ORIGINAL ARTICLE

Primary Prophylaxis for *Pneumocystis jirovecii* Pneumonia in People Living with HIV after Early Initiation of Highly Active Antiretroviral Therapy Era: Does It Still Need?

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Background: Co-trimoxazole is a mainstay for primary *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis in people living with human immunodeficiency virus (PLWH) whose CD4 count is <200 cells/mm^3. However, there is limited evidence of the outcome of co-trimoxazole to prevent PJP after early initiation of highly active antiretroviral therapy era.

Objective: To assess co-trimoxazole's efficacy and side effects in primary PJP prophylaxis in PLWH.

Materials and Methods: A retrospective study was performed from January 2010 to December 2019 at a single medical university hospital in Thailand. Adults aged 18 or older who received combination antiretroviral therapy (cART), had baseline CD4 <200 cells/mm^3, and were not diagnosed with PJP before the cART were enrolled. Patients with a history of sulfa allergy who received co-trimoxazole for treatment of other diseases, received drugs that had a therapeutic effect on *Pneumocystis jirovecii*, or lost important data were excluded.

Results: A total of 1,249 individuals, 227 patients (126 PLWH received co-trimoxazole and 101 PLWH did not receive co-trimoxazole [control group]) complied with eligibility conditions for analysis. The median (IQR) age was 34.7 (27.8 to 42.7) years. The median (IQR) baseline CD4 count in co-trimoxazole and control group were 52 (26 to 106) and 107 (75 to 151) cells/mm^3 (p<0.001), respectively. The prevalence of PJP after cART initiation in co-trimoxazole group and control group were 0.8% and 1.0% (p=1.00), respectively. The all-cause mortality rate in the co-trimoxazole group was 3.2%, while there was no death in the control group.

Conclusion: There is no significant difference between the rate of PJP in PLWH who receive and do not receive co-trimoxazole prophylaxis. Primary PJP prophylaxis in all PLWH whose CD4 count <200 cells/mm^3 may not be necessary for the era of highly effective cART, and the guideline recommendation should be reconsidered.

Keywords: HIV; Pneumocystis pneumonia; Co-trimoxazole; Primary prophylaxis

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Highly active antiretroviral therapy (HAART) is developed and widely available, but opportunistic infections (OIs) still a major burden in people living with human immunodeficiency virus (PLWH). The data from bureau of epidemiology of Thailand, *Pneumocystis jirovecii* pneumonia was the second most common opportunistic infection in Thailand from 1984 to 2006[(1)].

Pneumocystis jirovecii pneumonia (PJP) is an AIDS-defining illness in PLWH, occurring most frequently when the CD4 count is below 200 cells/mm³ and causes morbidity and mortality in an advanced patients[(2-4)]. PLWH with PJP could develop clinical worsening pneumonia with respiratory failure which requiring an intensive care unit admission. The mortality rate of PJP in PLWH is about 10 to 20%[(4-6)].

The world health organization (WHO) recommends starting co-trimoxazole prophylaxis in PLWH with CD4 <200 cells/mm³ to prevent PJP[(7)]. The guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV recommends starting

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primary PJP prophylaxis in adults and adolescents with HIV with CD4 count <200 cells/mm³ and should considered in person who have a CD4 cell percentage <14%[8]. The Thailand national guidelines on HIV/AIDS treatment and prevention 2020 also recommends starting primary PJP prophylaxis in PLWH with CD4 <200 cells/mm³, CD4 <14%, oropharyngeal candidiasis, or AIDS-defining illness while primary prophylaxis for other OIs is optional[9]. Some experts recommend starting primary PJP prophylaxis at CD4 200 to 250 cells/mm³ if ART initiation must be delayed and frequent monitoring of CD4 count is impossible[10]. The mainstay primary PJP prophylaxis is co-trimoxazole which has the wide range of side effects.

Co-trimoxazole is composed of trimethoprim and sulfamethoxazole which inhibits folate metabolism as known as anti-metabolite agents. Its spectrum covers many bacterial species and is the most effective agent against *Pneumocystis jirovecii* and commonly used for primary PJP prophylaxis in PLWH[7-9]. However, the risk of co-trimoxazole side effects may outweigh its benefit. The most common co-trimoxazole toxicity are acute kidney injury, hyperkalemia, hepatitis, neutropenia, allergic reaction [e.g., rash, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS)][11,12]. The incidence of co-trimoxazole side effects used for primary PJP prophylaxis in PLWH was 21 to 26%[13].

To date, there are widely available HAART which highly effective to raise CD4 count and suppress HIV viral load. The trend of the rate of OIs including PJP is decreased in HAART era[14]. A study of primary PJP prophylaxis in PLWH with HAART era has not been well reported. We therefore conducted a retrospective cohort study to investigate the efficacy and safety of primary PJP prophylaxis using co-trimoxazole in PLWH.

Materials and Methods

A retrospective cohort study from January 2010 to December 2019 at single medical university hospital, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand was performed. The present study was approved by the human research ethics committee, Khon Kaen University (approval number HE631232).

Subjects

The study included all PLWH visited Srinagarind Hospital from 1st January 2010 to 31st December 2019. Adult age of 18 or older, received combination antiretroviral therapy (cART), had baseline CD4 below 200 cells/mm³, and did not diagnose PJP prior to the cART were enrolled. PLWH who had history of sulfa allergy, received co-trimoxazole for a treatment of other diseases, received the drugs that had therapeutic effect to *Pneumocystis jirovecii* (e.g., clindamycin, primaquine, atorvaquone, pentamidine, and dapsone), or loss of the important data (e.g., baseline CD4 count, indication of co-trimoxazole initiation) were excluded.

PLWH were categorized into two groups: PLWH who received co-trimoxazole for primary PJP prophylaxis were classified as "co-trimoxazole group"; PLWH who did not receive co-trimoxazole were as "control group".

Definition

The diagnosis of PJP was established by clinical manifestation compatible with PJP and supportive evidence such as chest radiograph finding, arterial blood gas and clinical improvement after treatment. The diagnosis of PJP was made even without a demonstration of *Pneumocystis* organisms.

A combination antiretroviral therapy defined as combination of antiretroviral drugs composed of 3 or more agents.

Data collection

We retrospectively selected the medical records from a PLWH database. The medical records were retrieved and reviewed. The demographic data, clinical information and laboratory results were collected from outpatient department (OPD) medical records, inpatient department (IPD) medical records and electronic medical records program. Baseline data included age, gender, underlying diseases, date of first diagnosis of HIV, date of first visit, baseline opportunistic infections, history of sexual transmitted diseases, hepatitis B virus and hepatitis C virus, antiretroviral regimen and CD4 cell count were collected. The diagnosis of PJP and all-cause death were determined and compared between the two groups. The secondary outcomes were side effects caused by co-trimoxazole and new diagnosis of other opportunistic infections after cART. The data were recorded in case record form then exported and analyzed.

Statistical analysis

The results are composed of categorical and continuous data. The categorical data were reported as frequencies and percentages. The normal distributed continuous data were presented as mean and standard deviation (SD) while the non-normal distributed continuous data were presented as the median and interquartile range (IQR). Differences of categorical data between the two groups were compared using Chi-square or Fisher's exact test as appropriate. Continuous data between the two groups were compared using Student's t-test and Mann-Whitney test as appropriate. Kaplan-Meier analysis with the log-rank test was used to determine and compare the probability of developing PJP and side effects due to co-trimoxazole between the two

groups. All analysis was performed using SPSS program version 28.0 (Chicago, IL, U.S.A.) and R program. A p-value of less than 0.05 was accepted as statistically significant.

Results

A total of 1,249 individuals, 227 PLWH (126 PLWH received co-trimoxazole and 101 PLWH did not receive co-trimoxazole [control group]) complied with eligibility conditions for analysis (Figure 1). The median (IQR) age was 35.7 (28.5 to 43.2) years and 33.7 (26.6 to 42.5) years in co-trimoxazole and control group, respectively. Both groups are male predominant. The baseline characteristics of the patients are shown in Table 1.

The median (IQR) baseline CD4 count in co-trimoxazole group was statistically significantly lower than control group [52 (26 to 106) vs. 107 (75 to 151) cells/mm³ (p<0.001) respectively]. There were only 56 PLWH evaluated baseline HIV viral load which was not significantly different in both groups. PLWH in co-trimoxazole group had longer time to initiation cART compared to control group [24.5 (12.8 to 40.0) vs. 14.0 (5.0 to 25.5) days (p<0.001) respectively].

About one-fifth in each groups had baseline underlying diseases [19.8% vs. 18.8% (p=0.85) in co-trimoxazole and control group respectively]. The most common baseline underlying diseases in both groups were essential hypertension and dyslipidemia, respectively.

Concurrent opportunistic infections in co-trimoxazole group were significantly higher than control group [67.5% vs. 38.6% (p<0.001) respectively]. Tuberculosis was the most common co-opportunistic infections in both groups [35.7% vs. 28.7% (p=0.26) in co-trimoxazole and control group respectively]. Patients in co-trimoxazole group had co-infection with cryptococcosis higher than control group [16.7% vs. 2.0% (p<0.001) respectively].

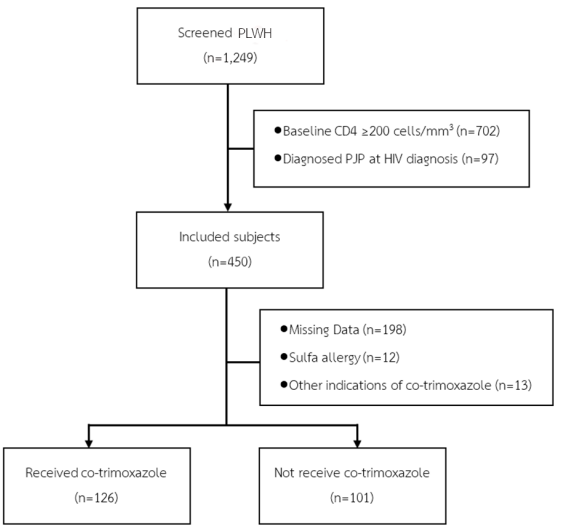

Figure 1. Consort diagram.

The prevalence of PJP after cART initiation in this cohort was 0.9% [co-trimoxazole group was 0.8% (n=1) and control group was 1.0% (n=1) (p=1.00)]. The prevalence and disease-free probability are shown in Table 2 and Figure 2. A PLWH in co-trimoxazole group presented with pulmonary tuberculosis with CD4 of 39 cells/mm³ at baseline. This PLWH developed PJP 1.4 months after being diagnosed with HIV infection and 1.2 months after initiating cART. A PLWH in the control group presented with pulmonary tuberculosis and disseminated talaromycosis with CD4 of 81 cells/mm³ at baseline. This PLWH developed PJP 10 months after being diagnosed with HIV infection and 11 months after initiating cART.

One-third (31.7%) of PLWH in co-trimoxazole group had side effects from co-trimoxazole. The side effects were skin drug eruptions, hepatitis, acute kidney injury, hyperkalemia, neutropenia, and nausea/vomiting. The most frequent side effect was skin drug eruptions (17% of co-trimoxazole group) which composed of fatal skin drug eruptions 31.8% as shown in Table 2.

PLWH in co-trimoxazole group had statistically significantly lower of CD4 at 12 months than PLWH in control group [50 (26 to 106) vs. 96 (67 to 156) cells/mm³ (p<0.001), respectively]. There were no difference of proportion of viral load <50 copies/mL at 12 months between both groups [co-trimoxazole group and control group were 86.4% and 85.4% (p=0.88), respectively].

All-cause mortality rate in co-trimoxazole group was 3.2% while no death in control group. The causes of death were PJP (n=1), lymphoma (n=1), ischemic heart disease (n=1), and suicidal (n=1). All-cause mortality probability is shown in Figure 3.

Discussion

CD4 counts below 200 cells/mm³ is a major risk factor for PJP[4]. Primary prophylaxis for PJP with co-trimoxazole in PLWH with CD4 counts <200 cells/mm³ has been widely recommended in national and international guidelines. Primary prophylaxis for PJP seem to be showed survival benefit in pre-cART era[15]. The recommendation about optional primary prophylaxis of the opportunistic infections other than PJP has been revised including cryptococcosis based on lower incidence of the disease and highly effective cART[16,17].

Our study had defined the efficacy of cotrimoxazole as primary PJP prophylaxis in PLWH who had CD4 counts <200 cells/mm³, as we observed a similar prevalence of PJP in both groups. No patient died in control group while 1 PLWH in co-trimoxazole group died from PJP. The

Table 1. Baseline characteristics between co-trimoxazole group and control group

Characters	Co-trimoxazole group n=126	Control group n=101	p-value
Age (IQR)	35.7 (28.5 to 43.2)	33.7 (26.6 to 42.5)	0.078
Female gender (%)	41 (32.5)	30 (29.7)	0.647
BMI (kg/m^2) (IQR)	19.9 (18.0 to 21.8)	20.1 (18.7 to 22.4)	0.303
GFR (mL/min/1.73 m^2) (IQR)	108.5 (97.6 to 118.6) n=104	108.0 (94.7 to 118.6) n=93	0.634
Baseline CD4 (cells/mm^3) (IQR)	52.0 (26 to 106)	107.0 (75 to 151)	<0.001
Baseline HIV viral load (copies/mL) (IQR)	161,946 (80,623 to 414,137) n=33	165,242 (30,780 to 362,497) n=23	0.511
Other medical conditions[a] (%)	25 (19.8)	19 (18.8)	0.854
Time from HIV diagnosis to start cART (days) (IQR)	24.5 (12.8 to 40.0)	14.0 (5.0 to 25.5)	<0.001
Concurrent opportunistic infection/malignancy (%)	85 (67.5)	39 (38.6)	<0.001
- Tuberculosis	45 (35.7)	29 (28.7)	0.263
- NTM	5 (4.0)	4 (4.0)	0.998
- Cryptococcosis	21 (16.7)	2 (2.0)	<0.001
- Talaromycosis	5 (4.0)	2 (2.0)	0.466
- Histoplasmosis	2 (1.6)	0 (0.0)	0.504
- Others[b]	40 (31.7)	23 (22.8)	0.059
Initial ART regimen[c] (%)			
- TDF/XTC/EFV	96 (76.2)	89 (88.1)	0.021
- AZT/3TC/NVP	5 (4.0)	3 (3.0)	0.735
- Others[d]	25 (19.8)	9 (8.9)	0.024

BMI=body mass index; cART=combination antiretroviral therapy; GFR=glomerular filtration rate, HIV=human immunodeficiency virus, IQR=inter quartile range; NTM=non-tuberculous mycobacteria

[a]Other medical conditions: Most common medical condition was essential hypertension (8.0% in both group) and dyslipidemia (6.3% and 6.9% in co-trimoxazole and control group respectively).

[b]Others: other concurrent opportunistic diseases in co-trimoxazole group (40 PLWH) consisted of 20 events of oral candidiasis, 13 events of herpes simplex virus (HSV)/herpes zoster (HZV), 3 events of cytomegalovirus (CMV), 1 event of each salmonellosis, lymphoma, Kaposi's sarcoma (KS), and cyclosporiasis. In control group (23 PLWH) consisted of 10 events of oral candidiasis, 9 events of HSV/HZV, 2 events of CMV, 1 event of each KS and acquired immunodeficiency syndrome dementia complex.

[c]ABC=abacavir; EFV=efavirenz; NVP=nevirapine; TDF=tenofovir disoproxil fumarate; XTC=lamivudine (3TC) or emtricitabine (FTC)

[d]Others: other initial ART regimens in co-trimoxazole group (25 PLWH) consisted of 11 PLWH with stavudine (d4T)/3TC/EFV, 6 PLWH with d4T/3TC/NVP, 3 PLWH with AZT/3TC/EFV, and 5 PLWH with other ART regimens. In control group (9 PLWH) consisted of 2 PLWH with TDF/XTC/rilpivirine (RPV), 2 PLWH with TDF/XTC/atazanavir/ritonavir, and 5 PLWH with other ART regimens.

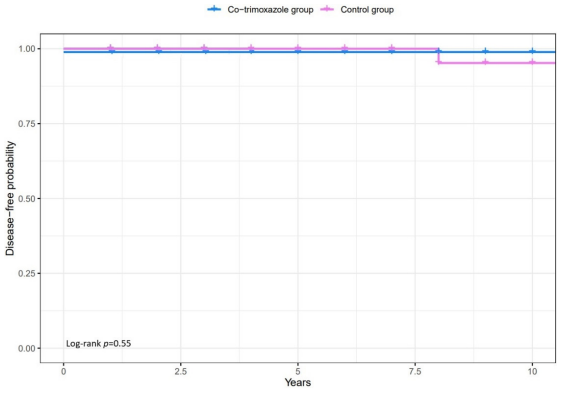

Figure 2. Kaplan-Meier plot for PJP free probability.

PLWH died from PJP had baseline CD4 counts 65 cells/mm^3 (6.2%), diagnosed pulmonary tuberculosis at the first diagnosis of HIV, and very poor compliance to treatment. The results from the present study suggested that primary PJP prophylaxis should not be required in all PLWH and there was no survival benefit from primary PJP prophylaxis in PLWH receiving cART, even though CD4 counts were below 200 cells/mm^3. In addition, the mortality rate of HIV-related PJP was also lower than the recent studies[3,4]. All PLWH in the present study had received cART could be a reason explained the results. Furthermore, cART was early initiated in all HIV-diagnosed patients without opportunistic infections and not depend on CD4 counts according to the Thai national guidelines established since 2017[18]. Manosuthi et al. found in retrospective study that almost all incidence of major opportunistic infections developed within three months after ART initiation[19]. According to data from bureau of epidemiology of Thailand, the prevalence

Table 2. Prevalence of PJP and adverse effect from co-trimoxazole

Characters	Co-trimoxazole group n=126	Control group n=101	p-value
Opportunistic diseases after cART initiation (%)	20 (15.9)	9 (8.9)	0.118
PJP prevalence after cART initiation (%)	1 (0.8)	1 (1.0)	1.00
CD4 at 12 months (cells/mm^3) (IQR)	50 (26 to 106) n=77	96 (67 to 156) n=55	<0.001
VL <50 copies/mL at 12 months (%)	51 (86.4) n=59	41 (85.4) n=48	0.879
Other opportunistic infection/malignancy after cART initiation (%)			
Tuberculosis	3 (2.4)	0	0.256
NTM	3 (2.4)	0	0.256
Talaromycosis	1 (0.8)	1 (1.0)	1.00
CMV	0	1 (1.0)	0.445
Others[a]	18 (14.3)	10 (10.0)	0.087
Adverse effect from co-trimoxazole (%)	40 (31.7)	0	<0.001
Skin exanthem[b]	22 (11.1)	0	
Hepatitis	11 (8.7)	0	
Acute kidney injury	3 (2.4)	0	
Hyperkalemia	2 (1.6)	0	
Neutropenia	2 (1.6)	0	
Nausea/Vomiting	7 (5.6)	0	
Mortality rate[c]	4 (3.8)	0	0.130

cART=combination antiretroviral therapy; CMV=cytomegalovirus; IQR=inter quartile range; NTM=non-tuberculous mycobacteria; PJP=*Pneumocystis jirovecii* Pneumonia; SD=standard deviation; VL=viral load

[a]Others: Other opportunistic diseases after cART intiation in co-trimoxazole group consisted of 1 event of each histoplasmosis, cryptococcosis, salmonellosis, and acquired immunodeficiency syndrome cholangiopathy, 2 events of oral candidiasis, 3 events of lymphoma, and 7 events of herpes simplex virus (HSV)/herpes zoster virus (HZV). Other opportunistic diseases after cART intiation in control group consisted of 1 event of each cryptococcosis, lymphoma, and Kaposi sarcoma, 2 events of salmonellosis, and 4 events of HSV/HZV

[b]Skin exanthem: maculopapular rash 15 PLWH, Stevens-Johnson syndrome/Toxic epidermal necrolysis 4 PLWH, Drug reaction with eosinophilia and systemic symptoms 3 PLWH

[c]Mortality rate: 1 PLWH from cryptococcosis, 1 PLWH from primary central nervous system lymphoma, 1 PLWH from ischemic heart disease, and 1 PLWH from suicide

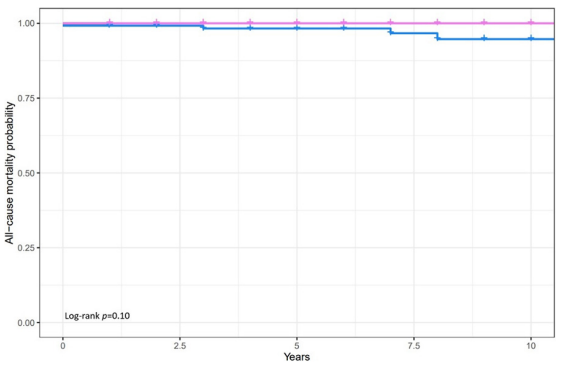

Figure 3. Kaplan-Meier plot for all-cause mortality free probability.

and incidence of all opportunistic infections seem to be decreased included PJP[1]. Recent studies had demonstrated the incidence of PJP was higher compared with the present study[13,20,21]. The fact that these prior studies conducted in pre-cART era and initiation of ART depended on CD4 counts could be explained this different finding.

About one-third (31.7%) of co-trimoxazole group had side effects of co-trimoxazole which skin drug eruptions was the most common side effect. The rate of side effects of co-trimoxazole was still high and slightly higher than the recent study which reported that the incidence of side effects of co-trimoxazole using for primary PJP prophylaxis in PLWH was 21 to 26%[13]. The proportion of side effects of co-trimoxazole were almost similar. These side effects were one of the reasons that affected prognosis of disease, interrupted, or delayed the treatment, and caused other morbidities such as renal dysfunction, cardiac arrhythmia, and cytopenia needed blood transfusion.

One hundred ninety-eight patients of included PLWH were excluded due to missing data. Most common missing data were undocumented baseline CD4 count 185 PLWH (93.4%) and loss to follow-up 11 patients (5.9%). All these patients did not report PJP. This missing data might not affect the result in the present study.

The results from the present study showed that the prevalence of PJP after initiation cART was low even though the patients did not receive primary PJP prophylaxis. The risk of side effects due to co-trimoxazole outweighed the benefit. Primary PJP prophylaxis in all PLWH whose CD4 count <200 cells/mm³ would not be necessary. Administration of primary PJP prophylaxis should be considered case by case.

However, there were some differences between baseline characteristics in both groups. In co-trimoxazole group may be assumed that patients were more poor immune status than control group because of low baseline CD4 and more baseline OIs in co-trimoxazole group. These were the points that we were concerned about in the analysis. There are some limitations in the present study included the retrospective study, the single-center analysis, and the small number of PLWH. Further large, randomized controlled studies are needed to establish.

Conclusion

There is no significant difference between the rate of PJP infection in PLWH who receive and do not receive co-trimoxazole prophylaxis. Primary PJP prophylaxis in all PLWH whose CD4 count <200 cells/mm³ may not be necessary in the era of highly effective cART and the guideline recommendation should be reconsidered.

What is already known on this topic?

International and Thai guideline recommend Co-trimoxazole for primary *Pneumocystis jirovecii* pneumonia prophylaxis in PLWH whom CD4 count <200 cells/mm³ with limited evidence regarding after early initiation of highly active antiretroviral therapy.

What this study adds?

The prevalence of *Pneumocystis jirovecii* pneumonia was low regardless of no Co-trimoxazole prophylaxis.

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Conflicts of interest

The authors declare no conflict of interest.

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