Benefits and Risks of Prolonged Cotrimoxazole Prophylaxis among People Living with HIV in Immune Reconstitution Phase: A Retrospective Cohort Study

Christian N. Francisco,[1] Marissa M. Alejandria[1,2] and Edsel Maurice T. Salvaña[1,3]

[1]*Section of Infectious Diseases, Department of Medicine, College of Medicine and Philippine General Hospital, University of the Philippines Manila*
[2]*Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila*
[3]*Institute of Molecular Biology and Biotechnology, National Institutes of Health, University of the Philippines Manila*

ABSTRACT

Objectives. To determine the effect of prolonged cotrimoxazole prophylaxis (CP) in reducing hospitalization and opportunistic infection rates among people living with HIV (PLHIV) with CD4 count >200 cells/mm^3.

Methods. We retrospectively reviewed 349 medical charts of PLHIV with CD4 count (or T-cell count) of >200 cells/mm^3 enrolled in an HIV treatment hub in Manila, Philippines, from January 2004 to July 2016. Demographic, clinical characteristics and outcomes were extracted. Descriptive statistics were generated. Chi-square test for two proportions was done to compare the difference in outcomes between the CP and non-CP groups.

Results. Of the 349 patients, majority (96.6%) were male with a mean age of 28 years (SD 6.4) and mean CD4 count of 373 cells/mm^3 (SD 148). CP was continued in 103 patients (29.5%) with mean duration of 1.7 (SD 1.9) years. The prolonged CP group had more events of adverse drug reactions (p<0.001), specifically minor cutaneous reactions (p<0.001) and immunologic failures (p<0.001), compared to the non-CP group. There were no statistically significant differences in the frequency of hospitalization, PJP (*Pneumocystis jirovecii* pneumonia), non-PJP, other respiratory illnesses, diarrhea, toxoplasmosis, tuberculosis, stage 3/4 events and mortality, between the prolonged CP and non-CP groups.

Conclusion. We did not observe any additional benefit in giving prolonged CP among PLHIV with CD4 count >200 cells/mm^3. More adverse effects were also seen in the CP group.

Key Words: HIV, AIDS, cotrimoxazole prophylaxis, cohort

INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) and opportunistic infections (OI) are the main cause of absenteeism, hospitalizations and mortality among people living with HIV (PLHIV).[1] Prevention of OI is a standard of care among patients with CD4 ≤200 cells/mm^3. Antiretroviral therapy (ART) indirectly prevents OI by promoting immune reconstitution while prophylactic medications act directly on the pathogens.[2]

Cotrimoxazole is one of the recommended prophylaxis in AIDS patients. Cotrimoxazole prophylaxis (CP) is initiated when CD4 count is ≤200 cells/mm^3. In this subgroup of patients, there was reduction in the incidence of *Pneumocystis jirovecii* pneumonia (PJP) and mortality among those on CP.[3-6] Termination of CP is recommended after

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Corresponding author: Christian N. Francisco, MD
Section of Infectious Diseases
Department of Medicine
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: christianfrancisco1@gmail.com

two consecutive CD4 count determination of >200 cells/mm^3 taken 3-6 months apart,[7] wherein modest immune reconstitution was achieved.[5,8]

The World Health Organization (WHO) provides a flexible guideline on the use of cotrimoxazole prophylaxis.[9] WHO recommends starting CP at CD4 count ≤350 cells/mm^3 and stopping when CD4 count improves to >350 cells/mm^3. However, in areas with high burden of infectious diseases or in areas where CD4 count determination is not readily available, WHO recommends prolonged or lifelong prophylaxis even if the CD4 count is >350 cells/mm^3.[9] This recommendation is supported by various African studies. Maintaining CP in this subgroup of patients reduces the incidence of death, hospitalization and malaria as shown in an African meta-analysis.[10] In addition, a randomized controlled trial done in the Republic of Côte d'Ivoire (Ivory Coast) showed reduction in the incidence of stage 3/4 events, pneumonia and tuberculosis in the CP group,[11] while diarrhea incidence was reduced among those maintained on CP as reported in a prospective cohort study in Uganda.[12]

In the Philippines, CP is initiated when CD4 count is ≤200 cells/mm^3 but with variable timing of discontinuation despite having a high burden of infectious diseases. There is no local data on the role of prolonged CP in improving clinical outcomes among Filipino PLHIV with CD4 count >200 cells/mm^3. We conducted a retrospective cohort study to compare the incidence of hospitalization and other infections between patients maintained on prolonged CP and not on CP.

METHODS

Study Design and Setting

This was a retrospective cohort study conducted at the HIV treatment hub of the Philippine General Hospital (PGH). The study was approved by the University of the Philippines Manila-Research Ethics Board (UPM-REB). All patient records were handled with strict confidentiality in accordance to the Philippine AIDS Law (Republic Act 8504). Subjects were identified using a study identifier (SID) number. All research data obtained were kept in a password-protected electronic database.

Study Population and Patient Selection

Assuming a hospitalization rate of 13% in the prolonged CP group and 19% in the non-CP group[13], the computed sample size was 1,170 patients (585 per group) with CD4 count ≥200 cells/mm^3 to detect a 6% difference in hospitalization with 80% power at 0.05 level of significance.

We retrospectively reviewed 876 medical records of patients enrolled from January 2004 to August 2016. We included 349 patients with CD4 count ≥200 cells/mm^3. Five hundred twenty-seven (527) patient records were excluded due to the following reasons: 507 had CD4 count <200 cells/mm^3, 8 had prior treatment with cotrimoxazole (non-prophylactic use), while 12 presented with the outcomes of interest prior to CD4 count improvement to ≥200 cells/mm^3.

We reviewed the clinic database from the date of enrollment until the last follow up visit. The following were recorded: age, sex, baseline and subsequent CD4 counts, presence and duration of cotrimoxazole prophylaxis, presence and duration of ART and other medications. The patients were categorized into the prolonged CP group and non-CP group. Prolonged CP was defined as continued administration of cotrimoxazole at CD4 count ≥200 cells/mm^3. Non-CP group consisted of patients whose cotrimoxazole prophylaxis were discontinued upon achieving a CD4 count of ≥200 cells/mm^3. Study outcomes were extracted from the time of CD4 count improvement (≥200 cells/mm^3) until the last recorded clinic follow up for both groups. The primary outcome was hospitalization from all causes.

Secondary outcomes included immunologic failure (defined as decrease in CD4 from ≥200 cells/mm^3 to <200 cells/mm^3), PJP pneumonia, non-PJP (defined as pneumonia caused by other bacterial pathogens) and respiratory illness (defined as any episode of viral/bacterial upper respiratory tract infections).

Data on adverse drug reaction (ADR), defined as any untoward drug related events such as minor cutaneous manifestations (rash), Stevens-Johnson syndrome (SJS) and severe anemia (hemoglobin <70 g/L), were also collected.

Statistical Analysis

Frequency distribution, measures of central tendency and measures of variability were generated. Chi-square test was performed using STATA Version 14 (Stata Corp, College Station, Texas, USA) to determine whether there was a significant difference in the frequencies between the two groups (prolonged CP versus non-CP groups).

RESULTS

A total of 349 patient records were included in the study analysis, 103 in the prolonged CP group and 246 in the non-CP group. Majority were males (96.6%) with a mean age of 28.3 years (SD 6.4). The mean estimated duration of HIV infection was 3.8 years (SD 2.1) and the mean duration of ART use was 2.7 years (SD 2.0).

Upon study entry, 145 were asymptomatic (41.5%). Among the 349 study participants included, 103 (29.5%) were on CP with a mean duration of 1.7 years (SD 1.8).

In the CP group, majority of the participants were in the 200-350 cells/mm^3 CD4 category (69.9%) while the remaining proportion (30.1%) had CD4 >350 cells/mm^3.

Baseline demographic, laboratory and clinical characteristics of the study participants are summarized in Table 1.

The CP group had significantly more cases of immunologic failures (24.3% vs 0.8%, p<0.001) and ADRs (31.1% vs 10.2%, p<0.001) compared to the non-CP group.

The most common ADR was minor cutaneous reactions (rash) which accounted for 86%. Sub-analysis of each specific ADR showed more cases of minor cutaneous reactions (rash) (26.2% vs 8.9%, p<0.001) while significant difference in the occurrence of SJS and severe anemia were not seen between the two groups (Table 2). In the CP group, 37.5% of all ADR were due to cotrimoxazole (9 minor cutaneous reactions, 1 severe anemia, 2 SJS). Other medications commonly implicated in the development of ADR in this group included ART (nevirapine, zidovudine) in 25.0% and anti-tuberculosis medications in 15.6%.

ART was the implicated drug in 44.0% of all ADRs in the non-CP group (minor cutaneous reactions (7), severe anemia (2), SJS(2). In this group, other drugs (Table 3)

Table 1. Baseline Characteristics of 349 PLHIV in Immune Reconstitution Phase with or without Prolonged Cotrimoxazole Prophylaxis

	CP (N=103)	Non-CP (N=246)
Mean age; SD (years)	28.4; 6.4	28.3; 6.3
Male Sex (%)	99 (96.1%)	238 (96.7%)
Mean CD4 count ; SD (cells/mm^3)	373; 148	372; 147
200-349 cells/mm^3 (%)	72 (69.9%)	111 (45.1%)
≥350 cells/mm^3(%)	31 (30.1%)	135 (54.9%)
Mean duration of CP at CD4 > 200; SD (years)	1.7; 1.9	N/A
ART use (%)	103 (100%)	216 (87.8%)
Mean duration of ART use (years)	2.7; 2.0	2.7; 2.0
Range of duration of ART use	230 days to 8 years	30 days to 7 years
Symptomatology at CD4 > 200 (%)		
Asymptomatic	46 (44.7%)	99 (40.2%)
Fever	7 (6.8%)	17 (6.9%)
Respiratory symptoms	16 (15.5%)	29 (11.8%)
Weight loss	8 (7.8%)	30 (12.2%)
Lymphadenopathy	20 (19.4%)	47 (19.1%)
Urethral/ Vaginal Discharge	2 (1.8%)	2 (0.8%)
Skin Lesions	26 (25.2%)	62 (25.2%)
Others	25 (24.3%)	50 (20.3%)
Other OI prophylaxis (%)		
Azithromycin	25 (24.3%)	12 (4.9%)
INH	24 (23.3%)	84 (34.1%)

Table 2. Outcomes among 349 PLHIV in Immune Reconstitution Phase with or without Prolonged Cotrimoxazole Prophylaxis

	CP (N=103)	non-CP (N=246)	p-value
Primary Outcome (%)			
Hospitalization	11 (10.7%)	17 (6.9%)	0.28
Secondary Outcomes(%)			
PCP	1 (0.9%)	0 (0%)	0.12
Non-PCP	1 (0.9%)	1 (0.4%)	0.52
Respiratory Illness other than Pneumonia	28 (27.2%)	63 (25.6%)	0.76
Active Tuberculosis(TB)	16 (15.5%)	27(10.9%)	0.24
Pulmonary TB	12 (11.6%)	17 (6.9%)	0.14
Extrapulmonary TB	3 (2.9%)	9 (3.6%)	0.73
Disseminated TB	1 (0.9%)	1 (0.4%)	0.52
Latent Tuberculosis	2 (1.8%)	1 (0.4%)	0.16
Diarrhea	10 (9.7%)	11 (4.5%)	0.06
Toxoplasmosis	1 (0.9%)	0 (0%)	0.12
Any stage 3 or 4 events	5 (4.9%)	6 (2.4%)	0.24
Immunologic Failure	25 (24.3%)	2 (0.8%)	**<0.001**
Development of resistance to current ART regimen	2 (1.9%)	6 (2.4%)	0.78
Mortality	3 (2.9%)	5 (2%)	0.61
Adverse Drug Reactions	32 (31.1%)	25 (10.2%)	**<0.001**
Minor cutaneous (rash)	27 (26.2%)	22 (8.9%)	**<0.001**
SJS	2 (1.9%)	2 (0.8%)	0.37
Severe Anemia	3(2.9%)	2 (0.8%)	0.13

Table 3. Common Implicated Medications for Adverse Drug Reactions among PLHIV in Immune Reconstitution Phase with or without Prolonged Cotrimoxazole Prophylaxis

CP (N=32)	Non-CP (N=25)
Cotrimoxazole – Anemia (1) SJS (2) Minor cutaneous (9) Isoniazid (INH) – Minor cutaneous (1) Tuberculosis Medications – Minor cutaneous (4) ART: Nevirapine (NVP) – Minor cutaneous (6) Zidovudine (AZT) – Anemia (2) Non-steroidal anti-inflammatory drugs (NSAIDS) – Minor cutaneous (4) Others (includes supplements, topical agents) – Minor cutaneous (3)	ART: NVP – SJS (2), Minor cutaneous (7) AZT – Anemia (2) INH – Minor cutaneous (2) TB Medications – Minor cutaneous (4) NSAIDS – Minor cutaneous (2) Others (includes supplements, topical agents) – Minor cutaneous (6)

Table 4. Reasons for Hospitalizations and Mortality among PLHIV in Immune Reconstitution Phase with or without Prolonged Cotrimoxazole Prophylaxis

CP (N=11)	Non-CP (N=17)
Severe anemia (3) SJS (2) PCP (1) PTB (1) unspecified (1) Mortality (3) – 2 PTB and immunologic failure 1 unknown cause	Severe anemia (2) SJS (2) PTB (1) Diarrhea (1) Herpes zoster (1) Severe cutaneous rash (1) Respiratory illness (3) FUO (1) Mortality (5) – 1 GI obstruction 1 immunologic failure 3 ART-naïve

that commonly caused ADRs included anti-tuberculosis medications (24.0%) and NSAIDS (8%). Patients who developed SJS and severe anemia were hospitalized and discharged improved.

There were also no significant differences in hospitalization, PJP, non-PJP, respiratory illness, active TB, latent TB, diarrhea, toxoplasmosis, other stage 3/4 events specifically oral candidiasis and herpes simplex, development of resistance to current ART regimen and mortality (Table 2).

The reasons for the hospitalizations in each group are summarized in Table 4. Among the patients who died, three were in the CP group [with active pulmonary TB and developed immunologic failure (2), unknown cause (1)] and five (5) were in the non-CP group [gastrointestinal obstruction (1), 1 immunologic failure (1), 3 ART-naïve (3)].

DISCUSSION

CP decreases the incidence of opportunistic infections among PLHIV with CD4 count <200 cells/mm^3, however good evidence is lacking on its benefit among those with CD4 count >200 cells/mm^3 or those who are in the immune reconstitution phase.[9,13,14]

In this study, patients on CP once had a CD4 count <200 cells/mm^3, which prompted its initiation and maintained thereafter until the CP termination criteria was fulfilled. The average increase in CD4 count was 150 cells/mm^3 for 6 months while on standard WHO recommended ART.[15] An average of two years of ART exposure was needed to achieve moderate immune reconstitution (CD4 >200 cells/mm^3) which was consistent to the mean duration (1.7 years) of CP in our cohort study.[16] There was a proportion of patients on prolonged CP who had a CD4 count >350 cells/mm^3 at the time of the study. This subgroup of patients were maintained on CP because they did not fulfill the CP termination criteria (2 consecutive CD4 count determination above 200 cells/mm^3 and CD4 count monitoring were not consistently done during the 3-6 months interval).

This study did not show the benefits of CP in reducing hospitalizations and other coinfections as reported in previous studies. However, our study showed that CP was not safe among PLHIV with CD4 count >200 cells/mm^3 due to the high incidence of ADR.

Cotrimoxazole is a known culprit for ADR with rash as the most common presentation.[17] Aside from the high immunogenicity of its sulfa-component, patients with lower CD4 count or those with initially low CD4 count have a higher risk for cutaneous ADR.[18]

In this study, 68.4% patients who experienced ADR had a CD4 count <350 cells/mm^3. Anemia was more common among those on CP as previously shown in a randomized controlled trial in children and adolescents in Africa.[13] These findings are in agreement with the result of this study. However, it should be noted that zidovudine induced anemia was the main reason for the occurrence of this outcome in both groups. The effect of poly-pharmacy in ADR needs to be investigated.

The incidence of immunologic failure was higher in the CP group. This might not be due to the effect of cotrimoxazole but rather on the difference in the level of

immunosuppression between the two groups. There was a higher proportion of patients in the 200-350 cells/mm^3 category in the CP (69.9%) as compared to the non-CP group (45.1%). The erratic rise and fall of CD4 count was commonly observed among patients who once had a very low CD4 count at the time of HIV diagnosis.[19] Due to the retrospective nature of this study, factors contributing to immunologic failure in this subgroup of patients (CD4 200-350 cells/mm^3) were not accounted for. These included physical stress, age, smoking habits, malnutrition, compliance to ART, HIV mutations and resistance.[20]

In this study, CP was not beneficial among PLHIV with CD4 count >200 cells/mm^3. There was no difference in the incidence of hospitalizations between the two groups. This is in contrast to the result of a randomized controlled trial in Africa that showed a decrease in the incidence of hospitalizations among patients who continued CP.[13] It is important to note that the reduction in hospitalization rates in that study were mostly due to malaria and other infections (sepsis and meningitis).[13] None in our cohort study was diagnosed with those coinfections.

Pneumonia (PJP and non-PJP) are common causes of morbidity among PLHIV and is usually seen among those who are severely immunocompromised. However, minimal risks still exist among PLHIV with CD4 >200 cells/mm^3.[21] The reduction in PJP and non-PJP rates were not shown in this study. The results agree with the findings of a cohort study involving 4050 PLHIV in Asia showing no difference in PJP rates between CP and non-CP groups. This observation also applies to those with CD4 count of 200 to >300 cells/mm^3.[5]

Published studies reporting on the reduction of non-PJP rates are conflicting.[11,22] The conflicting results might be due to the differences in the prevailing bacterial pathogens, resistance patterns and vaccination coverage among study participants. The low rates of non-PJP in our cohort study might be explained by the active vaccination practices in our treatment hub.

Our study is in agreement with the findings from other cohort studies showing no reduction in the rates of respiratory illnesses, diarrhea, toxoplasmosis and other stage 3 and 4 events.[11] These AIDS-defining conditions are commonly seen among the severely immunocompromised which could have explained the low number of outcomes in this study. Moreover, mild symptoms from non-specific respiratory illnesses (upper respiratory tract infections) and non-specific enteritis presenting as diarrhea might have been disregarded by the patient and physician, hence under reporting of cases.

Tuberculosis (TB) is common among PLHIV and the risk of infection is present regardless of the CD4 count level. Cotrimoxazole has an in vitro activity against *Mycobacterium tuberculosis*[23] but its clinical utility in preventing infection needs to be investigated. Based on the TREAT Asia HIV Observational Database (TAHOD), TB incidence was reduced among patients on CP but this effect was seen only among PLHIV with CD4 count <200 cells/mm^3. No significant reduction was found for those on CP among PLHIV with CD4 count >200 cells/mm^3.[24] In a separate African cohort study, a reduction in tuberculosis rate was not shown for all subgroups of CD4 count among those on CP.[11] These findings are consistent with our results showing minimal TB reduction even in areas with high TB prevalence.

Reduction in mortality and AIDS-related morbidity is the main goal of early ART initiation. Prophylactic medications prevent AIDS defining coinfections that increase the risk for death. Small number of mortalities were reported in our cohort study but the trend showed that mortality rate between groups were not statistically different.

Our result agreed with previous studies that CP has no benefit in reducing over-all cause of mortality.[11,22] However, reduction in mortality from malaria has been shown in areas where malaria is highly endemic.[22] This is due to the anti-*Plasmodium* activity of cotrimoxazole.[22,25]

There were some limitations in this study. The retrospective nature of the study prevented us to account for outcomes that were not recorded in the medical charts, including mild symptoms that may not necessitate medical consult. Even though we included all eligible patients in the analysis, the desired sample size was not met. This limitation could explain the lack of significant differences for other major outcomes. Moreover, the small number of patients in immune reconstitution and small number of outcomes recorded prohibited further statistical tests to determine associated factors. A well designed double blinded randomized controlled trial, enrolling patients with no history of CD4 count <200 cells/mm^3, is necessary to provide more data on the benefits of CP.

CONCLUSION

This study did not show the beneficial effect of CP in reducing hospitalization and reduction in opportunistic infection rates among PLHIV with CD4 count >200 cells/mm^3. Moreover, patients on prolonged CP were at higher risk for developing ADR.

Statement of Authorship

All authors participated in data collection and analysis, and approved the final version submitted.

Author Disclosure

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