TRIMETHOPRIM-SULFAMETHOXAZOLE FOR *PNEUMOCYSTIS JIROVECII* PNEUMONIA PROPHYLAXIS AMONG HIV-POSITIVE PATIENTS IN THE ERA OF EARLY ANTIRETROVIRAL THERAPY INITIATION

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Abstract

Background: Trimethoprim-Sulfamethoxazole (TMP-SMX) is currently recommended for the primary prevention of *Pneumocystis jirovecii* pneumonia (PCP) among HIV-positive patients whose CD4 count is less than 200 cells/mm^3. However, adverse drug reactions (ADR) have been reported among some patients. In the era of early antiretroviral therapy (ART) initiation, the prevalence of PCP has gradually decreased. Therefore, to avoid unnecessary ADR, TMP-SMX might be less beneficial when the patient receives early ART initiation.

Objectives: The study aimed to evaluate the incidence of PCP, all-cause mortality, CD4 count at 6 months after ART, other opportunistic infections (OIs), and ADRs among HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis.

Methods: This retrospective cohort study was conducted in Ratchaburi Hospital between January 2014 and February 2022. HIV-positive patients with an initial CD4 count <200 cells/mm^3 or <14% and receiving early ART initiation within 2 weeks after HIV diagnosis were investigated. Patients with and without TMP-SMX prophylaxis were analyzed in terms of baseline characteristics, the incidence of PCP, all-cause mortality, other OIs and ADRs from TMP-SMX. The ratio of TMP-SMX vs. no TMP-SMX groups was 2:1.

Results: In total, 230 HIV-positive patients presenting an initial CD4 count <200 cells/mm^3 or <14% were included in this study. All patients received early ART initiation within 2 weeks after HIV diagnosis and showed good adherence. The incidence of PCP in the TMP-SMX prophylaxis group was 2 of 153 cases (1.31%) and in the no prophylaxis group was 3 of 77 cases (3.89%), OR 0.329; 95% CI, (0.053 – 1.998); p=0.226. CD4 count at 6 months after ART initiation significantly increased in the no prophylaxis group (277.4 vs. 179.5 cells/mm3; mean difference 97.92; 95% CI of difference, (65.15-130.69); p <0.001). All-cause mortality and other bacterial and OIs did not differ between the two groups. All adverse events from TMP-SMX were minor rashes, 13 of 153 cases (8.5%).

Conclusion: Among HIV-positive patients receiving early ART initiation, the incidence of PCP revealed no difference between with and without TMP-SMX prophylaxis. All-cause mortality and rate of OI were also comparable between the 2 groups.

Keywords: HIV, Early antiretroviral therapy, *Pneumocystis jirovecii* pneumonia, Trimethoprim-Sulfamethoxazole, Prophylaxis

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Introduction

Currently, HIV can be diagnosed quickly and accurately. Anti-retroviral agents are more effective with fewer side effects and more accessibility, resulting in better quality of life and longer life expectancy.[1, 2] However, some HIV-positive patients, with low CD4 count, experience opportunistic infections (OIs) due to delayed diagnosis and treatment.

The most common OIs among HIV-positive patients are tuberculosis, *Pneumocystis jirovecii* pneumonia (PCP), and cryptococcal meningitis.[1, 3] The incidence of PCP in the era before ART was 80 cases/1,000 population/year and decreased to 40 cases/1,000 population/year after introducing ART.[4]

According to the current guidelines on HIV treatment and prevention. PCP prophylaxis is recommended among HIV-positive patients with CD4 count <200 cells/mm^3 and can be discontinued either when the CD4 count is >200 cells/mm3 for at least three consecutive months or between 100 and 200 cells/mm3 with undetectable serum HIV RNA for three to six months.[5] Trimethoprim-Sulfamethoxazole (TMP-SMX) is a highly effective drug for PCP prophylaxis. However, serious adverse drug reactions (ADRs) have also been frequently reported.[6-8]

From related studies, comparing prophylaxis versus no prophylaxis groups, the prevalence of PCP did no significantly differ among HIV-positive patients already receiving ART.[9-12] However, a comparative study has not been conducted in Thailand. Therefore, to avoid ADRs from TMP-SMX, we hypothesized no difference in PCP prevalence PCP between TMP-SMX prophylaxis and nonprophylaxis groups when patients received early ART initiation. This study aimed to evaluate the incidence of PCP among HIV-positive patients receiving early ART with and without TMP-SMX for PCP prophylaxis.

Methods

This study was reviewed and approved by the Institutional Review Boards of Ratchaburi Hospital, Thailand (COA-RBHEC 027/2023). This retrospective cohort study was conducted in the HIV Clinic, Ratchaburi Hospital between January 2014 and February 2022. According to Teshale et al.,[9] the incidence of PCP was 5.2/100 persons-year in the prophylaxis group and 19.2 /100 persons-year in the never started prophylaxis group. Thus, the sample size in this study was 139 and 70, respectively. When considering a 10% dropout rate, the sample size was 153 cases in the TMP-SMX group and 77 cases in the nonTMP-SMX group.

HIV-positive patients aged at least 18 years old with an initial CD4 count <200 cells/mm^3 or <14% and receiving early ART initiation within two weeks after HIV diagnosis were eligible for this study. The patients were excluded if they had prior PCP, poor ARV adherence, and had already received drugs other than TMP-SMX for PCP prophylaxis. Patients with and without TMP-SMX prophylaxis were analyzed in terms of baseline characteristics, the incidence of PCP, all-cause mortality, other OIs and ADRs from TMP-SMX.

Data collection

The patient's clinical and laboratory parameters were collected from the hospital electrical database (HOSxP). Baseline characteristics included age, sex, initial CD4 count, co-infection, OIs and co-morbidity and initial laboratory investigation at the time of HIV diagnosis.

Definitions

Parameters in this study are defined as the following; HIV positive status was defined as having three positive serum anti-HIV testing results.[13] *Pneumocystis jirovecii* pneumonia was diagnosed using clinical settings including signs, symptoms and chest X-ray compatible with PCP infection (bilateral symmetrical interstitial infiltration) with one of the following diagnostic methods[5, 14]: positive for *Pneumocystis jirovecii* from sputum smear, bronchoalveolar lavage or positive biopsy using GMS staining, direct immunofluorescent staining or Polymerase Chain Reaction for PCP or symptoms improving after empirical treatment of PCP.

Early ART initiation was defined as receiving ART within two weeks after HIV diagnosis. Under the current HIV guidelines, either rapid

ART initiation within seven days or same-day ART was recommended. However, for those positive for OIs, we chose two weeks as the optimal timing of early ART initiation in this study.[13, 15]

Adherence was defined as "good" at ≥95% e.g., <2 doses of 30 doses or <3 doses of 60 doses were missed. Between 85 and 94% was defined as "poor" (3 to 5 doses of 30 doses or 3 to 9 doses of 60 doses were missed) as documented by the ART healthcare provider. [16]

Minor drug rash was defined as mild cutaneous reactions to drugs not seriously compromising clinical conditions and early improvement with full recovery. [17]

Outcome assessment

The primary outcome was to evaluate the incidence of PCP in HIV-positive patients receiving early ART with and without TMP-SMX for PCP prophylaxis. The secondary outcome was to evaluate all-cause mortality, CD4 count at six months after ART, other bacterial and OIs and ADRs from TMP-SMX.

Statistical analysis

Categorical variables were reported as frequencies and percentages. Mean ± standard deviation was used for normally distributed continuous variables and median with interquartile range (percentile 25 and 75) for nonnormally distributed variables. The normality of the distribution of variables was examined using the Kolmogorov-Smirnov test. For demographic data, categorical variables were compared using chi-square or Fisher's exact test and continuous variables were compared using the Mann-Whitney U test.

To compare the incidence of PCP infection between the two groups, univariate analysis was performed and reported by odds ratio (OR) and 95% confidence intervals (CI). For all tests performed, a two-tailed $p<0.05$ was considered statistically significant. SPSS, Version 26.0 was used to perform all statistical analysis.

Results

From January 2014 to February 2022, 230 HIV-positive patients presenting an initial CD4 count <200 cells/mm^3 or <14% were included in this study. All patients had early ART within two weeks after HIV diagnosis with good adherence. The enrollment flowchart is shown in **Figure 1**.

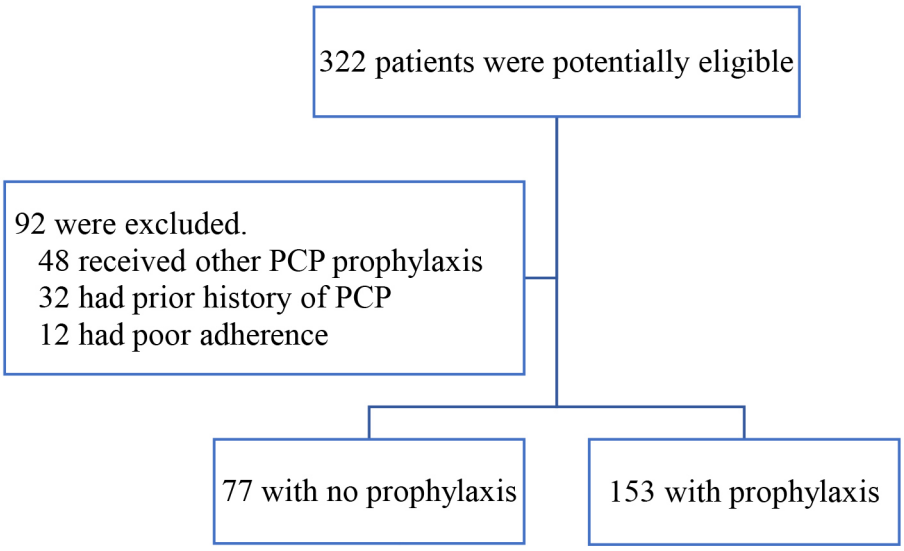

Figure 1. Enrollment flow chart of HIV-positive patients with and without prophylaxis during the study period (6-month follow-up)

The baseline characteristics of 230 patients are shown in **Tables 1 and 2.** Of 230 patients, 77 patients had no TMP-SMX and 153 patients had TMP-SMX prophylaxis. At the time of HIV diagnosis, all patients had a mean age of 38.68 ±11.65 years old and the median initial CD4 count was 77 cells/mm^3, interquartile range (IQR) = 77.00 to 157.25. Most patients were male (63.5%). In the prophylaxis group, the median initial CD4 count was significantly lower (67 vs. 139 cells/mm^3, p <0.001) and the rate of tuberculosis was higher (13.7% vs. 3.9%, p = 0.021). Other comorbidity, co-infection and initial laboratory investigation were comparable between groups. The median duration of ART initiation after diagnosis of HIV was two weeks.

PCP in the TMP-SMX prophylaxis group was 2 of 153 cases (1.31%) and the in no prophylaxis group was 3 of 77 cases (3.89%), OR= 0.33; 95% CI, (0.05 to 1.99); p = 0.226. CD4 count at six months after ART in the no prophylaxis group was significantly increased (277.4 vs. 179.5 cells/mm3; mean difference 97.92; 95% CI of difference, (65.15 to 130.69); p<0.001). All-cause mortality and other bacterial and OIs did not differ between the two groups. All adverse events from TMP-SMX were minor rashes, 13 of 153 cases (8.5%). When performing subgroup analysis using CD4 count levels, those having CD4 count <100 cells/mm^3 revealed a higher prevalence of PCP in the nonTMP-SMX prophylaxis group (10 vs. 2.0%, respectively). However, no statistical significance was noted.

Table 1. Baseline characteristics of 230 HIV-positive patients receiving early ART with and without TMP-SMX for PCP prophylaxis

Factors	No prophylaxis N = 77	PCP prophylaxis N = 153	*p*-value
Age, year [mean ± SD]	36.83 ± 11.33	39.61 ± 11.73	0.088
Male, N (%)	52 (67.5)	94 (61.4)	0.365
Initial CD4 count, cell/mm^3 [median (IQR)]	139 (63.50,239.00)	67 (29.00,125.50)	< 0.001
Initial CD4 count, % [mean ± SD]	9.05 ± 4.36	6.17 ± 4.08	< 0.001
Duration of ART initiation after diagnosis, weeks [median (IQR)]	2 (2,2)	2 (2,2)	0.090
Duration of follow-up, years [median (IQR)]	3 (1,4)	4 (3,6)	0.080
Co-infection			
Hepatitis B, N (%)	5 (6.5)	11 (7.2)	0.845
Hepatitis C, N (%)	4 (5.2)	4 (2.6)	0.447
Syphilis, N (%)	10 (13.0)	10 (6.5)	0.101
Isolated cryptococcal antigenemia, N (%)	1 (1.3)	3 (2.0)	1.000
Opportunistic infection			
No OIs, N (%)	64 (83.1)	125 (81.7)	0.791
Tuberculosis, N (%)	3 (3.9)	21 (13.7)	0.021
CMV infection, N (%)	1 (1.3)	2 (1.4)	1.000
Talaromycosis, N (%)	1 (1.3)	1 (0.7)	1.000
Histoplasmosis, N (%)	1 (1.3)	0 (0)	0.335
Candidiasis, N (%)	7 (9.1)	4 (2.6)	0.046

Table 1. Baseline characteristics of 230 HIV-positive patients receiving early ART with and without TMP-SMX for PCP prophylaxis (Cont.)

Factors	No prophylaxis N = 77	PCP prophylaxis N = 153	*p*-value
Comorbid disease			
No disease, N (%)	63 (81.8)	108 (70.6)	0.066
CAD, N (%)	0 (0)	0 (0)	-
Hypertension, N (%)	8 (10.4)	18 (11.8)	0.756
DM, N (%)	4 ((5.2)	7 (4.6)	1.000
CKD, N (%)	1 (1.3)	0 (0)	0.335
Stroke, N (%)	1 (1.3)	0 (0)	0.335
Cirrhosis, N (%)	1 (1.3)	1 (0.7)	1.000
Other, N (%)	10 (13.0)	29 (19.0)	0.671

Abbreviations: ART, Antiretroviral therapy; CAD, Coronary artery disease; CMV, Cytomegalovirus; DM, Diabetes mellitus; CKD, Chronic kidney disease; mm3, Cubic millimeters; OIs, Opportunistic infections; PCP, Pneumocystis pneumonia; TMP-SMX, Trimethoprim-Sulfamethoxazole

Table 2. Initial laboratory investigation at the time of HIV diagnosis of 230 HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis

Factors	No prophylaxis N = 77	PCP prophylaxis N = 153	*p*-value
Hb, g/dL [mean ± SD]	12.08 ± 2.40	11.74 ± 2.08	0.269
Hct, % [mean ± SD]	36.77 ± 6.82	35.59 ± 5.77	0.171
WBC, cell/mm^3 [median (IQR)]	5730 (4710, 7035)	5260 (4080, 6385)	0.053
ANC, cell/mm^3 [median (IQR)]	3280 (2370, 4566))	2856 (2164, 2856)	0.053
Platelet, cell/mm^3 [median (IQR)]	244000 (201500, 326500)	243000 (191000,303000)	0.239
BUN, mg/dL [mean ± SD]	9.93 ± 3.41	11.05 ± 5.45	0.153
Creatinine, mg/dL [mean ± SD]	0.86 ± 0.21	0.88 ± 0.44	0.721
Potassium, mmol/L [mean ± SD]	3.98 ± 0.44	4.00 ± 0.54	0.846
TB, mg/dL [median (IQR)]	0.38 (0.25, 0.53)	0.44 (0.30,0.54)	0.113
DB, mg/dL [median (IQR)]	0.20 (0.14, 0.24)	0.21 (0.15,0.28)	0.092
AST, U/L [median (IQR)]	23.50 (20.00, 30.75)	27.00 (21.00,41.00)	0.053
ALT, U/L [median (IQR)]	21.50 (16.00, 33.25)	25.00 (16.00,40.00)	0.273
ALP, U/L [median (IQR)]	80.00 (64.00, 110.00)	85.00 (71.00,117.00)	0.088
Albumin, g/dL [mean ± SD]	4.16 ± 0.51	3.95 ± 0.64	0.053
Globulin, g/dL [mean ± SD]	4.29 ± 0.76	4.34 ± 0.80	0.745

Abbreviations: ANC, Absolute neutrophil count; ALT, Alanine transaminase; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; DB, Direct bilirubin; g/dL, gram per deciliter; Hb, Hemoglobin; Hct, Hematocrit; mm3, cubic millimeters; mg/dL, milligram per deciliter; mmol/L, millimole per liter; OIs, opportunistic infections; PCP, Pneumocystis pneumonia; TB, Total bilirubin; U/L, units per liter

Table 3. Primary outcome of 230 HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis.

Factor	No prophylaxis N = 77	PCP prophylaxis N = 153	OR (95% CI)	*p*-value
Primary outcome				
Incidence of PCP, N (%)	3 (3.89)	2 (1.31)	0.33 (0.05 – 1.99)	0.226

Abbreviation: PCP, Pneumocystis pneumonia.

Table 4. Secondary outcome of 230 HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis

Factor	No prophylaxis N = 77	PCP prophylaxis N = 153	Mean difference or OR (95% CI of diff)	*p*-value
Secondary outcome				
Mortality at 6 months	0 (0)	1 (0.65)	-	1.000
Death from OI, N (%)	0 (0)	0 (0)	-	-
Death from other causes, N(%)	0 (0)	1 (0.65)	-	1.000
CD4 at 6 months				
CD4 count, cell/mm^3 [mean ± SD]	277.44 ± 129.96	179.52 ± 90.61	Mean difference 97.92 (65.15 - 130.69)	< 0.001
CD4 count, % [mean ± SD]	15.30 ± 5.81	11.21 ± 5.26	Mean difference 4.09 (2.59 - 5.59)	< 0.001
Other bacterial infection, N (%)				
GI, N (%)	0 (0)	1 (0.7)	-	1.000
Other infection*, N (%)	0 (0)	0 (0)	-	-
Other OIs				
Tuberculosis, N (%)	1 (1.3)	2 (1.3)	OR 1.01 (0.09 – 11.27)	0.996
Talaromycosis, N (%)	0 (0)	0 (0)	-	-
Histoplasmosis, N (%)	0 (0)	1 (0.7)	-	1.000
Toxoplasmosis, N (%)	0 (0)	0 (0)	-	-
Adverse drug reactions (ADRs) of Trimethoprim-Sulfamethoxazole				
Minor rash, N (%)	0 (0)	13 (8.5)	-	0.005
SJS/TEN, N (%)	0 (0)	0 (0)	-	-
Serious ADRs, N (%)	0 (0)	0 (0)	-	-
Nausea/Vomiting, N (%)	0 (0)	0 (0)	-	-

*Other infections: H&N, RS, CVS, GI, NS, SST, MSK, LN

Abbreviations: ADRs, Adverse drug reactions; CVS, Cardiovascular system; GI; Gastrointestinal; H&N, Head and neck; LN, Lymph node; mm^3, Cubic millimeters; MSK, Musculoskeletal; NS, Nervous system; OI, Opportunistic infection; PCP, Pneumocystis pneumonia; RS, Respiratory system; SST, Skin and soft tissue; SJS/TEN, Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis

Table 5. Subgroup analysis by CD4 count of PCP prevalence of 230 HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis

CD4 count, cell/mm^3	No prophylaxis N = 77	PCP prophylaxis N = 153	OR (95%CI)	*p*-value
<100	3/30 (10.0%)	2/102 (2.0%)	0.18 (0.02-1.13)	0.068
100-199	0/23 (0%)	0/48 (0%)	-	-
≥ 200	0/24 (0%)	0/3 (0%)	-	-

Abbreviation: mm^3, Cubic millimeters

Discussion

In this retrospective cohort study, from January 2014 to February 2022, the incidence of PCP in the TMP-SMX vs. the nonTMP-SMX prophylaxis group was 2 of 153 cases (1.31%) and 3 of 77 cases (3.89%) respectively, with OR 0.33; 95% CI 0.05 to 1.99; p= 0.226. Similar to a related study[10], this result emphasized that the incidence of PCP did not significantly increase among HIV-positive patients with early ART initiation not receiving TMP-SMX prophylaxis. Nonetheless, the incidence of failed TMP-SMX prophylaxis in this study was lower than in related studies (1.31 vs. 11%).[11, 12]

In contrast to the current guidelines on HIV treatment and prevention recommend that recommend PCP prophylaxis in all cases when patients had CD4 <200 cells/mm^3 [5, 13, 15], subgroup analysis in our study showed that all PCP patients in both groups had initial CD4 count <100 cells/mm^3 (OR= 0.18; 95% CI 0.02 to 1.13; p = 0.068). HIV-positive patients with an initial CD4 count >100 cells/mm^3 did not develop PCP during the study period. Similar to the related systematic review[18], the risk of PCP increased more among HIV-positive patients with CD4 <100 cells/mm^3 compared with CD4 count between 101 and 200 cells/mm^3. Furthermore, the Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) study[19] investigated the safety of discontinuation of PCP prophylaxis among patients with CD4 <200 cells/mm^3 receiving virological suppression. The event rate of PCP among HIV-positive patients with CD4 counts between 101 and 200 cells/mm^3 with or without TMP-SMX prophylaxis was similar. Therefore, discontinuing PCP prophylaxis in this group might also be safe when their serum HIV RNA was undetectable. However, from the COHERE study, when patients had CD4 <100 cells/mm^3, PCP prophylaxis could significantly reduce the incidence of PCP, which was similar to other related studies.[9, 10] In contrast to ours, among patients with CD4 <100 cells/mm^3, the incidence of PCP was not statistically significant between groups (but tended to increase in the nonprophylaxis group 10 vs. 2%). This might have been due to the small sample size when performing subgroup analysis. These data could imply that even early initiating ART within two weeks, PCP prophylaxis might be essential among patients with CD4 <100 cells/mm^3 but not in the group with CD4 >100 cells/mm^3.

The mortality rate at six months between groups did not differ; however, we did not calculate the sample size for this secondary outcome. Interestingly, the mean CD4 count at six months after ART initiation in the nonTMP-SMX prophylaxis group increased higher than the other (277.4 vs. 179.5 cells/mm^3; mean difference 97.92; 95% CI of difference, (65.15 to 130.69); p<0.001). However, this finding had to be interpreted carefully due to the significantly lower initial CD4 count in the prophylaxis group posing a potential bias in our study.

Thirteen of 153 cases (8.5%) in the TMP-SMX group reported minor drug rash. No other

ADRs were found in this study. This could have stemmed from the high prevalence of TMP-SMX hypersensitivity reaction in Thailand, 1 to 3% in the general population and up to 34% among patients with HIV.[6]

Our study possessed two strengths: the complete medical records in our electronic database, and the benefit from data collection. However, this study encountered some limitations. First, our study constituted a retrospective cohort. Second, the sample size in the nonTMP-SMX prophylaxis group was small (77 patients). Third, this study was conducted in a single center; our patients might not represent the general population in Thailand. Fourth, the definition of early ART initiation in this study was two weeks from HIV diagnosis, which was still late compared with the current HIV guidelines promoting the same-day or rapid ART initiation within seven days. Fifth, potential bias was shown in baseline characteristics; a significantly lower initial CD4 count in the prophylaxis group was noted. This could have affected the incidence of PCP and CD4 levels six months after ART initiation. Therefore, future studies should be conducted prospectively matching baseline CD4 count between groups and conducted among patients receiving the same day or rapid ART within seven days after HIV diagnosis to clarify the true results and whether it would be necessary to prescribe primary PCP prophylaxis when initiating early ART.

Conclusion

Among HIV-positive patients receiving early ART initiation, the incidence of PCP did not differ between groups with or without TMP-SMX prophylaxis. All-cause mortality and OI rate were also comparable between the two groups. In the non- prophylaxis group, CD4 count after ART initiation also increased higher and ADR from TMP-SMX was lower. These findings supported that TMP-SMX prophylaxis might not be necessary when we initiate early ART among HIV-positive patients presenting CD4 <200 cells/mm^3.

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Conflict of interest

The authors declare they have no conflicts of interest.

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