

Causes of Hospitalization and Death among Newly Diagnosed HIV-Infected Adults in Thailand

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Abstract

More than half of newly diagnosed HIV-infected patients enter to care with a low CD4 count. A retrospective cohort study was conducted among newly diagnosed HIV-infected adults who were hospitalized. Of 148 patients, median (interquartile range [IQR]) age was 39.3 (30.5-47.1) years and 114 (77%) patients were male. Baseline median (IQR) CD4 count was 79 (24-218) cells/mm³. The median (IQR) length of hospital stay was 8 (4-16) days. Half of the patients were hospitalized with AIDS-defining illness (ADI). Common opportunistic infections were *Pneumocystis jirovecii* pneumonia (20.3%) and tuberculosis (18.9%). CD4 count was statistically significantly associated with hospitalization with ADI (odds ratio: 0.85, per 10 cells/mm³ increased; 95% confidence interval: 0.80-0.90). The mortality was 5.4%. In conclusion, half of newly diagnosed Thai HIV-infected patients were hospitalized with ADI. Early detection of HIV infection leading to early antiretroviral therapy initiation and prevention of serious complications is essential.

Keywords

AIDS, death, HIV, hospitalization, Thailand

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Introduction

HIV infection has been reported for over 3 decades, and the number of AIDS cases has increased annually. Global summary by Joint United Nations Programme on HIV/AIDS in 2016 reported that the number of patients living with HIV is 37.6 million.¹ In 2016, Thailand had a total of 427 332 HIV-infected patients and 6268 patients were new cases.² The National AIDS Program in Thailand was established with the availability and accessibility of antiretroviral therapy (ART) throughout the country in 2001. According to the Thai National Guidelines 2017, HIV-infected individuals with any CD4 count can access ART.³ Survival and quality of life of individuals with HIV-infection were subsequently improved.

After the introduction of ART in some countries, the number of hospital admissions for treating AIDS-defining illness (ADI) has declined.^{4,5} In contrast, hospitalization with non-ADI increased with metabolic diseases, such as diabetes mellitus, cardiovascular disease, and cerebrovascular disease complication.⁶⁻⁸ However, the prevalence of HIV-infected individuals with late presentation to care did not decrease after the wide introduction of ART in Asia.^{9,10} More than half of newly diagnosed HIV-infected individuals presented with CD4 count less

than 200 cells/mm³ and/or symptoms related to opportunistic infections (OIs). Individuals with older age, male gender, heterosexual HIV exposure, and intravenous drug use were more likely to enter to care with a late presentation.^{9,10} Furthermore, late ART initiation in patients with very low CD4 counts is associated with morbidity and mortality.^{9,10} The 90-90-90 strategy is an ambitious treatment target to help end the AIDS epidemic.¹¹ This means that we are still far away from the first 90 number, which is the percentage of people who are diagnosed with HIV infection.

In Thailand and Singapore, the most common cause of hospitalization among HIV-infected patients was OIs.^{12,13} In low socioeconomic and developing countries, the most common OIs which were the causes of hospitalization were tuberculosis and *Pneumocystis jirovecii* pneumonia.^{12,14,15}

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What Do We Already Know About This Topic?

More than half of newly diagnosed HIV-infected patients in developing countries enter to care with a low CD4 count, which leads to complications, disability, and death.

How Does Your Research Contribute to the Field?

Newly diagnosed Thai HIV-infected patients were hospitalized with AIDS-defining illness.

What Are Your Research's Implications Toward Theory, Practice, or Policy?

Early detection of HIV infection leads to early antiretroviral therapy initiation and prevention of serious complications related to HIV infection. National strategic HIV/AIDS plans should be scaled up for achieving the 90-90-90 targets.

These patients had advanced symptoms such as prolonged fever, weight lost, dyspnea, or chronic diarrhea depending on the levels of CD4 counts.¹⁴ In this study, we aimed to determine the causes of hospitalization and death among newly diagnosed HIV-infected adults in Thailand. Clinical characteristics and laboratory investigations including factors associated with hospitalization with ADI were determined. The results of this study may be helpful for the Thai government to revise national policy and guidelines on HIV/AIDS care.

Materials and Methods

A retrospective cohort study was conducted among adult HIV-infected patients who were hospitalized at Ramathibodi Hospital (a 1200-bed university hospital in Bangkok, Thailand) between January 2011 and December 2016. The list of the patients was retrieved from the hospital database using the *International Classification of Diseases, Tenth Edition* codes to identify those hospitalized patients who were diagnosed with HIV infection. The codes of B20-B24 and Z21 were used to identify the patients. Inclusion criteria were (1) age ≥ 15 years old and (2) firstly diagnosed HIV infection by positive blood samples for anti-HIV antibody in this hospital. Anti-HIV with ARCHITECT HIV Ag/Ab Combo (Abbott GmbH & Co. KG, Germany) was used for screening. If the first test was positive, at least additional 2 tests were performed, for example, Determine HIV-1/2 Ag/Ab Combo (Orgenics Ltd, Israel) and Wondfo Diagnostic Kit for HIV 1/2 Antibody (Guangzhou Wondfo Biotech Co, Ltd, China). We excluded hospital admissions for pregnancy and child birth which were not associated with disease or injury.

Clinical and demographic data including age at HIV diagnosis, gender, route of HIV acquisition, comorbidity, CD4

count, coinfection with hepatitis B virus (HBV) or hepatitis C virus (HCV) or syphilis, and final diagnosis at discharge were obtained by reviewing of medical records. In addition, chemistry laboratory, radiological findings, microbiological testing, and pathological findings were reviewed. Data including hospital admission date, discharge date, length of stay, and discharge status were also obtained. We divided the discharge diagnosis into ADI and non-ADI accordingly, in order to determine the impact of HIV infection on hospitalization. The diagnosis of ADI was done using the list of diseases published by Centers for Disease Control and Prevention.¹⁶

Mean values (with standard deviations) or median values (with interquartile range [IQR]) and frequency were used to describe the patients' characteristics for continuous and categorical data, respectively. χ^2 test or Fisher exact test and Student *t* test were used to compare categorical variables and continuous variables between the 2 groups, respectively. Univariate and multivariate logistic regression analyses to determine the factors associated with hospitalization with ADI were performed. Variables that presented *P* value $< .10$ were considered in a multivariate logistic regression model after the assessment of multicollinearity of variance inflation factors. Variables were selected into a multiple logistic regression model with forward stepwise selection and those which attained a level of significance (*P* $< .05$) were retained in the model. The odds ratio (OR) and its 95% confidence interval (CI) were estimated. A *P* value $< .05$ was considered statistically significant. All statistical analyses were performed using Stata statistical software version 12.0 (StataCorp. 2011, Stata Statistical Software: Release 12, College Station, Texas: StataCorp LP.).

Ethical Approval and Informed Consent

Ethical approval for this study was obtained from the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (approval number: ID 12-59-22).

Results

During 6 years of the study period, 1297 admissions of HIV-infected patients were identified. A total of 148 newly diagnosed HIV-infected adults were included in the study which accounted for 11.4% of the admissions. Of all, 27 (11.2%) of 241, 18 (10%) of 180, 25 (14.0%) of 178, 28 (20.4%) of 137, 25 (11.8%) of 211, and 25 (8.0%) of 311 patients were newly diagnosed HIV-infected adults hospitalized in the years 2011, 2012, 2013, 2014, 2015, and 2016, respectively. Median (IQR) age at HIV diagnosis was 39.3 (30.5-47.1) years, and 114 (77%) patients were male. Ninety-one (61.5%) patients, 41 (27.7%) patients, and 3 (2%) patients had a heterosexual, homosexual, and intravenous drug use as the route of HIV acquisition, respectively. Most of them (48%) had no scheme of health insurance and they needed to pay for themselves, followed by 27% had universal coverage, and 16.2% had civil service welfare health insurance scheme. For 22 (14.8%) patients who had

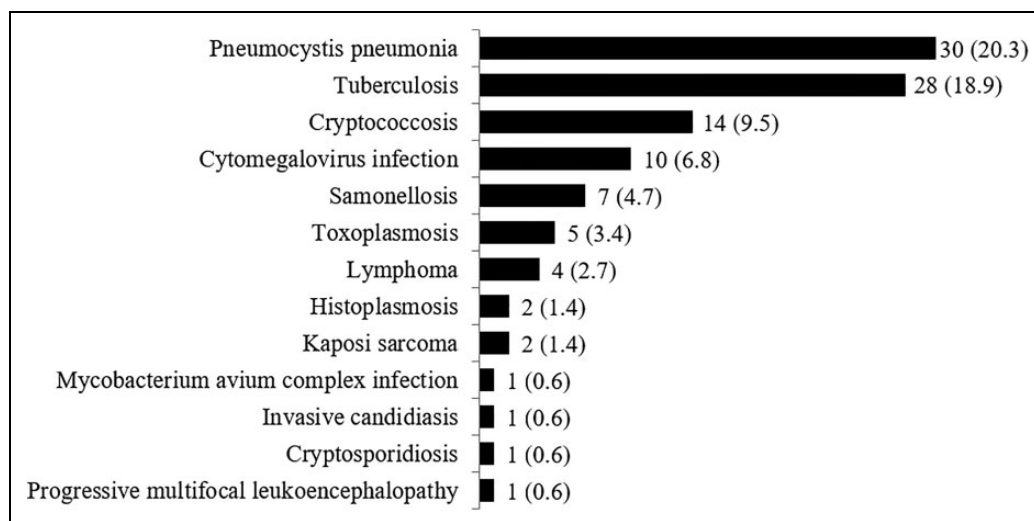


Figure 1. Final diagnosis at the discharge of newly diagnosed HIV-infected patients (AIDS-defining illness), number (%).

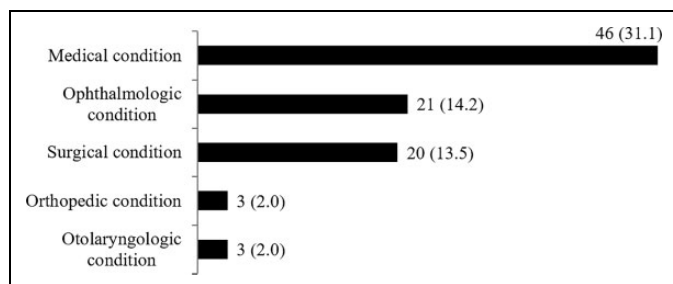


Figure 2. Final diagnosis at the discharge of newly diagnosed HIV-infected patients (non-AIDS-defining illness), number (%).

comorbidity, the common ones were hypertension (6.0%) and diabetes mellitus (3.4%). Median (IQR) CD4 count was 79 (24-218) cells/mm³. For other coinfection, 21 (14.1%) patients had a history of syphilis, 14 (9.5%) had chronic HBV infection, and 14 (9.5%) had chronic HCV infection. Median (IQR) duration of hospitalization was 8 (4-16) days, and 6 (4.1%) patients were admitted to intensive care unit.

Of all, 74 (50%) patients were hospitalized with ADI. The most common ADI were *P jirovecii* pneumonia (20.3%), tuberculosis (18.9%), and cryptococcosis (9.5%; Figure 1). Tuberculosis was diagnosed by having the positive results of one of the following investigations: culture, polymerase chain reaction, or pathological finding. The causes of non-ADI were medical condition (eg, sepsis, myocardial infarction, and Guillain-Barré syndrome; 31.1%), ophthalmologic condition (eg, ocular syphilis, keratitis, and endophthalmitis; 14.2%), and surgical condition (eg, perianal abscess and blunt abdominal injury; 13.5%; Figure 2).

The comparison of baseline characteristics and laboratory investigations between newly diagnosed HIV-infected patients who were hospitalized with ADI and those who were hospitalized with non-ADI is shown in Table 1. Patients who were

hospitalized with ADI had lower median hemoglobin (11.1 versus 12.1 mg/dL, $P = .004$), lower median percentage of lymphocyte (17.5% versus 27%, $P < .001$), lower median CD4 count (29 versus 218 cells/mm³, $P < .001$), higher median aspartate aminotransferase (AST; 52 versus 31 mg/dL, $P < .001$), higher median alkaline phosphatase (ALP; 121 versus 87 mg/dL, $P < .001$), and lower median albumin (27.2 versus 32.5 mg/dL, $P < .001$). Duration of hospitalization was significantly longer among patients who were hospitalized with ADI compared to those who were hospitalized with non-ADI (9.5 versus 7 days, $P = .005$).

The predicting factors of hospitalization with ADI by univariate logistic regression were hemoglobin (OR: 0.83; 95% CI: 0.71-0.97, $P = .020$), percentage of lymphocyte (OR: 0.77 per 5% increased; 95% CI: 0.67-0.89, $P < .001$), albumin (OR: 0.55 per 5 mg/mL increased; 95% CI: 0.41-0.74, $P < .001$), and CD4 count (OR: 0.85 per 10 cells/mm³ increased; 95% CI: 0.80-0.90, $P < .001$; Table 2). By forward stepwise multivariate logistic regression, the only predicting factor of hospitalization with ADI was CD4 count (OR: 0.85, per 10 cells/mm³ increased; 95% CI: 0.80-0.90, $P < .001$).

For discharge status, 136 (92%) patients were discharged home, 4 (2.7%) patients were transferred to another hospital, and 8 (5.4%) patients died. The comparison of patients' characteristics according to discharged status (eg, death and alive) is shown in Table 3. Lower median CD4 count (32 versus 84 cells/mm³, $P = .042$), higher median AST (70.5 versus 41 mg/dL, $P = .039$), and higher median ALP (143.5 versus 97 mg/dL, $P = .027$) were determined in patients who died. The cause of death among 7 patients was ADI. AIDS-defining illnesses associated with death were cerebral toxoplasmosis (1 patient), pulmonary tuberculosis (1 patient), histoplasmosis (1 patient), Kaposi sarcoma (1 patient), lymphoma (1 patient), Salmonella septicemia (2 patients), cryptococcosis (2 patients), cytomegalovirus infection (3 patients), and *P jirovecii* pneumonia (4 patients). Six of these 7 patients had more

Table 1. Comparison of Baseline Characteristics and Laboratory Investigations among Newly Diagnosed HIV-Infected Patients Who Were Hospitalized With AIDS-Defining Illness and Those Who Were Hospitalized with Non-AIDS-Defining Illness.

Variables	Causes of Hospitalization		P Value
	AIDS-Defining Illness (N = 74)	Non-AIDS-Defining Illness (N = 74)	
Median (IQR) age, years	39.3 (32.1-47.1)	39.3 (28.9 to 47.1)	.538
Male gender, n (%)	57 (77.0)	57 (77.0)	1.000
Route of HIV acquisition, n (%)			.031
Heterosexual	51 (68.9)	40 (54.1)	
Homosexual	18 (24.3)	23 (31.0)	
Intravenous drug use	0	3 (4.1)	
Bisexual	4 (5.4)	1 (1.4)	
Maternal to child	0	1 (1.4)	
Health insurance scheme, n (%)			.239
Universal coverage	22 (29.7)	18 (24.3)	
Civil service welfare	14 (18.9)	10 (13.5)	
Social security	3 (4.0)	4 (5.4)	
Self-payment	30 (40.5)	41 (55.4)	
Others	5 (6.8)	1 (1.4)	
Had comorbidity, n (%)	10 (13.5)	12 (16.2)	.818
Laboratory investigations			
Median (IQR) CD4 count, cells/mm ³	29 (15-57)	218 (108 to 371)	<.001
Median (IQR) hemoglobin, mg/dL	11.1 (9.7-12.5)	12.1 (11 to 13.5)	.004
Median (IQR) WBC, cells/mm ³	6650 (4610-9760)	7505 (–5540 to 10 080)	.303
Median (IQR) PMN, %	73.5 (61-84)	64.5 (53 to 76)	.001
Median (IQR) lymphocyte, %	17.5 (10-25)	27 (16 to 35)	<.001
Median (IQR) creatinine, mg/dL	0.8 (0.7-1.0)	0.9 (0.7 to 1.0)	.423
Median (IQR) albumin, g/dL	27.2 (22.4-30.4)	32.5 (27.3 to 35.5)	<.001
Median (IQR) AST, mg/dL	52 (31-88)	31 (23 to 61.5)	<.001
Median (IQR) ALT, mg/dL	37 (25-60)	39 (27 to 54.5)	.765
Median (IQR) ALP, mg/dL	121 (81-189)	87 (68 to 118)	<.001
Median (IQR) duration of hospitalization, days	9.5 (6-21)	7 (3 to 14)	.005

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; PMN, polymorphonuclear neutrophils; WBC, white blood cell count.

Table 2. Predicting Factors of Hospitalization with AIDS-Defining Illness among Newly Diagnosed HIV-Infected Patients by Univariate Logistic Regression.

Characteristics	Odds Ratio	95% CI	P Value
Age, per 10 years older	1.09	0.84-1.42	.523
Male gender	1.00	0.46-2.15	1.000
Universal coverage health insurance scheme	1.32	0.64-2.73	.460
Comorbidity	0.81	0.32-2.00	.644
History of syphilis	0.38	0.14-1.00	.050
Chronic hepatitis B infection	0.83	0.27-2.52	.743
Chronic hepatitis C infection	0.81	0.27-2.46	.714
CD4 count, per 10 cells/mm ³ increased	0.85	0.80-0.90	<.001
Hemoglobin, per 1 g/dL	0.83	0.71-0.97	.020
WBC, per 1000 cells/mm ³ increased	0.96	0.88-1.04	.287
PMN, per 5% increased	1.18	1.06-1.32	.004
Lymphocyte, per 5% increased	0.77	0.67-0.89	<.001
Creatinine, per 1 mg/dL	1.35	0.66-2.76	.407
Albumin, per 5 mg/dL increased	0.55	0.41-0.74	<.001
AST, per 5 mg/dL increased	1.02	1.00-1.05	.085
ALT, per 5 mg/dL increased	1.01	0.99-1.03	.367
ALP, per 5 mg/dL increased	1.01	1.00-1.03	.109

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; PMN, polymorphonuclear neutrophils; WBC, white blood cell count.

than 1 ADI. The other one died from non-ADI, which was *Streptococcus agalactiae* septicemia and meningitis.

Discussion

This study identified the causes of hospitalization among newly diagnosed individuals with HIV infection in Thailand where ART has been recommended for all since 2014. Most of the patients were male with a heterosexual risk of HIV acquisition and had very low CD4 counts. Half of the patients were hospitalized with ADI. Different characteristics and laboratory investigations between patients who were hospitalized with ADI and those who were hospitalized with non-ADI were determined, such as hemoglobin level, percentage of lymphocyte, levels of liver function, and CD4 count. Significantly longer duration of hospitalization was detected in patients who were hospitalized with ADI. Only predicting factor for hospitalization with ADI was CD4 count levels. The lower the level of CD4 counts, the higher the odds of hospitalization with ADI compared to those who had higher level of CD4 counts.

AIDS-defining illnesses were reported among 35.7% of newly diagnosed HIV-infected adults in this Thai university

Table 3. Comparisons of Baseline Characteristics and Laboratory Investigations among Newly Diagnosed HIV-Infected Patients by Discharged Status.

Variables	Death (N = 8)	Alive (N = 140)	P Value
Median (IQR) age, years	43.8 (36.8-56.9)	39.3 (30.0-46.9)	.214
Self-payment scheme, n (%)	4 (50)	67 (47.9)	.906
Median (IQR) CD4 count, cells/mm ³	32 (18-41.5)	84 (26-229)	.042
Median (IQR) hemoglobin, mg/dL	11.9 (11.1-12.9)	11.6 (9.9-13.1)	.538
Median (IQR) WBC, cells/mm ³	7535 (3970-12 380)	7025 (5160-9780)	.835
Median (IQR) PMN, %	76.5 (62.5-85)	68 (58.5-80)	.384
Median (IQR) lymphocyte, %	17.5 (11-23.5)	22 (11.5-30.5)	.430
Median (IQR) creatinine, mg/dL	0.7 (0.6-0.9)	0.9 (0.7 -1.0)	.230
Median (IQR) albumin, g/dL	27.0 (22.2-29.1)	29.7 (24.2-33.6)	.204
Median (IQR) AST, mg/dL	70.5 (47.5-132.5)	41.0 (26.0-76.0)	.039
Median (IQR) ALT, mg/dL	40 (32.5-77)	38 (26-55)	.574
Median (IQR) ALP, mg/dL	143.5 (111-216)	97 (72-142)	.027
Median (IQR) duration of hospitalization, days	23 (8.5-59)	8 (4-16)	.076

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; PMN, polymorphonuclear neutrophils; WBC, white blood cell count.

hospital, and the overall mortality rate was 1.8% in 2006.¹⁷ During 2006 to 2008, tuberculosis, *P jirovecii* pneumonia, and cryptococcosis were the most common causes of hospitalization in HIV-infected patients in Thailand.¹² The studies regarding causes for hospitalization after introducing ART in the country among HIV-infected individuals in Nigerians, Uganda, and the United States showed that the major causes of hospitalization were mainly due to ADI.¹⁸⁻²⁰ The most common causes were tuberculosis, cryptococcal meningitis, and malignancies (eg, Kaposi sarcoma and lymphoma), which were associated with CD4 count less than 200 cells/mm³.¹⁸⁻²⁰ We found that half of the patients were hospitalized for OI treatment, which was similar to previous studies.^{12,19,20} However, health insurance scheme, especially universal coverage health insurance scheme, was not significantly associated with hospitalization with ADI. This may be explained by a small number of study population, and the median of CD4 count for each insurance scheme was not significantly different ($P < .05$). Our patients who were hospitalized with ADI had lower hemoglobin, lower percentage of lymphocyte, abnormal liver function tests, lower albumin, and lower CD4 counts, which are also reflected in chronic HIV infection, poor nutritional condition, and low immune status. These routine laboratory investigations, except CD4 counts, could suggest a health-care provider test HIV infection for their patients. Baseline characteristics of our patients and the patients of the studies in Singapore, the United States, and Colombia were similar including middle age, more male gender, low CD4 count, and abnormal complete blood count (eg, anemia and lymphocytopenia).^{13,14,20}

The previous study in the same hospital showed that 32% of hospitalizations were due to non-ADI. Of these, 20% were due to ophthalmologic condition, 10% were due to general surgical conditions, and 8% were due to other medical conditions.¹² In this study, medical conditions were the most common cause of

non-ADI hospitalization, which include myocardial infarction, pulmonary arterial hypertension, stroke, venous sinus thrombosis, and sepsis. Approximately 6% of our patients were hospitalized with complications of metabolic syndrome such as cerebrovascular disease and cardiovascular disease. The study in the United States reported that 6.6% of HIV-infected patients were hospitalized with metabolic syndrome (eg, diabetes, ischemic heart disease, and cerebrovascular disease).⁸ Most of our patients who were hospitalized with nonmedical condition (eg, perianal abscess, bone fracture, and keratitis) had no symptoms and signs of HIV infection. They were diagnosed with HIV infection by routine preoperative anti-HIV testing. The previous study in the same hospital reported that the most common reason for anti-HIV testing was preoperative screening (41.2%), which we could detect in the new cases.¹⁷ The study in Nigeria aimed to determine the prevalence of HIV infections in preoperative patients admitted for surgical procedures and found that 3.5% of the 200 patients were diagnosed as positive for HIV-1 and 2.²¹ In addition, among 201 patients who were screened and scheduled for nonurgent surgery in Ivory Coast, positive HIV results were found in 8.3% of cases.²² The 90-90-90 treatment target aims help end the AIDS epidemic. The first 90, which means 90% of all people living with HIV will know their HIV status, is the most difficult target to achieve. HIV diagnosis and/or new case finding was the greatest point to start.

The strength of the study was retrieving the information from many sources, such as chemistry laboratory, microbiological data, histopathology, and radiological imaging to confirm the causes of hospitalization as well as the cause of death. There are some limitations to this retrospective study. Firstly, there was missing data of clinical characteristics and laboratory investigations, especially in patients who were hospitalized with non-ADI, this was not unexpected in view of the nature of a retrospective study. Secondly, the sample size was small

because we included only patients with newly diagnosed HIV infection. We excluded HIV-infected patients who were diagnosed at another hospital. Lastly, the study was conducted in a university hospital setting, which might not reflect the whole picture of Thailand and other resource-limited settings where there are differences in national background and policy of HIV/AIDS care. Furthermore, some of our patients were referred from other clinics or smaller settings, which could lead to more advanced HIV diseases.

In conclusion, half of adult HIV-infected Thai individuals were hospitalized with ADI. Early detection of HIV infection is important for early ART initiation and prevents the consequence of serious complications. National strategic HIV/AIDS plans should be scaled up for achieving the 90-90-90 targets.

Authors' Note

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Declaration of Conflicting Interests

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