Letter to the Editor

Effects of Cotrimoxazole Prophylaxis Initiation and Discontinuation on Mortality and Attrition Rates among HIV Patients Who Initiate ART in Southwest China: An Observational Cohort Study*

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Combination antiretroviral therapy (ART) reduced AIDS-related mortality and increased survival among patients living with HIV by interrupting HIV replication, enhancing immune recovery, and preventing the onset of opportunistic infections[1]. In China, ART has rapidly been scaled up since the beginning of the National Free Antiretroviral Treatment Program (NFATP) in 2003[2]. By the end of 2016, 489,411 individuals diagnosed with HIV were receiving free antiretroviral treatment in China. China is firmly committed to reducing overall AIDS-related mortality and HIV incidence within the country. However, similar to other low- and middle-income countries, the NFATP is challenged by high mortality and attrition shortly after patients initiate ART[3].

Cotrimoxazole prophylaxis is a combination of the antibiotics, trimethoprim and sulfamethoxazole, and is used to treat a variety of bacterial, fungal, and protozoan infections, including *Pneumocystis jirovecii* pneumonia, malaria, and cerebral toxoplasmosis[4]. In order to reduce the risk of AIDS-associated opportunistic infections, cotrimoxazole prophylaxis is recommended by the World Health Organization (WHO) for HIV-infected patients with severe or advanced HIV clinical disease (WHO stage 3 or 4), with a CD4 count of less than 350 or 200 cells/mm^3 (depending on the region)[5]. An earlier study reported, most of them being conducted in settings where malaria or severe bacterial infections were highly prevalent, that cotrimoxazole prophylaxis reduced early mortality after ART initiation in low- and middle-income countries[6]. Further research is urgently needed to assess how cotrimoxazole prophylaxis impacts mortality in the context of expanded ART policies in different epidemiological settings. In China, cotrimoxazole prophylaxis has been provided to patients with HIV exhibiting a CD4 cell count of < 200 cells/mm^3 or several opportunistic infections[7].

This HIV treatment observational cohort study was conducted in Guangxi Zhuang Autonomous Region of Southwest China, one of the top five provinces with the highest incidences of HIV cases in China (Sichuan, Yunan, Guangdong, Guangxi, and Guizhou). Eligibility criteria for the study participants included the enrollment into the NFATP between 2010–2015, age 18 years or older at the time of ART initiation, and ability to provide informed consent. The cohort study data was extracted from the NFATP database and data were censored on June 30, 2016. Ethical review and all methods were approved by the institutional review board (IRB) of the Guangxi Zhuang Autonomous Region Center for Disease Control and Prevention.

The baseline characteristics of the study participants included age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinical

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stage before ART, initial ART regimen, and year of ART initiation. The follow-up characteristics of the study participants included cotrimoxazole prophylaxis use, duration of ART, survival status, transferals to another clinic, cessation of ART, and loss to follow-up. The documentation of cotrimoxazole prophylaxis administration in the NFATP began in 2010. Loss to follow-up was defined as being absent for more than 90 days after the last appointment in an ART clinic, also defined as the date of withdrawal. Additional details concerning the Chinese national HIV treatment cohort study databases have been previously described[2,3].

We performed a time-to-event cohort analysis. The primary study endpoints were mortality and attrition. Attrition was defined as a loss to follow-up or cessation of ART as recorded in the NFATP database. Cox proportional hazard models were used to assess the effects of cotrimoxazole prophylaxis use during the first 6 months of ART on mortality and attrition among patients with HIV who initiated ART, stratified by the CD4 cell count (cells/mm^3) before ART, and to assess the effects of cotrimoxazole prophylaxis discontinuation during the second, third, fourth, and fifth 6 months post-ART initiation on mortality and attrition among HIV patients who started ART with a CD4 cell count (cells/mm^3) of < 200 before ART and also initiated cotrimoxazole during the first 6 months of ART. The effects of cotrimoxazole prophylaxis discontinuation on mortality and attrition were examined by comparing the following periods: the second 6 months of ART *vs.* the first 6 months of ART and the CD4 cell count (cells/mm^3) of < 200 during the 6 months of ART, the third 6 months of ART *vs.* the first 12 months of ART and the CD4 cell count (cells/mm^3) of < 200 during the 12 months of ART, the fourth 6 months of ART *vs.* the first 18 months of ART and the CD4 cell count (cells/mm^3) of < 200 during the 18 months of ART, and the fifth 6 months of ART *vs.* the first 24 months of ART and the CD4 cell count (cells/mm^3) of < 200 during the 24 months of ART. The following baseline covariates were included in the adjusted model: age, sex, marital status, route of HIV infection, WHO clinical stage before ART, initial ART regimen, and year of ART initiation. Time zero for the above-described data was defined as the date of the first 6, 12, 18, and 24 months of post-ART initiation, respectively. Two-sided *P*-values of ≤ 0.05 were considered statistically significant. We used the Statistical Analysis System (SAS 9.1^{TM} for Windows; SAS Institute Inc., NC, USA) for all data analyses.

A total of 45,213 study participants entered this HIV treatment cohort study analysis. Participant baseline characteristics are presented in Supplementary Table S1, available in www.besjournal.com. The proportions of patients with CD4 cell counts < 200, 200–349, 350–499, and ≥ 500 cells/mm^3 were 56.0%, 30.8%, 9.7%, and 3.5%, respectively. During the study follow-up, 3,421 deaths were observed, 4,363 patients were lost to the follow-up, and 1,756 patients stopped ART.

The overall mortality rate was 2.92 [95% class interval (*CI*): 2.83–3.02] per 100 person-years (PY). The mortality rate in patients with HIV exhibiting a CD4 cell count (cells/mm^3) of < 200 before ART who did not and did use cotrimoxazole prophylaxis during the first 6 months of ART was 5.98 and 3.12 per 100 PY (P < 0.001), respectively. In the adjusted models, cotrimoxazole prophylaxis use during the first 6 months of ART among patients with HIV exhibiting a CD4 cell count (cells/mm^3) of < 200 before ART was associated with a significant reduction in mortality [compared to the lack of cotrimoxazole prophylaxis use during the first 6 months of ART, adjusted hazard ratio (AHR) = 0.52, 95% *CI*: 0.48–0.57]. Among the patients with HIV exhibiting CD4 cell counts (cells/mm^3) of 200–349 and ≥ 350 before ART, the cotrimoxazole prophylaxis use during the first 6 months of ART was not significantly associated with a reduction in mortality (Table 1). Cotrimoxazole prophylaxis use during the second, third, fourth, and fifth 6 months of ART were all associated with a significant reduction in mortality (compared to only using cotrimoxazole prophylaxis during the first 6 months of ART and CD4 cell count (cells/mm^3) of < 200 at 6 months of ART). Our study showed that continued cotrimoxazole prophylaxis use during the first 30 months of ART among HIV patients with CD4 cell count (cells/mm^3) of < 200 was significantly associated with a reduction in mortality, although no apparent reduction in mortality could be observed when cotrimoxazole prophylaxis was initiated among patients with HIV exhibiting a CD4 cell count (cells/mm^3) of ≥ 200 after 6 months of ART. Recent research suggests that HIV patients should not discontinue cotrimoxazole prophylaxis in regions with a high burden of infectious diseases, such as pneumonia, malaria, and diarrhea, which might have limited generalizability in China[8]. Our study provides compelling empirical evidence regarding the adoption, continuation, and discontinuation of cotrimoxazole prophylaxis use among patients with HIV after ART in China (Table 2 and Supplementary Table S2, available in www.besjournal.com).

The overall attrition rate was 9.53 (95% *CI*: 9.36–9.70) per 100 PY. Attrition rates in patients with HIV exhibiting a CD4 cell count (cells/mm^3) of < 200 before ART who did not and did use cotrimoxazole prophylaxis during the first 6 months of ART were 12.27 and 7.83 per 100 PY (P < 0.001), respectively. Cotrimoxazole prophylaxis use during the first 6 months of ART among patients with HIV exhibiting a CD4 cell count (cells/mm^3) of < 200 before ART was associated with a significant reduction in the attrition rate (compared to the lack of cotrimoxazole prophylaxis use during the first 6 months of ART, AHR = 0.63, 95% *CI*: 0.59–0.66); cotrimoxazole prophylaxis use during the first 6

Table 1. Effects of cotrimoxazole prophylaxis use during the first 6 months of ART on death among HIV-infected patients in Guangxi, China, 2010–2015, by CD4 cell count (cells/mm^3) before ART

CD4 cell count (cells/mm^3) before ART	Number	Deaths	Person-years	Deaths/100 person-years (95% *CI*)	HR (95% *CI*)	*P*-value	AHR* (95% *CI*)	*P*-value
Total	45,213	3,421	117047.44	2.92 (2.83–3.02)				
CD4 < 200	25,334	2,650	67143.32	3.95 (3.80–4.09)				
No+	7,587	1,158	19368.72	5.98 (5.64–6.31)	Reference		Reference	
Yes+	17,747	1,492	47774.60	3.12 (2.97–3.28)	0.51 (0.47–0.55)	< 0.001	0.52 (0.48–0.57)	< 0.001
CD4 200–349	13,934	640	37582.08	1.70 (1.57–1.83)				
No+	13,016	579	34997.77	1.65 (1.52–1.79)	Reference		Reference	
Yes+	918	61	2584.31	2.36 (1.78–2.94)	1.45 (1.11–1.89)	0.006	1.14 (0.87–1.50)	0.330
CD4 ≥ 350	5,945	131	12322.03	1.06 (0.89–1.24)				
No+	5,773	122	11927.94	1.02 (0.94–1.11)	Reference		Reference	
Yes+	172	9	394.09	2.28 (0.83–3.74)	2.16 (1.10–4.26)	0.026	1.58 (0.77–3.22)	0.209

Note. +No, did not start cotrimoxazole during the first 6 months of ART; Yes, did start cotrimoxazole during the first 6 months of ART. *HR = hazard ratio; AHR = adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, WHO clinical stage before ART, initial ART regiment, year of ART initiation.

Table 2. Effects of cotrimoxazole prophylaxis use during the first 6 months of ART on attrition among patients with HIV in Guangxi, China, 2010–2015, by CD4 cell count (cells/mm^3) before ART

CD4 cell count (cells/mm^3) before ART	Number	Attritions	Person-years	Attritions/100 person-years (95% *CI*)	HR (95% *CI*)	*P*-value	AHR* (95% *CI*)	*P*-value
Total	45,213	11,156	117047.44	9.53 (9.36–9.70)				
CD4 < 200	25,334	6,119	67143.32	9.11 (8.89–9.34)				
No+	7,587	2,377	19368.72	12.27 (11.79–12.75)	Reference		Reference	
Yes+	17,747	3,742	47774.60	7.83 (7.59–8.08)	0.62 (0.59–0.65)	< 0.001	0.63 (0.59–0.66)	< 0.001
CD4 200–349	13,934	3,631	37582.08	9.66 (9.36–9.97)				
No+	13,016	3,407	34997.77	9.73 (9.42–10.05)	Reference		Reference	
Yes+	918	224	2584.31	8.67 (7.56–9.77)	0.92 (0.81–1.06)	0.237	0.87 (0.76–1.00)	0.047
CD4 ≥ 350	5,945	1,406	12322.03	11.41 (10.83–11.99)				
No+	5,773	1,371	11927.94	11.49 (11.21–11.78)	Reference		Reference	
Yes+	172	35	394.09	8.88 (6.01–11.75)	0.81 (0.58–1.14)	0.230	0.81 (0.57–1.14)	0.219

Note. +No, did not start cotrimoxazole during the first 6 months of ART; Yes, did start cotrimoxazole during the first 6 months of ART. *HR = hazard ratio; AHR = adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, WHO clinical stage before ART, initial ART regiment, year of ART initiation.

months of ART among patients with HIV exhibiting CD4 cell counts (cells/mm^3) 200–349 and ≥ 350 before ART were marginally and not significantly associated with the attrition rate, respectively. Cotrimoxazole prophylaxis use during the second, third, fourth, and fifth 6 months of ART was associated with a significant reduction in the attrition rate (compared to only using cotrimoxazole prophylaxis during the first 6 months of ART and a CD4 cell count (cells/mm^3) of < 200 at 6 months of ART). Our study showed that continuous cotrimoxazole prophylaxis use during the first 30 months of ART among patients with HIV exhibiting a CD4 cell count (cells/mm^3) of < 200 was significantly associated with lower rates of attrition, suggesting that cotrimoxazole prophylaxis administration should be terminated after ART-induced recovery with a CD4 cell count (cells/mm^3) of ≥ 200 since 6 months of ART. Mitigating attrition is imperative in light of previous studies, describing that attrition could be a major cause of adverse HIV treatment outcomes[9]. Cotrimoxazole prophylaxis use could reduce AIDS-associated opportunistic infections, thereby improving quality of life among patients with HIV (Supplementary Table S3, available in www.besjournal.com).

Our study has several limitations. First, the data related to cotrimoxazole prophylaxis use were retrieved from an HIV treatment database, which might therefore exhibit inherent biases, such as reporting or recall bias. Second, as we performed an observational cohort study and not a randomization control trial, selection bias in our study might have raised issues, although we controlled for numerous potential baseline confounders in multivariable modeling. Third, our cohort study was conducted in Guangxi, which only represents 13% of all patients with HIV who received ART in China. Therefore, our findings might not be generalizable to China and other countries. Finally, we need to mention that our study did not include patients without ART.

In conclusion, the results of this large-scale observational cohort support the WHO recommended guidelines indicating that cotrimoxazole should be provided in conjunction with ART to patients with HIV exhibiting a CD4 cell count (cells/mm^3) of < 200 in China and other low- and middle-income countries.

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Conflicts of Interest The authors have no conflicts of interest to declare. The funders of the study had no role in study design; data collection, analysis, and interpretation; or writing of the paper. The corresponding author has full access to all data in the study and takes final responsibility for the decision to submit for publication.

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Author Contribution JZ, YR, PS, YW, and LL were responsible for study design and planning. QZ, ZS, GL, and HC contributed to data collection and management. JZ and YR contributed to data analysis. JZ, YR, SWP, HX, WY, YS, and LL contributed to interpretation of data. JZ, YR, SWP, and LL drafted the manuscript. All authors read and approved the final version of the report.

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Supplementary Table S1. Characteristics of patients with HIV started ART in Guangxi, China, 2010–2015

Variable	Number	%
Total	45,213	100.0
Age, years		
18–50	27,717	61.3
≥ 50	17,496	38.7
Sex		
Male	30,277	67.0
Female	14,936	33.0
Marital status		
Single	6,843	15.1
Married or cohabitation	31,277	69.2
Other	7,093	15.7
Route of HIV transmission		
Heterosexual intercourse	39,963	88.4
Homosexual intercourse	3,386	7.5
Intravenous drug use	867	1.9
Other	997	2.2
CD4 cell count (cells/mm^3) before ART		
< 200	25,334	56.0
200–349	13,934	30.8
350–499	4,362	9.7
≥ 500	1,583	3.5
WHO clinical stage before ART		
I/II	26,434	58.5
III/IV	18,779	41.5
Initial ART regimen		
The first-line ART containing D4T	8,014	17.7
The first-line ART containing AZT	18,764	41.5
The first-line ART containing TDF	13,698	30.3
The first-line ART containing LPV/r	4,353	9.6
Other	384	0.9
Year of ART initiation		
2010	5,673	12.6
2011	7,605	16.8
2012	9,062	20.0
2013	8,629	19.1
2014	9,267	20.5
2015	4,977	11.0

Supplementary Table S2. Effects of cotrimoxazole prophylaxis use every 6 months after ART initiation on mortality among patients with HIV in Guangxi, China, 2010–2015, with CD4 cell counts (cells/mm^3) of < 200 before ART

Variable		Number	Deaths	Person-years	Deaths/100 person-years (95% *CI*)	HR (95% *CI*)	*P*-value	AHR* (95% *CI*)	*P*-value
Cotrimoxazole prophylaxis use during the first 6 months of ART and CD4 cell count (cells/mm^3) < 200 at 6 months of ART	Cotrimoxazole prophylaxis use during the second 6 months of ART	9,815	491	29420.09	1.67 (1.52–1.81)				
Yes	No	3,240	271	9953.94	2.72 (2.41–3.04)	Reference		Reference	
Yes	Yes	6,575	220	19466.15	1.13 (0.98–1.28)	0.39 (0.33–0.47)	< 0.001	0.39 (0.32–0.46)	< 0.001
Cotrimoxazole prophylaxis use during the first 12 months of ART and CD4 cell count (cells/mm^3) < 200 at 12 months of ART	Cotrimoxazole prophylaxis use during the third 6 months of ART	4,807	152	14599.21	1.04 (0.88–1.2)				
Yes	No	1,272	55	3458.29	1.59 (1.18–2.00)	Reference		Reference	
Yes	Yes	3,535	97	11140.93	0.87 (0.70–1.04)	0.48 (0.35–0.67)	< 0.001	0.44 (0.31–0.61)	< 0.001
Cotrimoxazole prophylaxis use during the first 18 months of ART and CD4 cell count (cells/mm^3) < 200 at 18 months of ART	Cotrimoxazole prophylaxis use during the fourth 6 months of ART	2,816	79	9470.82	0.83 (0.65–1.01)				
Yes	No	804	35	2440.35	1.43 (0.97–1.9)	Reference		Reference	
Yes	Yes	2,012	44	7030.47	0.63 (0.45–0.81)	0.38 (0.25–0.60)	< 0.001	0.28 (0.17–0.44)	< 0.001
Cotrimoxazole prophylaxis use during the first 24 months of ART and CD4 cell count (cells/mm^3) < 200 at 24 months of ART	Cotrimoxazole prophylaxis use during the fifth 6 months of ART	1,531	30	5331.45	0.56 (0.37–0.76)				
Yes	No	545	16	1588.36	1.01 (0.78–1.24)	Reference		Reference	
Yes	Yes	986	14	3743.09	0.37 (0.18–0.57)	0.25 (0.12–0.51)	< 0.001	0.23 (0.11–0.47)	< 0.001

Note. *HR = hazard ratio; AHR = adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, WHO clinical stage before ART, initial ART regiment, year of ART initiation.

Supplementary Table S3. Effects of cotrimoxazole prophylaxis use every 6 months after ART initiation on attrition among patients with HIV in Guangxi, China, 2010–2015, with CD4 cell counts (cells/mm^3) of < 200 before ART

Variable		Number	Attritions	Person-years	Attritions/100 person-years (95% *CI*)	HR (95% *CI*)	*P*-value	AHR* (95% *CI*)	*P*-value
Cotrimoxazole prophylaxis use during the first 6 months of ART and CD4 cell count (cells/mm^3) < 200 at 6 months of ART	Cotrimoxazole prophylaxis use during the second 6 months of ART	9,815	1,659	29420.09	5.64 (5.37–5.90)				
Yes	No	3,240	872	9953.94	8.76 (8.19–9.33)	Reference		Reference	
Yes	Yes	6,575	787	19466.15	4.04 (3.77–4.32)	0.44 (0.40–0.48)	< 0.001	0.43 (0.39–0.48)	< 0.001
Cotrimoxazole prophylaxis use during the first 12 months of ART and CD4 cell count (cells/mm^3) < 200 at 12 months of ART	Cotrimoxazole prophylaxis use during the third 6 months of ART	4,807	491	14599.21	3.36 (3.07–3.65)				
Yes	No	1,272	178	3458.29	5.15 (4.41–5.88)	Reference		Reference	
Yes	Yes	3,535	313	11140.93	2.81 (2.51–3.11)	0.47 (0.39–0.57)	< 0.001	0.46 (0.38–0.55)	< 0.001
Cotrimoxazole prophylaxis use during the first 18 months of ART and CD4 cell count (cells/mm^3) < 200 at 18 months of ART	Cotrimoxazole prophylaxis use during the fourth 6 months of ART	2,816	250	9470.82	2.64 (2.32–2.96)				
Yes	No	804	100	2440.35	4.10 (3.31–4.88)	Reference		Reference	
Yes	Yes	2,012	150	7030.47	2.13 (1.80–2.47)	0.44 (0.34–0.56)	< 0.001	0.39 (0.30–0.50)	< 0.001
Cotrimoxazole prophylaxis use during the first 24 months of ART and CD4 cell count (cells/mm^3) < 200 at 24 months of ART	Cotrimoxazole prophylaxis use during the fifth 6 months of ART	1,531	97	5331.45	1.82 (1.47–2.17)				
Yes	No	545	29	1588.36	1.83 (1.52–2.13)	Reference		Reference	
Yes	Yes	986	68	3743.09	1.82 (1.40–2.24)	0.68 (0.44–1.05)	0.081	0.62 (0.40–0.97)	0.037

Note. *HR = hazard ratio; AHR = adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, WHO clinical stage before ART, initial ART regiment, year of ART initiation.