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Incidence of *Pneumocystis carinii* pneumonia in treatment-naïve HIV-infected adult patients receiving primary *Pneumocystis carinii* pneumonia chemoprophylaxis with 48-week antiretroviral initiation

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ABSTRACT

Objective: The objective of the study was to determine the incidence of primary *Pneumocystis carinii* pneumonia (PCP) between patients who received and did not receive primary PCP chemoprophylaxis and investigate adverse drug reactions (ADRs) related to the chemoprophylaxis use. **Method:** A retrospective study was conducted in Siriraj Hospital, Thailand. Data were collected from HIV-infected adults, initiated with highly active antiretroviral therapy (HAART) with initial $CD4^+$ <200 cells/mm^3. **Results:** Overall, 217 patients had a median initial $CD4^+$ of 83 cells/mm^3 (interquartile range: 33.5–150.5) (range: 0–199), most of the initial HAART regimen was non-nucleoside reverse transcriptase inhibitors based containing tenofovir disoproxil fumarate (94.94%), and 104 patients (47.93%) received chemoprophylaxis. The incidence between patients who received and did not receive prophylaxis found no statistically significant difference ($p = 0.133$). Only one event was found in a severely immunocompromised patient who did not receive the prophylaxis. The absolute risk reduction of primary PCP incidence, and rate of ADRs was 0.89% (95% confidence interval, −0.84, 2.61) and 10.58% in patients who received the chemoprophylaxis, respectively. **Conclusion:** The initiation of HAART in HIV-infected patients who had the initial $CD4^+$ cell count <200 cells/mm^3 may impact on reducing the risk of developing primary PCP. Aside from the patients who received the prophylaxis, most of the adverse reactions were skin disorders.

Keywords: Highly active antiretroviral therapy, Acquired immune deficiency syndrome, Primary *Pneumocystis carinii* pneumonia

INTRODUCTION

HIV-1 infection is the most common cause of acquired immune deficiency syndrome (AIDS) in humans[1] and a result of comorbidity by opportunistic infections (OIs).[2,3] Thailand reported the incidence of HIV infection in 2019 at approximately 470,000 cases (410,000–540,000) with a prevalence rate of 1.0% (0.8–1.2%) of Thailand's population.[4] Highly active antiretroviral therapy (HAART) has been a principal standard of treatment for HIV-infected patients, leading to significantly lower overall OIs incidence in the HAART era.[5] Unfortunately, *Pneumocystis carinii* pneumonia (PCP) is one of the most common OIs found in HIV-infected patients.[6,7] Among hospitalized HIV-infected patients with pneumonia, the risk of mortality for PCP was higher than lung infections caused by other OIs such as sputum smear-positive pulmonary tuberculosis or cryptococcal pneumonitis.[8] Furthermore, PCP also had a crucial impact on

HIV-infected patients during their first 6 months of beginning HAART with a risk-adjusted mortality hazard of 2.36 (95% confidence interval [CI], 1.66–3.36) for the patients who developed PCP.[9]

PCP is a preventable disease. Cotrimoxazole is the first-line chemoprophylaxis against primary PCP in HIV-infected patients with a $CD4^+$ cell count of fewer than 200 cells/mm^3 ($<0.2 \times 10^9$ cells/l).[10] Some patients who could not tolerate the first line and unaffordable alternative chemoprophylaxis or were suffering from pills burden may not be initially assigned the primary PCP prophylaxis for their therapy after starting HAART.[11,12] Nevertheless, HAART may play an important role in lowering the risk and reducing the number of PCP incidents.[7] From 2014, the initiation of the HAART strategy has changed. All HIV-infected patients are strongly suggested to start HAART as soon as possible for achieving earlier viral suppression,[13] which may result in the decline of the primary PCP incidence as well, but there is a lack of clearly conclusive evidence. From the literature review, there are controversies of primary chemoprophylaxis use against PCP among HIV-infected adults who have initiated HAART. Cheng *et al*.[14] found that the risk of primary PCP was significantly higher in HIV-infected patients who did not receive primary PCP prophylaxis as guidelines indicated or who had discontinued the prophylactic therapy early with an adjusted risk ratio of 5.32 (95% CI, 1.18–23.94) while Lim *et al*.[11] found it not to be a significantly higher risk concerning missed the prophylaxis initiation during treatment with HAART.

The incidence of primary PCP usually develops during the first 12 months of beginning antiretroviral therapy.[15] Therefore, this study aimed to determine the incidence of primary PCP in treatment-naïve HIV-infected adult patients with and without primary PCP prophylaxis during the first 48 weeks of HAART and investigate the incidence of adverse drug reactions (ADRs) related to the primary PCP chemoprophylaxis use. This study may clarify some vagueness of the chemoprophylaxis's risk and benefit from preventing primary PCP in the new antiretroviral therapy era. It could be a new piece of further guidance and evidence for implementing a new regulation of the primary prophylaxis for PCP use in naïve HIV-infected adults who initiated with HAART.

MATERIALS AND METHODS

Definitions

The definition of terms used in this study was as follows: (1) Primary PCP chemoprophylaxis; in clinical practice in Thailand, primary PCP prophylaxis was recommended for patients with HIV/AIDS who had a $CD4^+$ cell count lower than 200 cells/mm^3 ($<0.2 \times 10^9$ cells/l), from Thailand national guidelines on HIV/AIDS treatment and prevention for the HIV-infected patients. Furthermore, patients with readiness to access HIV infection treatment are recommended to start the prophylaxis against primary PCP within 2–4 weeks after initiating HAART.[10] Primary PCP chemoprophylaxis was defined as the use of medication for the prevention of PCP, including one of these medications: Cotrimoxazole, dapsone, dapsone with pyrimethamine, aerosolized pentamidine, or clindamycin with primaquine.[16-18] (2) HAART was defined as the use of at least three antiretroviral drugs for HIV infection, consisting of two nucleoside reverse-transcriptase inhibitors (NRTIs) and another one of antiretroviral drug classes, such as protease inhibitors (PIs) or non-NRTIs (NNRTIs)[19] or integrase strand transfer inhibitors (INSTIs).[10] (3) The WHO HIV clinical staging is the classification system for HIV-infected disease progression ranging from Stage I (asymptomatic) to Stage IV (AIDS). Presented HIV infection-related symptoms or OIs at baseline were categorized as describing patients' baseline clinical manifestations in this study.[20] (4) HIV viral suppression (HIV viral undetectable) was defined as having <40 copies of HIV RNA per milliliter of the blood test. (5) Primary PCP; the physician gave the diagnosis of primary PCP in the medical chart. It was categorized as presumptive in patients who presented with typical manifested symptoms of subacute dyspnea, fever, non-productive cough, and chest discomfort, together with the chest radiograph's abnormality, and responded from the standard therapy of PCP. Diagnosis of PCP with confirmed respiratory specimen was considered definitive.[21]

Study design

A retrospective cohort study was conducted among HIV-infected adult patients who had initiated HAART before June 31, 2018. The medical charts were followed for 48 weeks from HAART initiation to collect primary PCP incidence and ADRs related to the chemoprophylaxis use [Figure 1]. This study was approved by the Siriraj Institutional Review Board with a certificate of approval number SI 500/2019.

Setting and participants

HIV-infected adult patients who regularly attended follow-up visits from February 18, 2020, to July 16, 2020, were recruited from the infectious disease and immunodeficiency outpatient clinic (Siriraj Hospital, Bangkok, Thailand). The physician had preliminarily screened participants for the study criteria eligibility (i.e., who had a $CD4^+$ cell count <200 cells/mm^3 at HAART initiation) and asked if they could give the researchers voluntary permission to access their medical records, then the researcher performed the informed consent process. The study population was the naïve HIV-infected adults older than 18 years old, initiated HAART before June 31, 2018, with a $CD4^+$ cell count <200 cells/mm^3 ($<0.2 \times 10^9$ cells/l) at the baseline of therapy. Inclusion criteria were the following: (1) Patients provided the informed consent document to access their medical records. (2) Received HAART continuously during their follow-up visits. (3) Availability of the baseline $CD4^+$ cell count <200 cells/mm^3 ($<0.2 \times 10^9$ cells/l) which was measured no longer than 6 months before starting HAART or 3 months after starting HAART. (4) Patients received at least one follow-up visit after initiating HAART. This study included the patients who had ever taken antiretroviral drugs to treat hepatitis B virus infection and pre-exposure prophylaxis before presenting HIV seroconversion. Exclusion criteria were the following: (1) Patients had PCP before starting HAART and (2) patient's medical record was not complete or insufficient data for analysis. Sample size calculation was performed using the log-rank test of survival in two groups formula. The Z value for 95% confidence of 1.96 and the value for power of 80%

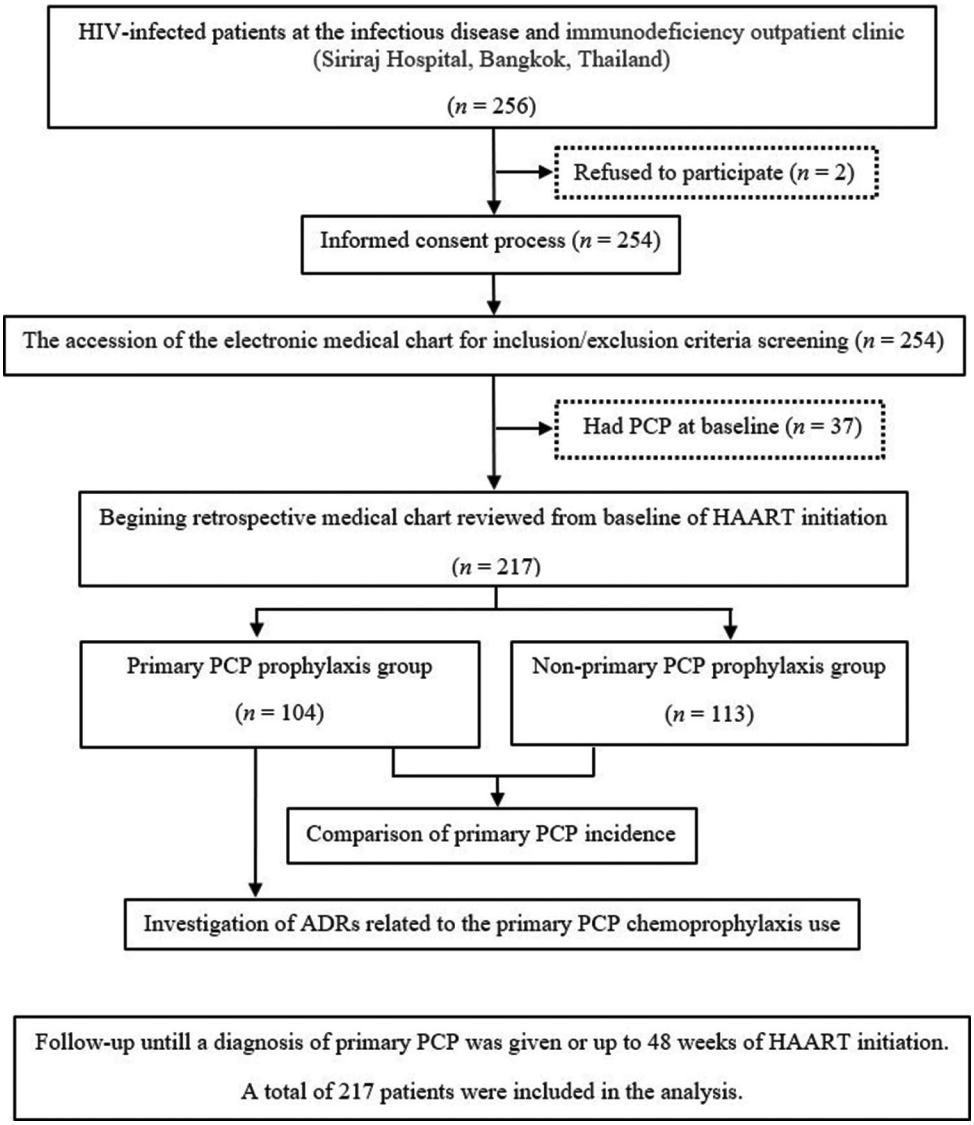

Figure 1: The study flow diagram

were used. The incident rate of primary PCP in HIV-infected patients who initiated HAART was estimated from the literature review, using 0.3/100 person-years and 2.88/100 person-years for the patient group with and without primary PCP prophylaxis drug, respectively.[14,22] At least 69 patients per group were required for the analysis.

Variables and outcomes

In this study, there was the primary PCP chemoprophylaxis use as an independent variable. The dependent variable and the main outcome were the primary PCP incidence during the first 48-week HAART initiation. Comparing the incidence found between patients who received and did not receive the chemoprophylaxis, if its use was related to the probability of primary PCP-free disease during 48 weeks of HAART implementation, the survival analysis (free of the disease) was used to detect the difference. The secondary outcome was the ADRs related to the primary PCP chemoprophylaxis use among patients in the chemoprophylaxis group.

Data collection

There was a major issue of concern about individual HIV-infected patient's confidentiality. The data were collected from the patients who had provided informed consent documents. The date of patient initiation of HAART was the starting point for data collection. Sociodemographic and clinical data were extracted from electronic medical chart records for 48 weeks after initiation of HAART, including sex, age, risks of HIV infection, WHO HIV clinical stage, history of OIs, underlying diseases, the use of alcohol/smoking, date of HIV diagnosis, the start date of HAART, HAART regimen, the baseline of $CD4^+$ cell count and blood HIV viral load, the $CD4^+$ levels and viral loads at week 12, 24, and 48 after starting HAART, the start date of primary PCP prophylaxis drug and dosage, the discontinuation date of primary PCP prophylaxis drug, the $CD4^+$ level, and viral load during discontinuation of primary PCP prophylaxis drug, the date of primary PCP diagnosis, adverse effects related to the prophylaxis use, and non-compliance with primary PCP prophylaxis and antiretroviral

drugs use. As for incomplete 48 weeks after HAART initiation, the date of loss to follow-up or patient referral was collected. The endpoints of data follow-up for primary PCP incidence were 48 weeks after initiating HAART except for the patients who had developed primary PCP or did not have primary PCP but their last observed follow-up time was <48 weeks after initiating HAART, such as lost to follow-up or referred to another hospital was defined as censored. The adverse effects were collected from the medical chart records diagnosed by the physician and reassessed by the ADR Surveillance Center pharmacists. All patients who experienced adverse effects of prophylaxis use are notified in the hospital ADR computerized alert system. A total of 256 patients were preliminarily screened by the physician's coinvestigator. Patients who refused to participate (n = 2) and had PCP at baseline (n = 37) were excluded from the study. In this study, 217 patients met the inclusion/exclusion criteria and were included in the final analysis.

Statistical analysis

The data analysis was performed using the SPSS program version 22 (SPSS Co., Ltd., Bangkok Thailand). Mean (standard deviation; + SD), median (interquartile range [IQR]), and frequency (%) were used to describe patient characteristics and descriptive results. The incidence of primary PCP was diagnosed by the physician. Both presumptive and definitive primary PCP diagnoses were used to calculate the incidence rate using the sum of the primary PCP events divided by the sum of individual times at risk throughout the observation period. The log-rank test of survival analysis was a statistical comparison of primary PCP incidence rate between the patients who received primary PCP chemoprophylaxis those who did not receive primary PCP chemoprophylaxis. In addition, to describe the risk reduction in the primary PCP incidence rate between patients in with and without chemoprophylaxis groups, we calculated absolute risk reduction (ARR) with a 95% CI. $p < 0.05$ was considered statistically significant.

RESULTS

Patients' characteristics

At the end of the study, 217 patients were eligible for the inclusion/exclusion criteria with a total follow-up time of 197.35 person-years. There were 137 males (63.1%), and 15% of females were pregnant. The median age, $CD4^+$ cell count, and percentage of $CD4^+$ T cell ($CD4^+$ %) at baseline were 39 years (IQR: 30–48), 83 cells/mm^3 (IQR: 33.5–150.5) (0.083 × 10^9 cells/l, IQR: 0.0335–0.1505), and 6.06% (IQR: 3.05–10.04), respectively. The risk of HIV infection was mostly sexual transmission. In this study, 156 patients (71.9%) were reportedly heterosexual. According to the history of OIs before HAART implementation, 114 patients had 147 episodes. The three highest OIs were oral candidiasis 26.27%, herpes zoster infection 8.76%, and lung tuberculosis 8.29%. Baseline characteristics categorized by patients who received and did not receive primary PCP prophylaxis use, as shown in Table 1. Dual-NRTI plus NNRTI formed the majority of the initial HAART regimen found in 211 patients (97.24%), and 104 patients (47.93%) received primary PCP prophylaxis drug following guideline recommendation. Implementation of primary PCP chemoprophylaxis was divided into three patterns: Patients who were started prophylactic before (40/104; 38.46%), concurrent (17/104; 16.35%), and after (47/104; 45.19%) initiation of HAART. The median values of week interval between the date of beginning the prophylaxis and HAART were as follows: 1 week (1–3), 0 weeks, and 4 weeks (2–9), respectively. The regimens of initial HAART and primary PCP prophylaxis were described, as shown in Tables 2 and 3, respectively.

After patients were assigned to start HAART, $CD4^+$ cell counts had a gradual increase in both groups from weeks 12, 24, and 48 following HAART initiation [Figure 2]. Virological response to HAART rapidly occurred. Proportions of patients who achieved undetectable viral load were seen within 12 weeks and tended to be considerably increased from week 24 through week 48 with patients in the received and did not receive that prophylaxis groups were 58.54% versus 68.18%, 82.50% versus 78.75%, and 86.73% versus 93.75%, respectively.

In this study, 41 patients in the prophylaxis group (39.42%; 41/104) and 42 patients in the non-prophylaxis group (37.17%; 42/113) required initial HAART modification, but the frequencies of patients who required initial HAART regimen modification were quite identical. Furthermore, poor adherence to HAART was reported in both the prophylaxis group (4.81%, n = 5) and the non-prophylaxis group (1.78%, n = 2).

Among 104 patients who received primary PCP prophylaxis, 66 patients (63.46%) discontinued the prophylaxis after HAART initiation when during their recovery, an immune parameter was detected with the $CD4^+$ cell count >200 cells/mm^3 (>0.2 × 10^9 cells/l) along with achieving undetectable viral load. Discontinuation of the prophylaxis was only when their viral load test reduced to the lowest practical level which was found among 21 patients (20.19%). In this study, 17 patients (16.35%) were found whose $CD4^+$ cell count value nor their viral load level approached the criteria based on guideline recommendation for discontinuation of prophylaxis.

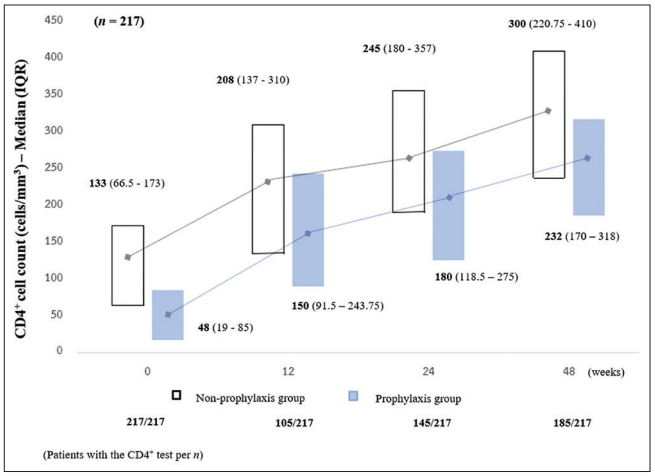

Figure 2: The median $CD4^+$ cell count at baseline and during 48 weeks of highly active antiretroviral therapy initiation

Table 1: Baseline characteristics of patients who received and did not receive the prophylaxis

Characteristics	All patients (*n*=217)	Primary prophylaxis (*n*=104)	Non-primary prophylaxis (*n*=113)
	***n* (%)**	***n* (%)**	***n* (%)**
Male	137 (63.1)	71 (68.27)	66 (58.41)
Age (years) – median (IQR)	39 (30–48)	41 (33–49)	38 (26.5–47.5)
Initial CD4+, (cells/mm^3) – median (IQR)	83 (33.5–150.5)	48 (19–85)	133 (66.5–173)
Initial CD4+ %, median (IQR)	6.06 (3.05–10.04)	4.33 (1.99–6.52)	9 (5–12.37)
Range of initial CD4+cell count, (cells/mm^3)			
100–199	94 (43.3)	22 (21.20)	72 (63.70)
50–99	48 (22.1)	30 (28.80)	18 (15.90)
<50	75 (34.6)	52 (50.00)	23 (20.40)
WHO clinical staging of HIV			
I	69 (31.8)	20 (19.23)	49 (43.36)
II	44 (20.3)	21 (20.19)	23 (20.35)
III	70 (32.3)	38 (36.54)	32 (28.32)
IV	34 (15.6)	25 (24.04)	9 (7.97)
Initial HIV viral load, (copies/ml)			
Mean log10 (± SD)	4.91+1.18	5.21+0.62	4.63+1.50
No data	180 (82.95)	86 (82.69)	94 (83.19)
HIV infection with comorbidity conditions	41 (18.89)	17 (16.35)	24 (21.24)
Cigarette smoking	20 (9.22)	9 (8.65)	11 (9.73)
Social drinker	15 (6.91)	13 (12.5)	2 (1.77)
HAART initiation after diagnosis of HIV (days), median (IQR)	14 (4–41)	16 (6–46.5)	11 (3–36.5)
History of HAART treatment			
Modification of initial HAART regimen	83 (38.25)	41 (39.42)	42 (37.17)
HAART non-adherence	7 (3.23)	5 (4.81)	2 (1.77)

Multiply unit of cells/mm3 by 0.001 to obtain SI unit (10^9 cells/l)

Risk/Incidence of primary PCP

In the period of 48 weeks of HAART initiation, censored observation occurred in five patients due to loss to follow-up (n = 3) and was referred to other hospitals (n = 2). Only one patient was diagnosed with a definitive primary PCP during a total of 197.35 person-years of observation with an overall incidence rate of 0.51/100 person-years. By the time, the event had occurred in the non-primary PCP prophylaxis group, there was no event case of primary PCP found among patients with primary PCP prophylaxis. The incidence rate could be barely seen as 0.99/100 person-years in the non-primary PCP prophylaxis group versus 0/100 person-years in the primary PCP prophylaxis group. The overall probability of primary PCP disease-free survival was 99.5% during 48 weeks after HAART initiation from Kaplan–Meier analysis. Rates of primary PCP disease-free survival stratified using the prophylaxis were 99.1% versus 100%, respectively. Furthermore, log-rank test analysis showed that there was no significant difference in disease-free survival probabilities or risks of the incidence of primary PCP between the two groups. The ARR of primary PCP incidence was 0.89% (95% CI, −0.84, 2.61) for treatment with primary PCP chemoprophylaxis.

Characteristics of a male patient who developed primary PCP; this was only one episode of definitive primary PCP diagnosis that occurred in a patient with a low baseline CD4$^+$ cell count of 6 cells/mm^3 after observation for 4 weeks following HAART initiation in the non-primary PCP prophylaxis group. His baseline of the World Health Organization (WHO) clinical staging of HIV was in Stage IV because of various opportunistic coinfections, including oral candidiasis, *Mycobacterium haemophilum,* and cytomegalovirus infections; and it was these conditions that led him to the clinical setting and the first diagnosis of positive HIV serum test.

ADRs related to primary PCP chemoprophylaxis

About 10.58% (11/104) of patients with the prophylaxis group reported ADRs related to primary PCP prophylaxis. Most of adverse effects were skin reactions (n = 8), including maculopapular rash (n = 3), pruritus (n = 2), fixed drug eruption (n = 1), maculopapular rash with angioedema (n = 1), and Stevens–Johnson syndrome (SJS) (n = 1). A median of these reactions had occurred within 19 days (IQR: 7.75–51.75) after the prophylaxis initiation. Drugs induced transaminitis (n = 2) developed within a couple of months after starting primary PCP prophylaxis. Furthermore, dyspnea with low blood pressure (n = 1) was reported in the medical record, which occurred rapidly following the second dose of

Table 2: Initial HAART regimen prescription pattern

Initial HAART regimens	All patients (*n*=217)	Primary prophylaxis (*n*=104)	Non-primary prophylaxis (*n*=113)
	n (%)	*n* (%)	*n* (%)
NNRTI-based regimen			
Efavirenz plus			
Tenofovir/lamivudine	117 (53.92)	54 (51.93)	63 (55.74)
Tenofovir/emtricitabine	77 (35.49)	34 (32.69)	43 (38.1)
Zidovudine/lamivudine	2 (0.92)	1 (0.96)	1 (0.88)
Stavudine/lamivudine	1 (0.46)	-	1 (0.88)
Zidovudine/tenofovir/lamivudine	1 (0.46)	1 (0.96)	-
Zidovudine/tenofovir/emtricitabine	1 (0.46)	1 (0.96)	-
Rilpivirine plus			
Tenofovir/emtricitabine	7 (3.23)	6 (5.78)	1 (0.88)
Tenofovir/lamivudine	2 (0.92)	2 (1.92)	-
Nevirapine plus			
Stavudine/lamivudine	2 (0.92)	1 (0.96)	1 (0.88)
Tenofovir/lamivudine	1 (0.46)	-	1 (0.88)
PI-based regimen			
Lopinavir-ritonavir plus			
Zidovudine/lamivudine	2 (0.92)	2 (1.92)	-
Tenofovir/lamivudine	1 (0.46)	-	1 (0.88)
INSTI-based regimen			
Raltegravir plus			
Zidovudine/lamivudine	1 (0.46)	-	1 (0.88)
Tenofovir/emtricitabine	1 (0.46)	1 (0.96)	-
Tenofovir/emtricitabine/efavirenz	1 (0.46)	1 (0.96)	-

HAART: Highly active antiretroviral therapy, NNRTI: Non-nucleoside reverse-transcriptase inhibitors, PI: Protease inhibitors, INSTI: Integrase strand transfer inhibitors

prophylaxis. We found seven out of 11 patients who developed ADRs stopped those offensive drugs immediately after being diagnosed with adverse reactions related to the drug use of primary PCP prophylaxis, and four out of 11 patients substituted the initial chemoprophylaxis drug against primary PCP and continued with the durable alternative prophylaxis regimen until the responsiveness of HAART had reached the standard criterion.

DISCUSSION

In this retrospective cohort study, we compared the incidence of primary PCP between patients who received and did not receive primary PCP prophylaxis among HIV-infected patients. There was no statistically significant difference in the incidence of PCP during a follow-up of 48 weeks after initiation of HAART. Only one case of a patient who did not receive prophylaxis experienced a primary PCP.

The incidence rate of primary PCP during the initiation of HAART in HIV-infected adult patients with the $CD4^+$ cell count <200 cells/mm^3 (<0.2 × 10^9 cells/l) was documented from 0.3 to 3.00/100 person-years. These incident rates depended on the rate of chemoprophylaxis acquisition, study design, and the prophylaxis discontinuation.[11,14,15,22,23] Interestingly, in this subgroup analysis, patients who early discontinued the prophylaxis before reaching $CD4^+$ cell counts above 200 cells/mm^3 (>0.2 × 10^9 cells/l) or undetectable viral load revealed that there was no such event.

Among HIV-infected patients who indicated for initiation of prophylactic drug against primary PCP, but in practice did not get the prophylaxis at the beginning of HAART may be due to the pill burden or drug allergy.[11,12] The results from a retrospective study found that the risk of developing primary PCP increased in HIV-infected patients without a standard chemoprophylaxis drug with an adjusted risk ratio = 5.32 (95% CI, 1.18–23.94). Unfortunately, most of the unexpected incidents occurred in the low HAART adherence patients.[14] The benefit of primary PCP prophylaxis was described in a simulation model among HIV-infected patients receiving HAART in the United States. Estimation of the lifetime costs and quality-adjusted life expectancy (QALE) of using the prophylaxis until the $CD4^+$ had recovered to more than 200 cells/mm^3 (>0.2 × 10^9 cells/l) could prevent 343 cases of primary PCP per 1000 patients with cost 5100 US Dollar per QALE.[24] In this study, the incidence between patients who received and did not receive the prophylaxis was not statistically significantly different. A prospective cohort study showed that the treatment of HIV-infected patients without prophylaxis during 90% of HAART utilization rate did

Table 3: Characteristics of primary PCP prophylaxis regimen (n=217)

Prescription pattern of primary PCP prophylaxis regimen	*n* (%)
Received primary PCP prophylaxis according to guideline recommendations	
Yes	104 (47.93)
No	113 (52.07)
Reasons for not prescribing primary PCP prophylaxis	113 (100)
No record	87 (77.00)
Having a skin rash from the use of HAART and treatment of coinfections	12 (10.62)
History of hypersensitivity to primary PCP prophylaxis	6 (5.31)
Elevated liver function tests	5 (4.42)
Having a skin rash from other causes before starting HAART	2 (1.77)
Patients refused the use of primary PCP prophylaxis	1 (0.88)
Primary PCP prophylaxis regimens	104 (100)
Sulfamethoxazole/trimethoprim (800/160 mg) once-daily	57 (54.81)
Sulfamethoxazole/trimethoprim (400/80 mg) once-daily	42 (40.38)
Dapsone (100) once-daily oral	4 (3.85)
Pyrimethamine, sulfadiazine, and leucovorin	1 (0.96)

PCP: *Pneumocystis carinii* pneumonia

not significantly increase the risk of primary PCP occurrence with an incidence rate ratio = 1.39 (95% CI, 0.46–4.12), but not for mortality. Without prophylaxis, the risk of death may be higher because of severe immunocompromisation, which is a barrier to obtaining the prophylaxis because of undergoing treatment for various co- OIs.[11]

This study noticed that as the virological response to HAART occurred rapidly, the percentage of virally suppressed patients increased in both groups steadily following HAART initiation. Consequently, the possibility of developing primary PCP was not significantly higher in the non-prescribed prophylactic patients. The early HAART initiation after the diagnosis of HIV infection was found among the patients in this study with a median lag time of 14 days (IQR; 4–41). In addition, the HIV-infected patients have followed antiretroviral adherence. We found only seven patients (3.23%) in this study who reported non-adherence.

We did not perform an intervention or experiment in this study. More details about factors associated with the primary PCP incidence among AIDS patients receiving HAART should also be demonstrated. Thus, the primary PCP prophylaxis uses as a non-independent risk factor for developing primary PCP could be not an obvious conclusion. Some evidence from the literature review may explain the results of this study. First, with the use of HAART, the PCP incidence has reduced in the range of 2.0–15.6 times from the previous HAART era.[5] Subgroup analysis from a large study in the USA found that the HIV-infected patients who continued with HAART were likely to develop PCP in the lower $CD4^+$ scale, with a median of 29 cells/mm^3 (0.029 × 10^9 cells/l).[25] A large study in Europe found that the $CD4^+$ cell count levels did not differ between the HIV-infected patients undergoing HAART and the HAART-naïve patients with a median of 30 cells/mm^3 (0.03 × 10^9 cells/l).[26] Concordant with our findings was the occurrence of a primary PCP that appeared only in the case of an ultra-low $CD4^+$ level of 6 cells/mm^3 (0.006 × 10^9 cells/l). Therefore, patients with severe immunocompromisation remain at risk of developing PCP during HAART. Second, for the $CD4^+$ cell count level, a retrospective study demonstrated the risk of primary PCP incidence in HIV-infected adults who neither had HAART nor PCP prophylaxis initiated. There was a low probability of incidence of PCP in patients with a $CD4^+$ test >100 cells/mm^3 (>0.1 × 10^9 cells/l). Most patients who developed primary PCP had the median $CD4^+$ cell count value of 26 cells/mm^3 (0.026 × 10^9 cells/l).[27] These evidences may explain our results, in which the incidence of PCP in our study was not observed in HIV-infected patients without prophylaxis, with a median of 133 cells/mm^3 (0.133 × 10^9 cells/l) at the beginning of HAART. Third, the HIV viral load was also an independent risk factor for predicting the occurrence of PCP in HIV-infected patients. The risk ratio of developing the incidence of PCP increased proportionately with the higher viral load level.[28] In contrast, lower viral load resulted in a lower risk of developing PCP. In this study, patients seemed to be continuously increasing in their number of undetectable viral levels from week 12 through week 48 of HAART initiation.

Approximately 10.58% of patients had adverse reactions from primary PCP prophylaxis. Most of the adverse reactions were skin disorders. From the literature reviews, 13.70% of HIV-infected patients with chemoprophylaxis against PCP suffered from skin reactions.[14] During the 20 years of compiling studies reported in Thailand on SJS and toxic epidermal necrolysis (TEN), 22% of adult patients with SJS or TEN events were associated with cotrimoxazole.[29] Furthermore, a study discovered that 6.80% of patients had other threatening adverse reactions, such as leukopenia.[14]

Interpretation should be cautious with several limitations in this study. First, this retrospective cohort study was an analysis of HIV-infected patients from a single tertiary public teaching hospital, which may differ from patients' characteristics in other individual health-care settings. Second, it is neither randomized control nor a prospective observational study, but a retrospective data observation from current patients who underwent regular treatment in the hospital. The analysis included only the medical records from HIV-infected individuals who gave consent to us. Therefore, it is not possible to know the exact number of primary PCP incidents among patients who have been referred to another hospital, died, or could not be followed up, so the results of this study may represent conclusions only for those who regularly follow-up in a health-care setting. Third, because of the limitation of study design, it was not possible to quantify HARRT adherence data. We used reports of "patients taking medications regularly" that doctors had recorded in the medical records to assess the HAART adherence rate. Finally, because this study showed a very low incidence of primary PCP disease amid a high proportion of viral suppressive patients, the impact of HAART could be a probable cause to reduce the risk of developing primary PCP.[9] It may explain why the non-primary PCP prophylaxis

patients with an initial meager $CD4^+$ cell count showed no difference from a virally suppressed percentage compared with the prophylaxis group and might reflect the indifferent incidence among HIV-infected patients who received and did not receive primary PCP prophylactic drugs. However, this might be statistically significant in a larger sample size and in particular with HIV-infected patients with a range of $CD4^+$ cell count below 50 cells/mm^3 ($<0.05 \times 10^9$ cells/l) at baseline of HAART initiation.

CONCLUSION

In the condition of good viral suppression, the incidence rate of primary PCP was noticeably low in this study. The naïve HIV-infected adult patients with $CD4^+$ cell count <200 cells/mm^3 ($<0.2 \times 10^9$ cells/l), who concurrently started HAART with and without primary PCP prophylaxis, may suggest the benefits from HAART initiation to lower the risk of primary PCP disease. However, HIV-infected adult patients with severely immunocompromisation should start PCP prophylaxis concurrent with HAART. Besides, there should be close monitoring of the ADRs related to prophylaxis use and the occurrence of primary PCP until detectable response to HAART. Finally, a feasible good study design should clarify these findings in further study.

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