

CO-TRIMOXAZOLE PREVENTIVE THERAPY REDUCES ACTIVE PULMONARY TUBERCULOSIS RISK IN PEOPLE LIVING WITH HIV/AIDS ON ANTIRETROVIRAL AT WANGAYA HOSPITAL IN DENPASAR, BALI, INDONESIA: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Objective: To evaluate whether co-trimoxazole preventive therapy (CPT) and other contributing factors, among people living with HIV/AIDS (PLWHA) on antiretroviral (ARV) are effective to reduce active pulmonary tuberculosis (APT) at Wangaya Hospital, Denpasar, Bali, Indonesia.

Methodology: A prospective cohort study was conducted to evaluate the use of CPT in reducing APT. In this study, 403 PLWHA on ARV 151 participants accepted CPT as the first group and 252 PLWHA refused CPT as the second group. Eight participants among the first group and 48 participants among the second group were confirmed APT. Revisits were scheduled every a month to replenish pills and to confirm APT. The CPT effectiveness, sociodemography and laboratory, and reducing APT risk after prospective cohort entry were analyzed using Chi-square with significant $p < 0.05$. Statistical software package SPSS 15.0 was used for statistical analysis.

Results: Two hundred fifty-one (62.2%) of the participants were males and 152 (37.8%) females. Eight (2.0%) of the first group were confirmed APT and 48 (12.0%) of the second group were confirmed APT ($p = 0.004$). In bivariate analysis (Chi-square), we found that sex ($p = 0.019$), smoking ($p = 0.000$), alcohol consumption ($p = 0.000$), previous history of tuberculosis (TB) ($p = 0.000$), and CD4 cell counts (< 69 cell/ μ L) ($p = 0.002$) were significant APT risk factors. There was significantly less APT risk among the participants who accepted CPT compared with participants refused CPT ($p = 0.002$).

Conclusions: This study found that CPT was significantly associated with reduce of APT risk in PLWHA. Furthermore, there were significantly added the preventive effect of CPT; sex, smoking, alcohol consumption, previous history of TB, and CD4 cell counts.

Keywords: Human immunodeficiency virus, Co-trimoxazole preventive therapy, Active pulmonary tuberculosis.

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INTRODUCTION

Cotrimoxazole, fixed-dose trimethoprim-sulfamethoxazole, is a low cost and widely utilized broad-spectrum antibiotic used to prevent opportunistic infections in people living with HIV/AIDS (PLWHA) [1-3]. Co-trimoxazole preventive therapy (CPT) has been shown to decrease mortality, morbidity, and hospitalizations among PLWHA [4-6]. It has been recommended as part of the essential care and it supports package for PLWHA at Wangaya Hospital in Denpasar, Bali, Indonesia. It is a broad-spectrum antimicrobial agent active against several aerobics Gram-negative and Gram-positive bacteria, fungi, and protozoa species. In a previous study, mostly clinical isolates of mycobacterium tuberculosis (MTB) from different patients were found to be sensitive to co-trimoxazole. Other studies demonstrated that sulfamethoxazole had an *in vitro* bacteriostatic activity against MTB [7-9].

Recommendations for co-trimoxazole used in adults PLWHA vary by setting. In the United States and Europe, co-trimoxazole is recommended for PLWHA adults with severe immunosuppression (CD4 counts < 200 cells/ mm^3) to decrease mortality, morbidity, and hospitalizations due to opportunistic infections (pulmonary TB). Whether CPT prevents active pulmonary tuberculosis (APT) is still uncertain [10-12].

The aim of this study is to evaluate the reduced of APT risk in PLWHA on antiretroviral (ARV) accepting and refusing CPT at Wangaya Hospital in Denpasar, Bali, Indonesia.

METHODOLOGY

Study population and design

A prospective cohort study was conducted between January 2015 and December 2018. A total of 403 PLWHA on ARV as participants in

this study consisted of 151 participants who accepted CPT and 252 participants refused CPT. Participants routinely visited every month but also incidentally visited for acute illnesses. We evaluated the effectiveness of daily CPT (for 6 months) which reduced the risk of APT in PLWHA on ARV, sociodemography, laboratory (hemoglobin, white blood cells, neutrophil, lymphocyte, neutrophil/lymphocyte ratio, and CD4). They were collected at enrollment after being completed by physicians. We evaluated the APT during 6 months taking 960 mg co-trimoxazole once a day orally [13]. APT was confirmed by a routine diagnostic procedure such as TB screening, Chest X-ray, and laboratory investigations acid-fast bacilli (AFB).

HIV: Human immunodeficiency virus, TB: Tuberculosis, CBC: Cell blood counts, CD4: Cluster differentiation, CXR: Chest X-ray, AFB: Acid-fast bacilli, ATD: Antituberculosis drugs, ART: Antiretroviral therapy, PLWHA: People living with HIV/AIDS, APT: Active pulmonary tuberculosis, CPT: Co-trimoxazole preventive therapy

For all of eligible participants (PLWHA aged ≥ 18 years) were performed interview, TB screening and giving information on CPT, cell blood count (CBC), and the adherence to the appointed schedule. If there was a suspicion for TB (at least one of the positive symptom screening components), then a radiological and bacteriologic examination (AFB) was done to identify the MTB. If it was confirmed, they were given antituberculosis drugs according to the guideline. Participants who were unconfirmed TB continued to the clinical condition examinations such as nausea/vomiting and co-trimoxazole hypersensitivity. If there was any abnormality, participants were excluded from the study. Participants who were unconfirmed TB or without any clinical abnormality were divided into two groups. The first group: Participants

who were unconfirmed APT and accepted CPT. The participants who were unconfirmed APT but refused CPT as a second group. During 6 months CPT administration, a TB screening was done for every participants, also for the participants who refused CPT as a control. The participants flowchart in this study is described in Fig. 1.

The independent variables were age, sex, body weight, laboratory result (CBC: Hemoglobin, white blood cells, neutrophil, lymphocyte, and CD4⁺), and WHO clinical stage. Enrolled participants received labeled containers with 60 co-trimoxazole tablets (sulfamethoxazole 400 mg/trimethoprim 80 mg), were told to take two tablets daily for 30 days, and were given monthly refill appointments. The dependent variables were APT, confirmed by presumptive diagnostic (routine diagnostic procedure). APT were compared between participants accepted CPT and participants refused CPT.

Statistical analysis

Effectiveness of CPT on APT in PLWHA on ARV after prospective cohort entry was analyzed using Chi-square with $p < 0.05$, it was considered statistically significant. Statistical software package SPSS 15.0 was used for statistical analysis.

Ethical clearance

Ethical clearance was obtained No: 02/RSUDW/Litbang/2015 from the local ethical committees. We collected data from PLWHA who visited Wangaya Hospital, Merpati Clinic of Denpasar, Bali, Indonesia and completed at least 6 months (this period is considered the time period in which CPT is effective) follow-up from the ethical clearance granted date.

RESULTS

A prospective cohort study was conducted during January 2015 and December 2018. A total of 403 participants (PLWHA) were enrolled in this study. The mean age (years): 37.31 ± 9.83 year, 251 (62.20%) of the participants are males and 152 (37.80%) females, 311 (77.30%) on secondary education, 132 (32.70%) to be smokers, 153 (37.90%) alcohol consumption, and 165 (41.00%) previous history of TB or presence of a TB patient in the family, the mean of weight (kg) 52.25 ± 9.04 . Baseline CD4 cell counts: 73.55 ± 52.51 (Table 1).

In the bivariate analysis (Chi-square), we found that male confirmed with APT was statistically significant more frequent than female ($p = 0.019$) (Table 2).

This study found that male was more likely to develop APT compared with female ($p = 0.019$). A higher proportion of cases was smoking compared to the controls ($p = 0.000$). Alcohol consumption was more common among the participants with APT than the controls ($p = 0.000$). A previous history of TB or presence of a TB patient in the family was one of the most important risk factors of APT ($p = 0.000$).

To find out the association between CPT and APT among PLWHA, the participants were divided into two groups, the first group: 146 participants received CPT and 257 participants did not receive CPT (second group). In this study, we confirmed APT 8 (2.00%) among the first group (PLWHA on ARV, received CPT) during the 6 months follow-up, but 48 (12.00%) among the second group (PLWHA on ARV, refused CPT) were confirmed APT

($p = 0.004$; odds ratio [OR]=0.252; 95% confidence interval [CI]=0.094–0.675) (Table 3).

This study found that CPT has a protective effect against TB and it is consistent with other previous studies. CPT has beneficial effects in increasing CD4 counts as well as reducing APT risk ($p = 0.002$).

DISCUSSION

Co-trimoxazole is a broad spectrum antimicrobial agent, synergistically block folic acid microbial synthesis, a vital cofactor in thymidine, and purine manufacture. Sulfamethoxazole is a competitive inhibitor

Table 1: Participant characteristic data (age, sex, weight, hemoglobin, and white blood cell) (n=403)

Variable	n (%) / mean \pm SD
Age (year)	37.31 \pm 9.83
Sex	
Male	251 (62.20%)
Female	152 (37.80%)
Education level	
No formal education	8 (2.00%)
Primary education	47 (11.60%)
Secondary education	311 (77.30%)
Tertiary education	37 (9.20%)
Smoking	
Yes	132 (32.70%)
No	271 (67.30%)
Alcohol consumption	
Yes	153 (37.80%)
No	250 (62.20%)
Previous history of tuberculosis or presence of a tuberculosis patient in the family	
Yes	165 (41.00%)
No	238 (59.00%)
Weight (kg)	52.25 \pm 9.04
Cell blood count	
Hemoglobin (g/dl)	11.78 \pm 2.48
WBC (103/ μ L)	5.33 \pm 2.40
Neutrophil (109 cells/L)	3.34 \pm 1.98
Lymphocyte (cells/ mm^3)	1.01 \pm 0.51
NLR	4.49 \pm 5.17
CD4 cell counts (cells/ μ L)	73.55 \pm 52.51

WBC: White blood cells, NLR: Neutrophil lymphocyte ratio, CD4: Cluster differentiation-4, SD: Standard deviation

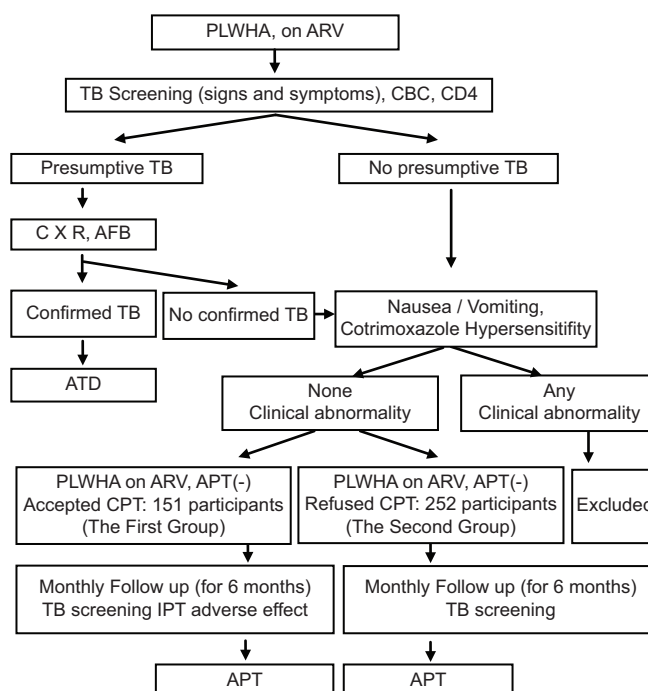


Fig. 1: Participants flowchart.

of dihydrofolic acid synthesis, trimethoprim acts downstream of sulfamethoxazole to inhibit the physiologically active tetrahydrofolic production. The fixed-dose combination (trimethoprim-sulfamethoxazole) blockades two sequential enzymes to prevent bactericidal activity [14,15]. In a previous study, mostly clinical isolates of MTB from different patients were found sensitive to co-trimoxazole. The other study demonstrated that sulfamethoxazole had *in vitro* bacteriostatic activity against MTB [7,9,16-18].

This study showed significantly association between the factors such as sex, smoking, alcohol consumption, previous history of TB or presence of a TB patient in the family, CD4 cell counts, and CPT with APT. In the other hand, no significant association between the risk factors of APT such as age, weight, hemoglobin, WBC, neutrophil, lymphocyte, and neutrophil-lymphocyte ratio (NLR) with APT (Table 2).

We found that there was a statistically significant association between sex and APT. Male had 2 times higher risk to develop APT compared to female ($p=0.019$; OR=2.75; CI 95%=1.15–6.57). Another study Ku *et al.* 2019, found that male was more likely to develop APT compared with female ($p<0.001$) [19]. Kibret *et al.*, 2013, reported that males were more likely to develop APT than females ($p=0.003$; crude odds ratios [COR]=1.73; 95% CI=1.21–2.46) [20]. However, it is different with Taha *et al.*, 2011, reported that female was statistically significant more frequent than male ($p=0.007$) [21].

Smoking may cause immune impairment, damages ciliary clearance, and it may increase the APT risk [22–24]. In this study, smoking was identified as a risk factor for APT ($p=0.000$; OR=5.944; 95% CI: 2.74–12.89). Similarly reported by other studies such as Alemu *et al.*, 2016, finding that smoking statistically significant associated with APT ($p<0.0001$; adjusted odds ratio [AOR]=5.47; 95% CI=2.26–13.22) [25]. Kibret *et al.*, 2013, found that smoking was statistically significant associated with increased of APT ($p<0.0001$; COR=3.34; 95% CI=2.087–5.35) [20]. Taha *et al.*, 2011, reported that smoking as a risk factor for APT ($p<0.001$) [21].

Long-term alcohol consumption may modulate the immune response, impaired immunity, and it will more likely to develop APT [26,27].

We found that alcohol consumption statistically significant associated with APT ($p=0.000$; OR=5.214; 95% CI=2.374–11.452). Another study Alemu *et al.*, 2016, finding that alcohol drinking statistically significant associated with APT ($p=0.006$; AOR=2.49; 95% CI=1.29–4.80) [25]. Kibret *et al.*, 2013, found that alcohol drinking was statistically significant associated with increased of APT ($p<0.0001$; COR=2.39; 95% CI=1.63–3.52) [20].

This study found that a previous history of TB or TB patient in the family was statistically significant associated with APT ($p=0.000$; OR=7.520; 95% CI: 3.137–18.027). Alemu *et al.*, 2016, found that TB patient in the family was statistically significant associated with APT ($p=0.011$; AOR=2.66; 95% CI=1.25–5.66) [25]. In the other hand, Taha *et al.*, 2011, found that a previous history of TB was not associated with APT ($p=0.7$) [21].

CPT has beneficial effects in enhancing the immunological state (increasing CD4 counts and reducing viral load [VL]) [28]. CPT reduces mortality in HIV infected adults with pulmonary TB [29,30]. CD4 counts <200 cells/ μL were independent determinants for increased APT. PLWHA with low CD4 counts was more likely to develop APT or other opportunistic infections [31–34]. In this study, the level of CD4 cell counts <69 cell/ μL was identified as the risk factor for the development of APT ($p=0.002$; OR=3.41; 95% CI: 1.53–7.63). Similarly to other studies, Ku *et al.* 2019, found that CD4 cell counts 101–200 cell/ μL was identified as the risk factor for the development of APT ($p<0.001$) [19]. Alemu *et al.*, 2016, found that CD4 cell counts <200 cell/ μL statistically significant associated with APT ($p<0.0001$; AOR=7.22; 95% CI=3.39–15.37) [25]. Taha *et al.*, 2011, found that associated with APT ($p=0.001$) [21].

Table 2: Association between APT and other variables (sex, age, weight, hemoglobin, WBC neutrophil, lymphocyte, NLR, and CD4) (n=403)

Variables	APT/case (n=56) (%)	No APT/control (n=347) (%)	p-value	Odd ratio	CI 95%
Sex					
Male	45 (11.20)	206 (51.00)	0.019*	2.750	1.150–6.574
Female	11 (2.80)	141 (35.10)			
Age (years)					
<35	30 (7.60)	164 (10.60)	0.438	1.327	0.648–2.718
≥ 35	26 (6.40)	183 (45.40)			
Smoking					
Yes	38 (9.60)	93 (23.10)	0.000*	5.944	2.740–12.894
No	18 (4.40)	254 (62.90)			
Alcohol consumption					
Yes	40 (10.00)	112 (27.90)	0.000*	5.214	2.374–11.452
No	16 (4.00)	235 (58.20)			
Previous history of TB or presence of a TB patient in the family					
Yes	45 (11.20)	120 (29.90)	0.000*	7.520	3.137–18.027
No	11 (2.80)	227 (56.20)			
Weight (kg)					
<51	29 (7.20)	148 (36.0)	0.328	1.427	0.698–2.919
≥ 51	27 (6.80)	199 (49.40)			
Hemoglobin (g %)					
<11.4	32 (8.00)	153 (37.80)	0.147	1.698	0.826–3.494
≥ 11.4	24 (6.00)	194 (48.20)			
White blood cell ($10^3/\mu\text{L}$)					
<4.80	24 (6.00)	175 (43.40)	0.404	0.736	0.358–1.514
≥ 4.80	32 (8.00)	172 (42.60)			
Neutrophil ($10^3/\mu\text{L}$)					
<3.17	22 (5.60)	178 (44.20)	0.211	0.631	0.305–1.305
≥ 3.17	34 (8.40)	169 (41.80)			
Lymphocyte ($10^3/\mu\text{L}$)					
<0.95	29 (7.20)	172 (42.60)	0.836	1.079	0.528–2.204
≥ 0.95	27 (6.80)	175 (43.40)			
NLR					
<3.39	21 (5.20)	179 (44.60)	0.106	0.549	0.263–1.145
≥ 3.39	35 (8.80)	168 (41.40)			
CD4 cell counts (cell/ μL)					
<69	42 (10.40)	159 (39.40)	0.002*	3.414	1.528–7.628
≥ 69	14 (3.60)	188 (46.60)			

Bivariate analysis (Chi-square) with significant $p<0.05^*$. NLR: Neutrophil lymphocyte ratio, CD4: Cluster differentiation 4, TB: Tuberculosis, CI: Confidence interval

Table 3: Association between co-trimoxazole preventive therapy and active pulmonary tuberculosis (n=403)

Variables	Received CPT (n=146) (%)	Refused CPT (n=257) (%)	p-value	Odd ratio	CI 95%
Active pulmonary tuberculosis					
Yes	8 (2.00)	48 (12.00)	0.004*	0.252	0.094–0.675
No	138 (34.30)	209 (51.80)			

Bivariate analysis (Chi-square) with significant $p < 0.05^*$. CPT: Co-trimoxazole preventive therapy, CI: Confidence interval

CPT (sulfamethoxazole) has been found to be active against MTB *in vitro* [7-9]. Some observational studies suggested CPT decreased the risk of APT in PLWHA and supported a direct antitubercular effect from co-trimoxazole. Therefore, CPT has a protective effect against TB [3,25,35]. This study found that daily CPT reduced APT risk among PLWHA on ARV at Wangaya Hospital in Denpasar, Bali, Indonesia. During the 6 months follow-up, there were confirmed 8 (2.00%) APT among the first group (PLWHA, on ARV, accepted CPT) but 48 (12.00%) among the second group (PLWHA, on ARV, refused CPT). The PLWHA on ARV receiving CPT was less likely to develop APT than PLWHA on ARV did not receive CPT ($p=0.004$; OR=0.252; 95% CI=0.094–0.675). It showed that CPT had a protective effect against TB. This was consistent with other studies. Ku *et al.* (2019) found that co-trimoxazole prophylaxis was significantly associated with incident TB diagnosis ($p < 0.001$). In multivariate analyses, higher VL (1000–4999 copies/mL HR 2.18, 95% CI (1.06–4.48), $p=0.034$ and ≥ 5000 copies/mL HR 2.38, 95% CI (1.63–3.47), $p < 0.001$ were associated with the increased hazard of developing TB compared to VL < 400 copies/mL [19]. Alemu *et al.* (2016) reported that CPT had a beneficial effect in enhancing CD4 cell counts as well as reducing VL and they also found that CPT had a protective effect against TB ($p < 0.0001$; AOR=0.32; 95% CI=0.19–0.55) [25]. Kibret *et al.*, 2013, found that daily CPT reduced APT risk among PLWHA ($p < 0.0001$; COR=0.27; 95% CI=0.14–0.53) [20].

This study reported that there was no statistically significant association between hemoglobin level, WBC, lymphocyte, neutrophil, and NLR with APT.

CONCLUSIONS

Our study found that CPT was significantly associated with reduce of APT risk in PLWHA. The other clinical evidence that significantly added the preventive effect of CPT were sex, smoking, alcohol consumption, previous history of TB or presence of a TB patient in the family, and CD4 cell counts.

Limitations of study

The limitation of this study and the diagnostic of APT cases were confirmed with TB screening, a radiological and bacteriologic examination (AFB) without confirmation with the MTB positive culture results. Recall bias may have affected the accuracy of information related to the substance use in cigarette smoking and alcohol consumption.

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AUTHORS' CONTRIBUTIONS

Ketut Suryana made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. Hamong Suharsono took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. Dwijo Anargha Sindhughosarevised it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

The authors declared that there are no conflicts of interest related to this study.

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