unique opportunistic mycosis in the northern Indochina region.[6] However, there have been no comprehensive reports regarding HIV-related illnesses from the Philippines in the ART era.

Despite the diversity of results produced in individually published studies, a systematic comparison of the prevalence of HIV-related OIs among Asian countries has not been performed. Accordingly, we aimed to describe the demographic and clinical characteristics of newly diagnosed HIV patients at four tertiary hospitals providing HIV care in Japan, northern Thailand, northern Vietnam, and the Philippines and to investigate the factors associated with major HIV-related OIs adjusting for country of origin, age, sex, HIV-related risk behaviors, and immune status at the time of HIV diagnosis.

MATERIALS AND METHODS

Study design and data collection. We included all ART-naïve patients ≥ 15 years old with an available initial CD4 + T-cell count (CD4 count) who were enrolled/registered at the following sites: Nagoya Medical Center (NMC; Nagoya, Japan), Lampang Hospital (LPH; Lampang, northern Thailand), Bach Mai Hospital (BMH; Hanoi, northern Vietnam), and Philippine General Hospital (PGH; Manila, Philippines).

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Age, sex, self-reported mode of HIV transmission, baseline CD4 count (cells/μL), clinical stage at the time of HIV diagnosis, and OIs diagnosed at the initial visit before initiation of ART were collected from patients' medical records. Patients who were initially registered at the hospitals during the following periods were included: NMC, October 2008 to November 2011; LPH, January 2003 to December 2010; BMH, October 2009 to September 2010; and PGH, January 2004 to December 2011.

Study sites. All four study sites are government-funded hospitals that provide HIV treatment within each country. NMC is a tertiary hospital located in Nagoya City, one of the largest cities in Japan. NMC is a referral hospital for the AIDS treatment core hospitals that are located in the central region of Japan, serving three other surrounding prefectures. LPH is the largest government referral hospital in northern Thailand and is located in Lampang Province, which has the fifth highest prevalence of HIV in Thailand.[17] LPH has an HIV clinic that has provided HIV testing and medical treatment since 1995. BMH is the largest tertiary hospital in northern Vietnam. The Department of Infectious Diseases officially launched the HIV Outpatient Clinic and the HIV Admission Ward in November 2009, which provides free ART. BMH also functions as a voluntary counseling and testing site. PGH is the largest tertiary hospital in the Philippines and is located in the capital city of Manila. In 1995, PGH established the STD-AIDS Guidance Intervention Prevention Unit, where both walk-in patients and interhospital referrals can receive anonymous testing for HIV as well as ART.

Reporting of OIs. In this study, clinical stage was categorized based on the World Health Organization–revised clinical staging of HIV/AIDS.[18] Each OI was diagnosed at each study site as outlined by their local or international guidelines, which included the following: the anti-HIV treatment guidelines by the Ministry of Health, Labor and Welfare, Japan,[19] the Clinical Management of HIV/AIDS Patients at Day Care Centers in LPH,[20] the Guidelines for HIV/AIDS Diagnosis and Treatment by the Vietnam Ministry of Health,[21] and the Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos (Supplemental Table 1).[22] All OIs diagnosed before the initiation of ART were collected. Disease recurrences were not included.

Statistical analyses. Chi-square tests were used to identify differences in the categorical variables between countries, and Kruskal–Wallis tests were performed to compare continuous variables. The proportion of HIV-related illnesses was calculated in patients with stage 3 or 4 HIV/AIDS. Of the HIV-related illnesses, TB, PCP, cryptococcosis, CMV retinitis, and herpes zoster were considered as major HIV-related infections in Asia based on previous publications[6] and the fact that their diagnoses were less likely to be influenced by limited access to endoscopy, pathological examinations, or advanced microbiological techniques such as polymerase chain reaction or blood culture of *Mycobacterium*. Their prevalences were determined with a 95% confidence interval (CI) calculated using the Wilson score method. Logistic regression analyses were conducted to evaluate the factors associated with major HIV-related infections in all HIV-infected patients. Multivariable logistic regression models were adjusted for age at registration, sex, self-reported mode of HIV transmission, and country of origin. Age was divided by a factor of 10 to indicate the odds ratio per increase in decade. All analyses were conducted with STATA IC version 12.0 (Stata Corp., College Station, TX).

Ethical considerations. Institutional approval was obtained from the ethics committees of NMC and the Institute of Tropical Medicine, Nagasaki University. De-identified data from previously approved cohort studies were obtained from the collaborators at PGH, LPH, and BMH. All procedures adhered to country-specific laws on HIV and AIDS, including the Japanese regulations regarding HIV disclosure and the Philippine AIDS Prevention and Control Act. No patients were directly contacted or re-examined for this study.

RESULTS

Demographic and clinical characteristics. Data from 1,510 newly registered ART-naive HIV-infected patients were available from the four study sites (NMC, $N = 367$; LPH, $N = 442$; BMH, $N = 387$; and PGH, $N = 314$). After excluding patients younger than 15 years (two at NMC and three at BMH), 1,505 patients were included in the analysis.

The demographic and clinical characteristics of the patients are summarized in Table 1. Overall, the median (interquartile range) age at registration was 32 years (27–39 years), and this age varied significantly by study site, with younger patients visiting PGH ($P < 0.001$). Approximately, 90% of patients at NMC were Japanese, and half of the rest were Asian foreigners. Most patients at LPH, BMH, and PGH were Thai, Kinh, and Filipino, respectively. The majority of the patients at NMC and PGH were male, and the proportions of male patients at NMC and PGH differed significantly from those of the other sites ($P < 0.001$). The different sex distributions were likely due to differences in risk group: PGH and NMC patients were mostly MSM, whereas LPH patients were mostly heterosexual. Although the majority of BMH patients were heterosexual, the second most common risk group was IDUs, the vast majority of whom were male (98.3%). Overall, 753 patients (52.7%) had already progressed to advanced immune deficiency; 49.8% ($N = 750$) had a CD4 count < 200 cells/μL and 29.4% ($N = 442$) had AIDS-defining illnesses (stage 4).

Pattern of OIs and HIV-related illnesses. Considerable variation was observed in the distribution of HIV-related illnesses. Figure 1 shows the proportions of major HIV-related infections among the patients with clinical stage 3 or 4 HIV/AIDS as indicated in Table 1. TB, including both pulmonary TB (PTB) and extrapulmonary TB, was the most common OI at PGH and BMH. In contrast, TB was rather rare at NMC. The prevalence of PCP was highest at NMC and lowest at BMH. Cryptococcosis was most frequently diagnosed at LPH. CMV retinitis and herpes zoster were diagnosed at all sites, although CMV antigenemia ($N = 35$, 27.3%) and CMV enteritis ($N = 2$, 1.6%) were diagnosed only at NMC. The prevalence of herpes zoster was only slightly higher at LPH than at the other hospitals. HIV encephalopathy and malignant lymphoma were diagnosed only at NMC. Interestingly, Kaposi's sarcoma was observed only at NMC and PGH, and its prevalence showed a significant association with MSM: seven patients with Kaposi's sarcoma among 552 MSM (1.3%) versus two patients among

TABLE 1
Characteristics of all patients from four hospitals

	NMC (*N* = 365)	LPH (*N* = 442)	BMH (*N* = 384)	PGH (*N* = 314)	*P* value
Age at registration	37 [31, 45]	34 [29, 40]	31 [28, 35]	28 [25, 33]	< 0.001
Male	343 (94.0)	213 (48.2)	246 (64.1)	301 (95.9)	< 0.001
Risk behavior					
Heterosexual	68 (18.6)	395 (89.4)	228 (59.4)	36 (12.1)	
MSM/bisexual	263 (72.1)	12 (2.7)	3 (0.8)	258 (86.9)	
IDU	19 (5.2)	12 (2.7)	137 (35.7)	3 (1.0)	
Others	15 (4.1)	23 (5.3)	16 (4/2)	0 (–)	< 0.001
CD4 + T cell count (cells/μL)	234 [58, 386]	194 [29, 391]	111 [40, 337]	266 [74, 400]	< 0.001
CD4 + T cell count category (cells/μL)					
≥ 200	203 (55.6)	220 (49.8)	142 (37.0)	190 (60.5)	
51–200	75 (20.6)	79 (17.9)	122 (31.8)	57 (18.2)	
≤ 50	87 (23.8)	143 (32.4)	120 (31.3)	67 (21.3)	< 0.001
Clinical stage at the first visit					
Stage 1	226 (61.9)	221 (50.0)	141 (36.7)	128 (40.8)	
Stage 2	11 (3.0)	31 (7.0)	31 (8.1)	14 (4.5)	
Stage 3/4	128 (35.1)	186 (42.1)	211 (55.0)	104 (33.1)	
No information	0 (–)	4 (0.9)	1 (0.3)	68 (21.7)	< 0.001

BMH = Bach Mai Hospital; IDU = injecting drug user; LPH = Lampang Hospital; MSM = men having sex with men; NMC = Nagoya Medical Center; PGH = Philippine General Hospital. Values are given as actual count (%) for categorical variables or median [interquartile range] for continuous variables. If no information, "–" is displayed in the number column. CD4 is not taken into consideration in the staging.

936 non-MSM (0.2%) ($P = 0.011$). Esophageal candidiasis was commonly diagnosed at NMC and moderately diagnosed at BMH. As expected from previous reports,[23] penicilliosis was observed exclusively at BMH and LPH (Supplemental Table 2).

Factors associated with TB, PCP, cryptococcosis, CMV retinitis, and herpes zoster. Logistic regression analyses were performed to identify the factors associated with the five major HIV-related infections. All patients from the four hospitals were included in the analysis. Injection drug use, low CD4 count, and hospital of registration were significantly associated with TB in both the univariable and multivariable analyses (Table 2). Hospital of registration substantially affected the risk of TB diagnosis, with the highest adjusted odds ratio (aOR) for PGH (aOR = 42.2, 95% CI = 14.6–122.1), followed by BMH (aOR = 12.6, 95% CI = 3.9–40.3) and LPH (aOR = 6.6, 95% CI 2.1–21.1). Injection drug use remained independently associated with TB in the final multivariable logistic regression model. Factors associated with PCP in the univariable analysis were age, male gender, injection drug use, and CD4 count (Table 2). In the final multivariable model, only CD4 count and hospital of registration remained significantly associated with PCP. Notably, patients from LPH (aOR = 0.2, 95% CI = 0.1–0.4) and BMH (aOR = 0.1, 95% CI = 0.04–0.2) had significantly lower odds of PCP diagnosis than patients from NMC. The factors associated with cryptococcosis in the univariable analysis were low CD4 count and registration at LPH (Table 2). In the final multivariable model, a trend toward an increased risk of cryptococcosis was observed among patients at LPH (aOR = 6.2, 95% CI = 0.9–41.0). In contrast to the other OIs investigated, there were no significant regional differences in the diagnosis of CMV retinitis, even after adjusting for CD4 count (Table 2). Similarly, there were no regional differences in the risk of herpes zoster (Table 2).

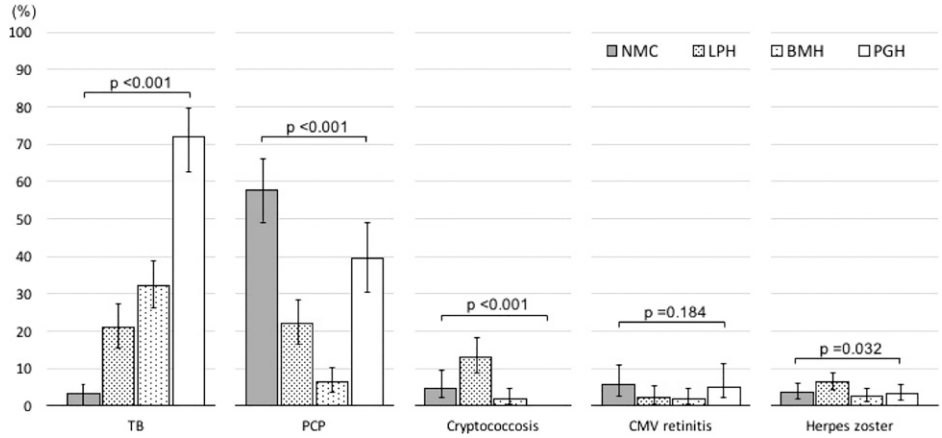

FIGURE 1. Prevalence of major human immunodeficiency virus (HIV)-related infections among patients infected with clinical stage 3 or 4 HIV at each hospital. NMC = Nagoya Medical Center ($N = 128$), LPH = Lampang Hospital ($N = 186$), BMH = Bach Mai Hospital ($N = 211$), and PGH = Philippine General Hospital ($N = 104$). TB = tuberculosis, PCP = *Pneumocystis* pneumonia, CMV = cytomegalovirus. TB includes pulmonary TB and extrapulmonary TB. The presence of both conditions was counted as one case. Error bars represent 95% confidence intervals calculated using the Wilson score method. *P* values were calculated using χ^2 tests.

TABLE 2
Associated factors for the major HIV-related infections among all patients

Risk factors	Crude OR (95% CI, *P* value)	Adjusted OR (95% CI, *P* value)
Tuberculosis		
Age*	1.0 (0.8–1.2, 0.891)	1.3 (1.1–1.5, 0.034)
Male	1.9 (1.3–2.8, 0.002)	1.3 (0.8–2.2, 0.320)
Risk behavior		
Heterosexual	1.0	1.0
MSM/bisexual	1.2 (0.9–1.8, 0.285)	0.8 (0.4–1.6, 0.441)
IDU	3.0 (1.9–4.6, < 0.001)	2.0 (1.1–3.6, 0.013)
CD4+ T cell count category (cells/μL)		
≥ 200	1.0	1.0
51–200	3.0 (2.0–4.5, < 0.001)	2.5 (1.9–4.0, < 0.001)
≤ 50	4.0 (2.7–5.9, < 0.001)	4.0 (2.6–6.1, < 0.001)
Hospital		
Nagoya Medical Center	1.0	1.0
Lampang Hospital	8.7 (3.1–24.7, < 0.001)	6.6 (2.1–21.1, 0.001)
Bach Mai Hospital	19.4 (7.1–53.8, < 0.001)	12.6 (3.9–40.3, < 0.001)
Philippine General Hospital	28.3 (10.2–78.5, < 0.001)	42.2 (14.6–122.1, < 0.001)
Pneumocystis jirovecii pneumonia		
Age*	1.5 (1.3–1.7, < 0.001)	1.2 (0.9–1.4, 0.141)
Male	2.1 (1.3–3.2, 0.001)	1.0 (0.6–1.8, 0.921)
Risk behavior		
Heterosexual	1.0	1.0
MSM/bisexual	1.6 (1.1–2.2, 0.007)	0.8 (0.4–1.4, 0.388)
IDU	0.4 (0.2–0.8, 0.016)	0.5 (0.2–1.3, 0.154)
CD4+ T cell count category (cells/μL)		
≥ 200	1.0	1.0
51–200	8.7 (4.5–16.8, < 0.001)	10.4 (5.3–20.5, < 0.001)
≤ 50	23.9 (13.0–43.9, < 0.001)	35.3 (18.7–66.6, < 0.001)
Hospital		
Nagoya Medical Center	1.0	1.0
Lampang Hospital	0.4 (0.8–0.6, < 0.001)	0.2 (0.1–0.4, < 0.001)
Bach Mai Hospital	0.1 (0.1–0.3, < 0.001)	0.1 (0.04–0.2, < 0.001)
Philippine General Hospital	0.6 (0.4–0.9, 0.013)	0.7 (0.4–1.2, 0.226)
Cryptococcosis		
Age*	1.0 (0.7–1.4, 0.996)	0.8 (0.5–1.3, 0.330)
Male	1.0 (0.5–2.2, 0.974)	1.0 (0.4–2.6, 0.984)
Risk behavior		
Heterosexual	1.0	1.0
MSM/bisexual	0.4 (0.1–1.0, 0.051)	3.4 (0.5–24.4, 0.221)
IDU	0.9 (0.3–2.8, 0.917)	2.6 (0.6–10.9, 0.202)
CD4+ T cell count category (cells/μL)		
≥ 200	1.0	1.0
51–200	4.6 (0.8–25.1, 0.080)	4.7 (0.8–26.5, 0.081)
≤ 50	27.1 (6.4–114.4, < 0.001)	25.9 (6.0–112.6, < 0.001)
Hospital		
Nagoya Medical Center	1.0	1.0
Lampang Hospital	3.4 (1.4–8.5, 0.008)	6.2 (0.9–41.0, 0.058)
Bach Mai Hospital	0.6 (0.2–2.3, 0.447)	0.8 (0.9–7.6, 0.877)
Philippine General Hospital	–	–
CMV retinitis		
Age*	1.1 (0.7–1.7, 0.553)	1.0 (0.6–1.6, 0.918)
Male	0.8 (0.3–2.2, 0.738)	0.4 (0.1–1.5, 0.157)
Risk behavior		
Heterosexual	1.0	1.0
MSM/bisexual	1.2 (0.5–3.2, 0.698)	1.2 (0.3–5.2, 0.822)
IDU	0.5 (0.1–3.7, 0.474)	0.6 (0.1–6.2, 0.691)
CD4+ T cell count category (cells/μL)		
≥ 200	1.0	1.0
51–200	11.5 (1.3–98.8, 0.026)	13.5 (1.5–117.3, 0.018)
≤ 50	26.2 (3.4–199.9, 0.002)	32.8 (4.2–253.0, 0.001)
Hospital		
Nagoya Medical Center	1.0	1.0
Lampang Hospital	0.5 (0.1–1.6, 0.227)	0.3 (0.1–1.5, 0.145)
Bach Mai Hospital	0.5 (0.2–1.9, 0.326)	0.3 (0.1–1.8, 0.203)
Philippine General Hospital	0.8 (0.3–2.6, 0.749)	0.9 (0.3–3.0, 0.838)
Herpes zoster		
Age*	1.1 (0.8–1.4, 0.712)	1.0 (0.7–1.3, 0.999)
Male	1.1 (0.6–2.0, 0.702)	1.4 (0.7–3.0, 0.341)

(continued)

TABLE 2
Continued

Risk factors	Crude OR (95% CI, *P* value)	Adjusted OR (95% CI, *P* value)
Risk behavior		
Heterosexual	1.0	1.0
MSM/bisexual	0.9 (0.5–1.5, 0.635)	1.3 (0.4–3.7, 0.664)
IDU	0.7 (0.3–1.8, 0.424)	0.9 (0.3–2.9, 0.901)
CD4+ T cell count category (cells/μL)		
≥ 200	1.0	1.0
51–200	1.6 (0.9–3.0, 0.111)	1.6 (0.8–3.0, 0.152)
≤ 50	1.0 (0.5–1.9, 0.985)	0.9 (0.5–1.8, 0.729)
Hospital		
Nagoya Medical Center	1.0	1.0
Lampang Hospital	1.8 (0.9–3.6, 0.078)	2.6 (0.9–7.8, 0.084)
Bach Mai Hospital	0.7 (0.3–1.7, 0.450)	0.9 (0.3–3.2, 0.873)
Philippine General Hospital	0.9 (0.4–2.1, 0.787)	0.9 (0.4–2.4, 0.927)

CI = confidence interval; HIV = human immunodeficiency virus; IDU = injection drug user; MSM = men having sex with men; OR = odds ratio.
* Age was divided by a factor of 10 to indicate OR per decade increase in age.

DISCUSSION

This is the first study to comprehensively compare OIs among ART-naïve patients between four hospitals in Japan, northern Thailand, northern Vietnam, and the Philippines since the introduction of ART. The findings demonstrated considerable regional differences in the prevalence of major OIs, such as TB, PCP, and cryptococcosis, even after adjusting for age, sex, HIV-associated risk behavior, and CD4 count. We found a high prevalence of AIDS-defining OIs at our study sites despite the widespread availability of ART in all four countries during the study period. The distribution of OIs in each hospital mirrored the OI prevalences found in the respective reports by each country,[8,13–16,24–26] indicating that our study population was representative.

TB is the most common HIV-related OI in Asia and is especially common in resource-limited settings.[27] The risk of TB in the four hospitals in our study paralleled the prevalence of PTB in the general population of each country; from 1990 to 2010, the estimated PTB prevalence was 502 per 100,000 individuals in the Philippines, 334 in Vietnam, 212 in Thailand, and 27 in Japan.[28] Interestingly, the incidence of TB has been shown to increase inversely proportionally to per capita gross domestic product.[29] The occurrence of TB among HIV-infected patients in developing regions is largely affected by the burden of TB in their surroundings,[30] as overcrowded living conditions place them at risk for frequent exposure to *Mycobacterium tuberculosis*.[31] As previously reported,[32] we found an increased prevalence of TB among IDUs. This increased risk can be attributed to the poor hygiene and ventilation in areas where injection drugs are used.[32] The adverse immunomodulatory effects of illicit drugs have also been implicated in the increased susceptibility of IDUs to TB.[33]

Consistent with national data from Japan, PCP was the most common AIDS-defining illness at NMC.[14] Although PCP is considered prevalent in developed countries,[34] the aOR of PCP at PGH was similar to that at NMC in our study. In contrast, PCP was rare at BMH, which is consistent with previously published reports from Vietnam.[15,16] *Pneumocystis jirovecii* is a ubiquitous pathogen, but its prevalence is highest in Europe and the United States.[35] The increased frequency of PCP diagnosis in developed countries could be due to differences in access to cytological examinations of respiratory pathogens, which are typically performed via bronchoalveolar lavage; this differential access could contribute to the reportedly low prevalences of PCP found in lower-income countries.[34] Host genetic factors also affect susceptibility to PCP, although the precise mechanisms underlying these associations have not yet been illustrated. Possible protective genetic factors include apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3F, CCR5-Delta32 mutation heterozygosity, and Dectin-1.[36–38] Possible genetic factors increasing susceptibility to PCP include genotypes producing low mannose-binding lectin, CCRL2-F167Y mutation, and histidine-histidine homozygosity of the Fc segment receptors of IgG.[39–41] A cohort study conducted in the Netherlands also indicated the potential impact of these host factors on PCP development.[42] Therefore, these factors may have affected the regional differences in PCP identified in our study.

Penicilliosis was reported only at LPH and BMH; there were no known cases of penicilliosis at PGH or NMC during the study period. To date, only a few imported cases from Thailand have been reported in Japan.[43] Despite its typical presentation of skin lesions, penicilliosis is difficult to diagnose in nonendemic regions. A heightened awareness of the unique infections in neighboring countries is important given the recent increase in population mobility. Oroesophageal candidiasis is one of the most common OIs in Asia[12] and was the most prevalent at NMC. The diagnosis of esophageal candidiasis was relatively rare at LPH and PGH, although its prevalence may have been underestimated due to limited access to upper endoscopy.

LPH showed the highest prevalence of cryptococcosis, which is consistent with the previously reported prevalence of cryptococcosis among AIDS patients in Thailand from 1994 to 1998.[13] The endemicity of *Cryptococcus neoformans* in northern Thailand is typically attributed to frequent exposure to aerosolized feces from avian vectors.[44] A recent study from Chiang Mai University Hospital, Thailand, showed a lower prevalence of cryptococcal meningitis (5.2%),[45] likely concurrent with the recent improvements in living conditions and/or access to ART.

Consistent with previous reports from Europe, we did not find regional variations in CMV retinitis or herpes zoster.[1] However, the prevalence of CMV diseases in resource-limited settings was likely underestimated, as CMV infections other than retinitis were reported only at NMC. CMV viral load and antigen measurements are not routinely obtained in the work-up of HIV patients in resource-limited settings and should be a point of improvement in the next decade.

Most noninfectious AIDS-defining illnesses, lymphoma in particular, were diagnosed at NMC. Recently, the number of AIDS-defining malignancies (ADMs) has been increasing in Japan together with the increasing number of HIV-infected patients.[14] Retrospective studies in Thailand have reported a small number of ADMs: Kiertiburanakul and others[46] found that 1.8% of HIV-infected patients had ADMs; Rojanawiwat and others[47] identified no cases of primary central nervous system (CNS) lymphoma despite frequent detection of Epstein–Barr virus in cerebrospinal fluid; and Chariyalertsak and others[13] reported few cases of primary CNS lymphoma (0.1%) and Kaposi's sarcoma (0.2%) among the AIDS-defining illnesses occurring between 1994 and 1998. In Vietnam and the Philippines, information about ADMs is scarce. This trend in low prevalence of ADMs in resource-limited settings may be attributed to their nonspecific symptoms and/or the high mortality of patients with concomitant HIV-related OIs. HIV risk behaviors can strongly influence the prevalence of Kaposi's sarcoma. Human herpesvirus-8 (HHV-8), the oncovirus associated with Kaposi's sarcoma, is believed to be transmitted through anal intercourse. Hence, MSM are documented to have a higher risk of HHV-8 infection and Kaposi's sarcoma,[48,49] which is consistent with the findings among patients at NMC and PGH, where MSM constituted the majority of the cohort.

This study has several limitations. First, the data collection was not performed simultaneously. Overall, patient information from 2003 to 2011 was used. However, this information was limited to 3 years at NMC and 1 year at BMH. Second, the numbers of sites and subjects were not sufficient to discuss the tendency of HIV infection across Asia. Third, the analyses were limited by the completeness of medical records, and the OI diagnoses may have been affected by variations in clinical practices at each study site. Fourth, the availability and accessibility of diagnostic procedures differed between NMC and the other three sites. To minimize this limitation, we focused the regression analyses on HIV-related illnesses that were less likely to be influenced by limited resources. Finally, the HIV subtypes of the study population were not available. Because our study sites are key major hospitals in each region, the HIV subtype was considered identical to its national tendency: the major HIV subtypes are B in Japan,[50] B and CRF01_AE in the Philippines,[51,52] and CRF_01AE in Thailand and Vietnam.[53] There is no evidence that differences in subtype affect the incidence of OIs.

This is the first study to systematically compare the regional differences in major OIs in four Asian countries using logistic regression models. We found differences in the diagnoses of TB, PCP, and cryptococcosis between our study sites, whereas no regional differences in CMV retinitis or herpes zoster incidence were observed. These differences may be attributed to the geographical distribution of the pathogens, differences in HIV-related risk factors, clinical characteristics of the patients, and the availability of diagnostic procedures.

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SUPPLEMENTAL TABLE 1

Diagnostic criteria for opportunistic infections at the study sites

	Nagoya Medical Center	Lampang Hospital	Bach Mai Hospital	Philippine General Hospital
TB	Definite diagnosis	Definite diagnosis	Definite diagnosis	Definite diagnosis
	Mycobacterium culture	*Mycobacterium* culture	*Mycobacterium* culture	*Mycobacterium* culture
	Mycobacterium PCR			
	Clinical diagnosis	Clinical diagnosis	Clinical diagnosis	Clinical diagnosis
		Direct smear microscopy for AFB	Direct smear microscopy for AFB with pulmonary specimen and/or extrapulmonary specimen	Direct sputum smear microscopy for AFB
	Imaging studies including X-ray examination	Presence of clinical symptoms	Presence of clinical symptoms	Presence of clinical symptoms
		Prolonged dry cough	Prolonged dry cough	
		Productive cough, hemoptysis	Productive cough, hemoptysis	
		Weight loss, general malaise	Weight loss, general malaise	
		Prolonged fever	Prolonged fever	
		Night sweating	Night sweating	
		Chest X-ray examination	Chest X-ray examination	Chest X-ray examination
			AFB culture with pulmonary specimen or extrapulmonary specimen	
			Confirmation by a specialist	
	Therapeutic diagnosis	Therapeutic diagnosis	Therapeutic diagnosis	Therapeutic diagnosis
PCP	Definite diagnosis	Definite diagnosis	Definite diagnosis	Definite diagnosis
	Microscopic examination	Microscopic examination	Microscopic examination	Microscopic examination
	PCR			
	Clinical diagnosis(Yes for all of the following criteria)	Clinical diagnosis	Clinical diagnosis	Clinical diagnosis
		Presence of clinical symptoms	Presence of clinical symptoms	Presence of clinical symptoms: exertional shortness of breath and hypoxia
		Respiratory distress on exercise	Respiratory distress on exercise	Typical chest X-ray findings
	The following symptoms within 3 months	Dry cough	Dry cough	Low PaO_2
	Respiratory distress on exercise	Diffuse interstitial infiltrations of bilateral lungs by X-ray	Diffuse interstitial opacification of bilateral lungs by X-ray	
	Dry cough	Presence of hypoxemia	Presence of hypoxemia	
	Diffuse interstitial infiltrations of bilateral lungs by X-ray or CT scan OR diffuse positive findings of bilateral lungs by gallium lung scan	Decreased SpO_2	Decreased SpO_2	
	At least one of the following findings	Therapeutic diagnosis	Therapeutic diagnosis with co-trimoxazole	Therapeutic diagnosis
	$PaO_2 \leq 70$ mm of Hg (blood gas analysis)			
	DLCO ≤ 80%			
	Increased $AaDO_2$			
	Decreased SpO_2			
	Absence of bacterial pneumonia or abnormal β-D glucan			
Cryptococcosis	Microscopic examination of CSF or affected tissue	Microscopic examination of CSF or affected tissues	Microscopic examination of CSF or affected tissues	Microscopic examination of CSF or affected tissues
	Fungal culture	Blood culture	Blood culture	Cryptococcal Antigen Latex Agglutination System
		CSF analysis and India ink staining	CSF analysis and India ink staining	

(continued)

SUPPLEMENTAL TABLE 1
Continued

	Nagoya Medical Center	Lampang Hospital	Bach Mai Hospital	Philippine General Hospital
	Auxiliary diagnosis Cryptococcal antigen testing			
CMV retinitis	Fundoscopic examination	Fundoscopic examination	Fundoscopic examination	Fundoscopic examination Therapeutic diagnosis
Herpes zoster	Presence of typical skin regions: blisters in clusters with pain within a dermatome	Presence of typical skin regions: blisters in clusters with pain within a dermatome	Presence of typical skin regions: blisters in clusters with pain within a dermatome	Presence of typical skin regions: blisters in clusters with pain within a dermatome
Reference	HIV/AIDS diagnosis criteria (AIDS Surveillance Committee, Ministry of Health, Labor and Welfare, Japan) http://www.acc.go.jp/information/020/surveillance.html#s3_a	Ministry of Public Health. National guidelines for the clinical management of HIV infection in children and adults. 6th ed. Thailand: Ministry of Public Health; 2000.	Ministry of Health, Viet Nam. 2009. Guidelines for HIV/AIDS Diagnosis and Treatment. Ha Noi, Viet Nam.	Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos: 2006 UPDATE. Manila, the Philippines: Philippine Society for Microbiology and Infectious Diseases; 2006. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep. 2009 Apr 10;58(RR-4):1-207; quiz CE1-4.

AFB = acid-fast bacilli; AIDS = acquired immune deficiency syndrome; AaDO2 = alveolar arterial O_2 difference; CMV = cytomegalovirus; CSF = cerebrospinal fluid; CT = computed tomography; DLCO = diffusing capacity of lung carbon monoxide; HIV = human immunodeficiency virus; OR = odds ratio; PCP = *Pneumocystis* pneumonia; PCR = polymerase chain reaction; TB = tuberculosis.

The following are supplemental materials and will be published online only

SUPPLEMENTAL TABLE 2

Opportunistic illness profiles among HIV-infected patients with clinical stage 3 or 4

	NMC (*N* = 128)	LPH (*N* = 186)	BMH (*N* = 211)	PGH (*N* = 104)
Bacterial infection				
Pulmonary TB	0 (–)	23 (12.4)	39 (18.5)	53 (51.0)
Extrapulmonary TB*	4 (3.1)	18 (9.7)	39 (18.5)	29 (27.9)
Mycobacterium infection (non-TB)	5 (3.9)	1 (0.5)	13 (6.2)	0 (–)
Fungal infection				
Pneumocystis jirovecii pneumonia	74 (57.8)	41 (22.0)	13 (6.2)	41 (39.4)
Esophageal candidiasis	35 (27.3)	2 (1.1)	17 (8.1)	1 (1.0)
Oral candidiasis	24 (18.8)	50 (26.9)	31 (14.7)	1 (1.0)
Penicilliosis	0 (–)	15 (8.1)	35 (16.6)	0 (–)
Cryptococcus infection	6 (4.7)	24 (12.9)	4 (1.9)	0 (–)
Other mycosis	1 (0.8)	1 (0.6)	0 (–)	0 (–)
Viral infection				
CMV retinitis	7 (5.5)	4 (2.2)	4 (1.9)	5 (4.8)
Chronic herpes simplex virus infection	1 (0.8)	3 (1.6)	0 (–)	2 (1.9)
Progressive multifocal leukoencephalopathy	0 (–)	–	1 (0.5)	–
Herpes zoster†	13 (3.6)	28 (6.3)	10 (2.6)	10 (3.2)
Protozoal infection				
Toxoplasmosis	3 (2.3)	2 (1.1)	11 (5.2)	4 (3.9)
Isospora/cryptospora	0 (–)	–	0 (–)	0 (–)
Malignancy				
Kaposi's sarcoma	7 (5.5)	0 (–)	0 (–)	2 (1.9)
Lymphoma (including cerebral lymphoma)	6 (4.7)	–	–	–
Other HIV-related illness				
HIV encephalopathy	6 (4.7)	–	0 (–)	–
HIV cardiomyopathy	2 (1.6)	–	0 (–)	–
Wasting syndrome	7 (5.5)	1 (0.5)	32 (15.2)	–

BMH = Bach Mai Hospital; CMV = cytomegalovirus; HIV = human immunodeficiency virus; LPH = Lampang Hospital; NMC = Nagoya Medical Center; PGH = Philippine General Hospital; TB = tuberculosis. Values are given as actual count (%) for categorical variables. If no information, "–" is displayed in the number column.

* The number of patients with pulmonary tuberculosis and extrapulmonary tuberculosis were 0 in NMC, 2 in LPH, 10 in BMH, and 7 in PGH.

† The denominator of Herpes zoster is all patients at each hospital.