Cotrimoxazole prophylaxis decreases tuberculosis risk among Asian patients with HIV

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TREAT Asia HIV Observational Database (TAHOD) of IeDEA Asia-Pacific*

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Abstract

Introduction: Cotrimoxazole (CTX) is recommended as prophylaxis against Pneumocystis jiroveci pneumonia (PJP), toxoplasmosis, malaria and other serious bacterial infections in HIV-infected patients. Despite its in vitro activity against Mycobacterium tuberculosis, the effects of CTX preventive therapy on tuberculosis (TB) remain unclear.

Methods: Adults living with HIV enrolled in a regional observational cohort in Asia who had initiated combination antiretroviral therapy (cART) were included in the analysis. Factors associated with new TB diagnoses after cohort entry and survival after cART initiation were analysed using Cox regression, stratified by site.

Results: A total of 7355 patients from 12 countries enrolled into the cohort between 2003 and 2016 were included in the study. There were 368 reported cases of TB after cohort entry with an incidence rate of 0.99 per 100 person-years (0.01/100 pys). Multivariate analyses adjusted for viral load (VL), CD4 count, body mass index (BMI) and cART duration showed that CTX reduced the hazard for new TB infection by 28% (HR 0.72, 95% CI 0.56, 0.93). Mortality after cART initiation was 0.85/100 pys, with a median follow-up time of 4.63 years. Predictors of survival included age, female sex, hepatitis C co-infection, TB diagnosis, HIV VL, CD4 count and BMI.

Conclusions: CTX was associated with a reduction in the hazard for new TB infection but did not impact survival in our Asian cohort. The potential preventive effect of CTX against TB during periods of severe immunosuppression should be further explored.

Keywords: cotrimoxazole; sulphamethoxazole/trimethoprim; tuberculosis; HIV; AIDS; Asia; cohort studies; prophylaxis

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pulmonary tuberculosis [8]. A recent randomized controlled trial in Cambodia has found that absence of CTX prophylaxis in HIV-infected adult patients with smear-positive tuberculosis was associated with an increased rate of late mortality [9]. Several cohort studies also found a decreased risk of death in TB/HIV-coinfected patients receiving CTX preventive therapy in resource-limited settings [10,11]. A Swiss HIV Cohort Study suggested CTX reduced the incidence of TB among HIV-infected persons, and although a recent case–control study in Ethiopia also found CTX had a protective effect against TB [12,13], findings from a South African cohort study did not support a preventive effect [14]. This study aims to examine the incidence of TB and survival in HIV-infected patients receiving and not receiving CTX prophylaxis in a regional observational cohort in Asia.

2 | METHODS

2.1 | Study population

Patients were included if they were enrolled in the adult (age ≥ 18 years) TREAT Asia HIV Observational Database (TAHOD) of IeDEA Asia-Pacific from 2003 and had initiated combination antiretroviral therapy (cART). Patients who had not initiated cART or those who initiated with mono/dual therapy were excluded. All patients were analysed based on the intention-to-treat approach where patients were considered to be on cART for the entire follow-up time after cART had been initiated, regardless of whether treatment interruptions had occurred.

2.1.1 | Analysis (i): Factors associated with first TB diagnosis after TAHOD entry

Patients were included if they had at least one day of follow-up after cohort entry. TB diagnosis is defined as definitive when there is isolation (or culture) of Mtb complex from a clinical specimen. TB is presumptively diagnosed when there is demonstration of acid-fast bacilli in a clinical specimen, or in a histopathological lesion when a culture is not available, in a person with signs or symptoms compatible with tuberculosis; or evidence of resolution of disease where treatment with two or more antituberculosis medications have been prescribed and follow-up has been instigated. These diagnostic criteria have been used in TAHOD and published previously elsewhere [15-17]. A TB diagnosis up to seven days after cohort entry was included as prior TB events [16]. Patients without evidence of TB diagnosis during follow-up but have died with TB as the reported cause of death were also included as being diagnosed with TB on the date of death. Risk time for TB started from the date of cohort entry and ended on the date of TB diagnosis, defined as the outcome of this analysis. Factors associated with TB diagnosis after cohort entry was analysed using Cox regression, stratified by site. Patients who did not develop TB were censored at date of last follow-up. A TB diagnosis event could occur at any time either before or after cART initiation, but post-cohort enrolment. Time-fixed covariates included in the regression analysis were age at cohort entry, sex, HIV exposure category, hepatitis B/C co-infection and a history of prior TB events. Time-updated covariates were viral load (VL), CD4 count, body mass index (BMI), cART duration, and CTX and isoniazid use. Age, VL, CD4 and BMI were included as categorical variables based on clinically relevant categories for our patient group as well as taking into consideration the distribution of our data. Age was categorized into 10-year groups to illustrate the effects of hazard ratios (HRs) for each decade between 30 and 50 years of age. Viral load was categorized to represent different levels of detectable and undetectable viral loads [18,19]. CD4 cell count represented the different low levels below 200 cells/μL at which CTX was initiated. BMI categories were grouped as “overweight” and “not overweight.” If CTX or isoniazid was initiated in the 60 days prior to the diagnosis of a new TB diagnosis, the TB episode was coded as not exposed to CTX or isoniazid because these drugs may have been started as a result of TB symptoms rather than as preventative measures [14].

2.1.2 | Analysis (ii): Survival time after cART initiation

Patients who had at least one day of follow-up after cohort entry or cART initiation (whichever occurred last) were eligible for inclusion in the analysis. Risk time for mortality after cART initiation began from the date of cART initiation and ended on the date of death or date of last follow-up. For patients who initiated cART prior to cohort entry, survival time was left-truncated at cohort entry. Survival time was analysed using Cox regression, stratified by site. Time-fixed covariates were age at cART initiation, sex, HIV exposure category and hepatitis B/C co-infection. Time-updated covariates were new TB diagnosis after cohort entry, VL, CD4 count, BMI, and CTX and isoniazid use, which were coded in the same way as Analysis (i).

All regression models were fitted using a backward stepwise selection process. Covariates significant at p < 0.10 in the univariate analyses were chosen for inclusion in the multivariate models. Covariates with p < 0.05 were considered statistically significant in the final model. Non-significant covariates were presented in the tables adjusted for statistically significant predictors; however, they did not form part of the final multivariate model. Crude incidence rates for TB diagnosis and mortality were plotted for CTX by time-updated CD4 cell count category. Cox proportional hazards (PH) assumption was tested using Schoenfeld residuals and log−log plots.

2.2 | Sensitivity analyses

Several sensitivity analyses were performed to further assess the association with TB diagnosis:

- Sensitivity analysis (a) and (b): TB diagnosis was further classified as presumptive or definitive. Those with unreported TB classification were grouped into ‘presumptive’ TB cases. Fine and Gray competing risk regression, adjusted for site, was used to analyse factors associated with presumptive TB (sensitivity analysis (a)) and definitive TB (sensitivity analysis (b)).

- Sensitivity analysis (c) and (d): Risk factors for TB diagnosis was analysed separately for males (sensitivity analysis (c)) and females (sensitivity analysis (d)), using Cox regression methods, stratified by site.

Ethics approvals were obtained from the local institutional review boards of each TAHOD-participating site, the data
management and biostatistics centre (UNSW Sydney Ethics Committee) and the coordinating centre (TREAT Asia/amfAR). The informed consent was obtained or waived according to the regulation from the local institutional review boards of each TAHOD-participating site. All data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata software version 14.1 (StataCorp, College Station, TX, USA).

3 RESULTS

A total of 8718 patients were enrolled in TAHOD as of March 2015. There were 7465 patients (86%) who had initiated with three or more cART. Of the 7465 patients, 7355 had at least one day of follow-up from cohort enrolment and were included in Analysis (i). A total of 7328 patients were included in Analysis (ii) as they had at least one day of follow-up from the latter of cohort enrolment date or date of cART initiation (Figure 1).

3.1 Analysis (i): Factors associated with first TB diagnosis after cohort entry

A total of 7355 patients from Cambodia, China, Hong Kong SAR, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam were included between 2003 and 2015. Of the 7355 patients, 5150 (70%) were male, 3205 (44%) were aged between 31 and 40 years, 4682 (64%) acquired HIV through heterosexual exposure, 5050 (89% of 5644 tested) had no hepatitis B co-infection, 4544 (85% of 5331 tested) had no hepatitis C co-infection and 5856 (80%) had no prior TB diagnosis (Table 1). There were 368 (5%) new cases of TB reported after cohort entry with an incidence rate of 0.99/100 person-years (100 pys). The median follow-up time up to the TB diagnosis event was 4.6 years (interquartile range (IQR) 2.8 to 7.0). Of the 368 TB cases, 125 (34%) were presumptive, 141 (38%) were definitive and 102 (28%) did not report TB diagnosis category. There was a total of 26 patients who had died due to TB, but without prior evidence of TB diagnosis recorded in the database after cohort enrolment. The median CD4 cell count at time of TB diagnosis was 164 cells/µL (IQR 58 to 287) for presumptive TB, 205 cells/µL (IQR 89 to 336) for definitive TB and 162 cells/µL (IQR 25 to 293) for unknown category TB cases.

In the univariate analyses, sex ($p = 0.031$), VL ($p < 0.001$), CD4 count ($p < 0.001$), BMI ($p < 0.001$), cART duration ($p < 0.001$) and CTX use ($p < 0.001$) were significantly associated with incident TB diagnosis. In multivariate analyses, higher VL (1000 to 4999 copies/mL HR 2.18, 95% CI (1.06 to 4.48), $p = 0.034$; and $\geq 5000$ copies/mL HR 2.38, 95% CI (1.63 to 3.47), $p < 0.001$) were associated with increased hazard of developing TB compared to VL $< 400$ copies/mL. Conversely, higher CD4 count (51 to 100 cells/µL HR 0.57, 95% CI (0.38 to 0.86), $p = 0.007$; 101 to 200 cells/µL HR 0.42, 95% CI (0.30 to 0.58), $p < 0.001$; and $> 200$ cells/µL HR 0.11, 95% CI (0.08 to 0.15), $p < 0.001$) was associated with reduced hazard for TB compared to CD4 $\leq 50$ cells/µL. Other factors associated with reduced hazard for development of TB were BMI $\geq 25$ kg/m$^2$ (HR 0.46, 95% CI (0.31 to 0.69), $p < 0.001$) compared to BMI $< 25$ kg/m$^2$; longer cART durations (6 to 12 months HR 0.47, 95% CI (0.28 to 0.80), $p = 0.005$; and $> 12$ months HR 0.40, 95% CI (0.28 to 0.57), $p < 0.001$) compared to periods prior to cART initiation; and
Table 1. Factors associated with TB diagnosis after cohort entry

| Factor                                | No. of patients<sup>b</sup> | No. of TB diagnosis | Rate (/100 yrs) | Univariate HR (95% CI) | p-value<sup>c</sup> | Multivariate HR (95% CI) | p-value<sup>c,d</sup> |
|---------------------------------------|-----------------------------|---------------------|-----------------|------------------------|---------------------|--------------------------|------------------------|
| **Total**                             | 7355                        | 368                 | 0.99            |                        |                     |                          |                        |
| **Age at TAHOD entry (years)**        |                             |                     |                 |                        |                     |                          |                        |
| ≤30                                   | 1982                        | 100                 | 1.07            | 1                      | 0.944               | 1.30 (1.01, 1.67)        | 0.042                  |
| 31 to 40                              | 3205                        | 175                 | 1.05            | 1.13 (0.88, 1.45)      | 0.328               | 1.30 (1.01, 1.67)        | 0.042                  |
| 41 to 50                              | 1513                        | 73                  | 0.94            | 1.14 (0.83, 1.55)      | 0.418               | 1.47 (1.07, 2.01)        | 0.018                  |
| >50                                   | 655                         | 20                  | 0.59            | 0.82 (0.50, 1.33)      | 0.422               | 1.05 (0.64, 1.73)        | 0.842                  |
| **Sex**                               |                             |                     |                 |                        |                     |                          |                        |
| Male                                  | 5150                        | 280                 | 1.08            | 1.07                   | 1.07                | 1.07 (1.01, 1.13)        | 0.064                  |
| Female                                | 2205                        | 88                  | 0.78            | 0.76 (0.59, 0.98)      | 0.031               | 0.79 (0.62, 1.01)        | 0.064                  |
| **HIV exposure**                      |                             |                     |                 |                        |                     |                          |                        |
| Heterosexual contact                  | 4682                        | 253                 | 1.03            | 1                      | 0.125               | 1.13 (0.88, 1.45)        | 0.328                  |
| Homosexual contact                    | 1580                        | 50                  | 0.63            | 0.77 (0.52, 1.12)      | 0.176               | 0.88 (0.60, 1.30)        | 0.527                  |
| Injecting drug use                    | 555                         | 41                  | 1.99            | 1.49 (0.97, 2.29)      | 0.067               | 1.34 (0.87, 2.06)        | 0.182                  |
| Other/Unknown                         | 538                         | 24                  | 0.88            | 0.90 (0.57, 1.42)      | 0.661               | 0.96 (0.61, 1.51)        | 0.870                  |
| **Hepatitis B co-infection**          |                             |                     |                 |                        |                     |                          |                        |
| Negative                              | 5050                        | 234                 | 0.9             | 1                      | 1                   |                          |                        |
| Positive                              | 594                         | 26                  | 0.86            | 1.11 (0.74, 1.67)      | 0.624               | 1.07 (0.71, 1.62)        | 0.738                  |
| Not tested                            | 1711                        | 108                 | 1.33            | 1                      | 1                   |                          |                        |
| **Hepatitis C co-infection**          |                             |                     |                 |                        |                     |                          |                        |
| Negative                              | 4544                        | 186                 | 0.77            | 1                      | 1                   |                          |                        |
| Positive                              | 787                         | 42                  | 1.27            | 1.38 (0.94, 2.04)      | 0.102               | 1.28 (0.86, 1.90)        | 0.217                  |
| Not tested                            | 2024                        | 140                 | 1.45            | 1                      | 1                   |                          |                        |
| **Prior TB**                          |                             |                     |                 |                        |                     |                          |                        |
| No                                    | 5856                        | 239                 | 0.8             | 1                      | 1                   |                          |                        |
| Yes                                   | 1499                        | 129                 | 1.77            | 1.34 (1.06, 1.68)      | 0.013               | 1.22 (0.97, 1.54)        | 0.094                  |
| **Viral load (copies/mL)**            |                             |                     |                 |                        |                     |                          |                        |
| <400                                  | 76                          | 0.3                 | 1               | <0.001                 | 1                   |                          |                        |
| 400 to 999                            | 3                           | 0.55                | 1.45 (0.45, 4.63)| 0.534                 | 1.02 (0.32, 3.26)      | 0.979                   |
| 1000 to 4999                          | 9                           | 1.24                | 3.07 (1.51, 6.26)| 0.002                 | 2.18 (1.06, 4.48)      | 0.034                   |
| ≥5000                                 | 100                         | 2.93                | 5.35 (3.77, 7.60)| <0.001                | 2.38 (1.63, 3.47)      | <0.001                  |
| Missing                               | 180                         | 2.47                |                 |                        |                     |                          |                        |
| **CD4 (cells/µL)**                    |                             |                     |                 |                        |                     |                          |                        |
| ≤50                                   | 78                          | 9.91                | 1               | <0.001                 | 1                   |                          |                        |
| 51 to 100                             | 35                          | 4.05                | 0.49 (0.33, 0.74)| 0.001                 | 0.57 (0.38, 0.86)      | 0.007                   |
| 101 to 200                            | 77                          | 2.18                | 0.33 (0.24, 0.46)| <0.001                | 0.42 (0.30, 0.58)      | <0.001                  |
| >200                                  | 158                         | 0.5                 | 0.09 (0.06, 0.12)| <0.001                | 0.11 (0.08, 0.15)      | <0.001                  |
| Missing                               | 20                          | 3.58                |                 |                        |                     |                          |                        |
| **BMI (kg/m²)**                       |                             |                     |                 |                        |                     |                          |                        |
| <25                                   | 265                         | 1.09                | 1               |                        |                     |                          |                        |
| ≥25                                   | 27                          | 0.46                | 0.39 (0.26, 0.58)| <0.001                | 0.46 (0.31, 0.69)      | <0.001                  |
| Missing                               | 76                          | 1.09                |                 |                        |                     |                          |                        |
| **cART duration**                     |                             |                     |                 |                        |                     |                          |                        |
| Prior to cART initiation              | 53                          | 3.2                 | 1               | <0.001                 | 1                   |                          |                        |
| ≤6 months                             | 84                          | 5.43                | 1.72 (1.15, 2.58)| 0.008                 | 1.08 (0.70, 1.66)      | 0.727                   |
| 6 to 12 months                        | 29                          | 1.45                | 0.54 (0.32, 0.89)| 0.015                 | 0.47 (0.28, 0.80)      | 0.005                   |
| >12 months                            | 202                         | 0.63                | 0.33 (0.24, 0.46)| <0.001                | 0.40 (0.28, 0.57)      | <0.001                  |
| **Cotrimoxazole use**                 |                             |                     |                 |                        |                     |                          |                        |
| No                                    | 231                         | 0.75                | 1               |                        |                     |                          |                        |
| Yes                                   | 137                         | 2.13                | 1.71 (1.36, 2.15)| <0.001                | 0.72 (0.56, 0.93)      | 0.011                   |
Table 1. (Continued)

| Isoniazid use | No. of patients\(^b\) | No. of TB diagnosis | Rate (/100 yrs) | Univariate       | Multivariate\(^a\) |
|---------------|------------------------|---------------------|-----------------|------------------|--------------------|
|               |                        |                     |                 | HR (95% CI)      | p-value\(^c\)      |
|               |                        |                     |                 |                  |                    |
| No            | –                      | 353                 | 0.98            | 1                | 1                  |
| Yes           | –                      | 15                  | 1.31            | 1.20 (0.69, 2.08) | 0.520              |

\(^a\)Non-significant covariates were presented in the final model adjusted for the significant covariates; however, they did not form part of the final model; \(^b\) viral load, CD4, BMI, cART duration, cotrimoxazole and isoniazid use are time-updated variables; \(^c\) global p-values for age, VL and CD4 are tests for trend. All other global p-values are tests for heterogeneity excluding missing values; \(^d\) p-values in bold represent significant covariates in the final model.

Figure 2. TB incidence.

For those taking CTX at CD4 101 to 200 cells/µL, there was a 44% reduction in the hazard for development of TB (HR = 0.56, 95% CI (0.33 to 0.94), \(p = 0.03\)) compared to those no receiving CTX. No significance difference was found for among those with CD4 > 200 cells/µL HR = 1.30, 95% CI (0.85 to 2.00), \(p = 0.22\). In summary, CTX was associated with reduced hazards for TB among those with current CD4 ≤ 50 cells/µL and 101 to 200 cells/µL.

3.2 Analysis (ii): Survival time after cART initiation

A total of 7328 patients were included in the survival analysis (Table 2). The mortality rate was 0.85/100 yrs, with a median follow-up time of 4.63 years (IQR 2.80 to 6.92 years). In the adjusted model, factors associated with poorer survival were older age (41 to 50 years HR 1.49, 95% CI (1.05 to 2.13), \(p = 0.027\); and > 50 years HR 3.90, 95% CI (2.70 to 5.62), \(p < 0.001\)) compared to age ≤ 30 years; being hepatitis C antibody positive (HR 1.90, 95% CI (1.33 to 2.72), \(p < 0.001\)); having an incident TB diagnosis (HR 2.50, 95% CI (1.73 to 3.63), \(p < 0.001\)); and having VL ≥ 5000 copies/mL (HR 1.59, 95% CI (1.09 to 2.34), \(p = 0.017\)) compared to VL < 400 copies/mL. Factors associated with improved survival were female sex (HR 0.70, 95% CI (0.53 to 0.94), \(p = 0.017\)); higher CD4 count (51 to 100 cells/µL HR 0.42, 95% CI (0.29 to 0.62); 101 to 200 cells/µL HR 0.19, 95% CI (0.13 to 0.28); and > 200 cells/µL HR 0.06, 95% CI (0.04 to 0.09), all \(p < 0.001\)) compared to CD4 ≤ 50 cells/µL; and BMI ≥ 25 kg/m² (HR 0.40, 95% CI (0.24 to 0.68), \(p = 0.001\)) compared BMI < 25 kg/m². Those using CTX also had improved survival; however, this effect was not statistically significant (HR 0.78, 95% CI (0.58 to 1.03), \(p = 0.081\)). Crude mortality rates in those receiving and not receiving CTX, stratified by CD4 count, are shown in Figure 3. The hazard for mortality was only significantly lower in those receiving CTX at CD4 101 to 200 cells/µL (HR = 0.51, 95% CI (0.28 to 0.94), \(p = 0.031\)).

3.3 Sensitivity analyses (a) and (b)

Table S2 shows competing risk analysis of factors associated with having presumptive TB diagnosis after cohort entry, with definitive TB analysed as a competing risk (sensitivity analysis (a)). Of the 7355 patients, 227 met the definition of presumptive TB outcome for this sensitivity analysis, which included 102 cases of unreported TB category. The incidence rate was
Table 2. Survival time after cART initiation

|                                | Number of patientsb | Deaths | Rate (/100 yrs) | Univariate | Multivariatea |          |          |
|--------------------------------|---------------------|--------|----------------|------------|---------------|----------|----------|
|                                |                     |        |                | HR (95% CI) | p-valuec      | HR (95% CI)| p-valuec|
|                                |                     |        |                | p          | global        |          |          |
|                                |                     |        |                | p          | p             |          |          |
|                                |                     |        |                |            |               |          |          |
| **Total**                      | 7328                | 315    | 0.85           |            |               |          |          |
| **Age at ART initiation (years)** |                    |        |                |            |               |          |          |
| ≤30                            | 2309                | 74     | 0.68           | 1          | <0.001        | 1        | <0.001  |
| 31 to 40                       | 3110                | 116    | 0.71           | 1.12 (0.83, 1.50) | 0.473 | 1.13 (0.84, 1.53) | 0.419 |          |
| 41 to 50                       | 1347                | 64     | 0.92           | 1.40 (0.99, 1.97) | 0.056 | 1.49 (1.05, 2.13) | 0.027 |          |
| >50                            | 562                 | 61     | 2.16           | 3.40 (2.39, 4.84) | <0.001 | 3.90 (2.70, 5.62) | <0.001 |          |
| **Sex**                        |                     |        |                |            |               |          |          |
| Male                           | 5132                | 249    | 0.97           | 1          |               | 1        |          |
| Female                         | 2196                | 66     | 0.59           | 0.58 (0.44, 0.78) | <0.001 | 0.70 (0.53, 0.94) | 0.017 |          |
| **HIV exposure**               |                     |        |                |            |               |          |          |
| Heterosexual contact           | 4665                | 214    | 0.87           | 1          | <0.001        | 1        |          |
| Homosexual contact             | 1573                | 42     | 0.55           | 0.42 (0.28, 0.63) | <0.001 | 0.64 (0.42, 0.98) | 0.039 |          |
| Injecting drug use             | 554                 | 35     | 1.65           | 1.69 (1.10, 2.58) | 0.016 | 0.98 (0.60, 1.60) | 0.939 |          |
| Other/unknown                  | 536                 | 24     | 0.9            | 0.85 (0.53, 1.34) | 0.482 | 1.02 (0.63, 1.63) | 0.946 |          |
| **Hepatitis B co-infection**   |                     |        |                |            |               |          |          |
| Negative                       | 5036                | 193    | 0.75           | 1          |               | 1        |          |
| Positive                       | 591                 | 36     | 1.19           | 1.53 (1.07, 2.20) | 0.019 | 1.39 (0.96, 2.01) | 0.078 |          |
| Not tested                     | 1701                | 86     | 1.06           |            |               |          |          |
| **Hepatitis C co-infection**   |                     |        |                |            |               |          |          |
| Negative                       | 4536                | 172    | 0.72           | 1          |               | 1        |          |
| Positive                       | 786                 | 53     | 1.61           | 2.31 (1.64, 3.26) | <0.001 | 1.90 (1.33, 2.72) | <0.001 |          |
| Not tested                     | 2006                | 90     | 0.94           |            |               |          |          |
| **New TB diagnosis after TAHOD entry** |               |        |                |            |               |          |          |
| No                             | –                   | 276    | 0.78           | 1          |               | 1        |          |
| Yes                            | –                   | 39     | 2.94           | 3.82 (2.68, 5.43) | <0.001 | 2.50 (1.73, 3.63) | <0.001 |          |
| **Viral load (copies/mL)**     |                     |        |                |            |               |          |          |
| <400                           | –                   | 130    | 0.49           | 1          | <0.001        | 1        |          |
| 400 to 999                     | –                   | 3      | 0.51           | 0.97 (0.30, 3.08) | 0.958 | 0.69 (0.21, 2.24) | 0.537 |          |
| 1000 to 4999                   | –                   | 6      | 0.98           | 1.76 (0.76, 4.10) | 0.189 | 1.23 (0.53, 2.86) | 0.638 |          |
| ≥5000                          | –                   | 84     | 2.68           | 3.89 (2.68, 5.64) | <0.001 | 1.59 (1.09, 2.34) | 0.017 |          |
| Missing                        | –                   | 92     | 1.54           |            |               |          |          |
| **CD4 (cells/µL)**             |                     |        |                |            |               |          |          |
| ≤50                            | –                   | 89     | 10.39          | 1          | <0.001        | 1        | <0.001  |
| 51 to 100                      | –                   | 42     | 4.47           | 0.43 (0.30, 0.64) | <0.001 | 0.42 (0.29, 0.62) | <0.001 |          |
| 101 to 200                     | –                   | 60     | 1.65           | 0.17 (0.12, 0.25) | <0.001 | 0.19 (0.13, 0.28) | <0.001 |          |
| >200                           | –                   | 115    | 0.37           | 0.04 (0.03, 0.06) | <0.001 | 0.06 (0.04, 0.09) | <0.001 |          |
| Missing                        | –                   | 9      | 2.83           |            |               |          |          |
| **BMI (kg/m²)**                |                     |        |                |            |               |          |          |
| <25                            | –                   | 229    | 0.93           | 1          |               | 1        |          |
| ≥25                            | –                   | 16     | 0.28           | 0.33 (0.20, 0.55) | <0.001 | 0.40 (0.24, 0.68) | 0.001 |          |
| Missing                        | –                   | 70     | 1.07           |            |               |          |          |
| **Cotrimoxazole use**          |                     |        |                |            |               |          |          |
| No                             | –                   | 200    | 0.66           | 1          |               | 1        |          |
| Yes                            | –                   | 115    | 1.76           | 1.91 (1.46, 2.51) | <0.001 | 0.78 (0.58, 1.03) | 0.081 |          |
| **Isoniazid use**              |                     |        |                |            |               |          |          |
| No                             | –                   | 301    | 0.84           | 1          |               | 1        |          |
| Yes                            | –                   | 14     | 1.21           | 1.71 (0.96, 3.07) | 0.070 | 1.56 (0.86, 2.84) | 0.142 |          |

Non-significant covariates were presented in the final model adjusted for the significant covariates; however, they did not form part of the final model; bTB diagnosis, viral load, CD4, BMI, cotrimoxazole and isoniazid use are time-updated variables; cglobal p-values for age, VL and CD4 are tests for trend. All other global p-values are tests for heterogeneity excluding missing values; d p-values in bold represent significant covariates in the final model.
0.61/100 yrs. In the multivariate model, we saw similar risk factors and effect sizes as in Table 1, with hepatitis C co-infection (subhazard ratio (SHR): 1.69, 95% CI (1.08 to 2.65), p = 0.022) and prior TB diagnosis (SHR = 1.37, 95% CI (1.02 to 1.85), p = 0.039) being associated with having presumptive TB. In sensitivity analysis (b), where we assessed factors associated with definitive TB, with presumptive TB as a competing risk, the incidence rate was 0.38/100 yrs (Table S3). Due to the small number of events in this analysis, only VL, CD4 and age were associated with definitive TB diagnosis. However, when comparing the results across all three analyses (Table 1, Tables S2 and S3), the effects of each variable were similar, with CTX showing reduction in hazards for TB after adjusting for CD4 cell count.

3.4 Sensitivity analyses (c) and (d)

We assessed factors associated with TB diagnosis separately in males and females. Of the 5150 males, 280 (5%) were diagnosed with TB after cohort enrolment, with an incidence rate of 1.08/100 yrs (Table S4). Among 2205 females, there were 88 patients (4%) with TB diagnosis, with an incidence rate of 0.78/100 yrs (Table S5). In males, being hepatitis C co-infected and having high VL were associated with having TB. Males with high CD4 cell count, BMI above 25 kg/m², been on cART for longer than six months, and receiving CTX had reduced hazards for TB. For females, similar effects were seen; however, hepatitis C co-infection and CTX were no longer significantly associated with TB.

4 DISCUSSION

Our analysis found that cotrimoxazole preventive therapy reduced the hazard for incident TB infection by approximately one-third in HIV-infected adult patients, adjusted for HIV viral load, CD4 count, BMI and cART duration. This adds to clinical evidence supporting the potential additive preventive effect of CTX against tuberculosis in HIV-infected individuals [12,13]. We also found CTX was associated with reduced hazards for TB among those with current CD4 ≤ 50 and 101 to 200 cells/µL.

Previous clinical trials have shown that CTX prophylaxis reduced mortality and hospital admission for sepsicaemia and enteritis in HIV/TB-coinfected patients in West Africa, as well as death including tuberculosis and other HIV-associated conditions in Southeast Asia [8,9]. Such benefits are likely due to a vast array of antibacterial, antifungal, and antiparasitic effects from CTX. In addition, sulphamethoxazole has been found active against Mtb in vitro [5-7]. Several observational studies including ours suggested CTX decreased new TB incidence in HIV-infected individuals, supporting a direct antitubercular effect from CTX [12,13].

Our findings that higher BMI, greater CD4 cell count, and duration of receiving antiretroviral therapy more than six months were associated with lower incidence of new TB infection were also comparable to other studies [12-14]. The finding that a higher HIV viral load, regardless of cART or CD4 cell count was independently associated with an increased risk of new TB infection, is consistent with a previous study in Spain, suggesting that a high HIV viral load in treatment-naïve patients, in patients with treatment interruption or even in treatment-experienced patients with a failing antiretroviral regimen may be linked to an increased occurrence of active TB [20].

The reversal of the HRs for CTX once CD4 cell count was adjusted for reflects the confounding of CTX by CD4 cell count. CTX is normally prescribed as primary prophylaxis in patients with CD4 < 200 cells/µL [1], who are more likely to have poorer treatment outcomes. When CTX was analysed in the univariate analysis, the increased hazard for incident TB in those receiving CTX simply reflected the underlying confounding of increased TB in those with low CD4 counts. Once the confounding CD4 levels were controlled for in the multivariate analysis, that is once we compared the effects of CTX in patients within the same CD4 category, it was evident that CTX reduced the hazard for TB diagnosis.

Many studies have shown that CTX preventive therapy reduces mortality in HIV-infected patients [21,22]. A previous TAHOD study showed greatest absolute survival benefit from PJP prophylaxis, predominantly with CTX, in patients with a CD4 count less than 50 cells/µL [23]. While this study showed improved survival in those using CTX, the effect was only statistically significant in people with current CD4 101 to 200 cells/µL, possibly due to attenuation of the benefit by including only patients who had initiated cART in the current analysis.

We did not find differences in survival time according to isoniazid use in the multivariate analyses, which was likely due to the small number of patients that had actually received isoniazid preventive therapy (IPT) in our cohort. This finding might also reflect the fact that IPT is not delivered uniformly by physicians in concordance with WHO or local guidelines in our region [24].

While our study analysed data on a substantial number of patients from a prospective cohort in a region where TB burden is high, several important limitations are noted. Firstly, not all new TB cases were laboratory-confirmed with positive culture results since we used both definite and presumptive definitions for TB diagnosis. While this helps to avoid underascertainment of TB cases, we may have missed other
patients who were unknown to be receiving care outside of the HIV clinical setting. We also performed sensitivity analyses, and the effects of each variable were similar in new cases with both definite and presumptive TB diagnosis. Tuberculin skin testing (TST) results were not recorded in our cohort since patients with possible latent TB infection were not excluded from the analyses. Although the prescription of prophylactic CTX was documented, we did not specifically assess adherence to CTX or precise dosage of CTX in our cohort sites. A recent pharmacokinetic/pharmacodynamic study showed that the serum level of sulphamethoxazole is comparable with other drugs with anti-TB activity, like pyrazinamide, at a standard prophylactic dose of 960 mg CTX once daily, as recommended by WHO [25]. As we have considered TB diagnosis within 60 days of initiation of CTX to be considered as not exposed to CTX, this may accentuate the protective effect of CTX if TB cases were diagnosed soon after cART initiation. Lastly, the susceptibility test results to CTX or other antimycobacterial agents for the microbiologic isolates were not collected in our TAHOD database. Nevertheless, other studies have shown that the minimal inhibitory concentration of sulphamethoxazole is not significantly different in patients infected with MDR-TB or drug-susceptible TB and that resistance to sulphafoxazole was not frequent in TB/HIV-infected patients taking CTX prophylaxis [26,27].

5 | CONCLUSIONS

Our study found that cotrimoxazole preventive therapy was associated with a reduction in the hazard for incident TB infection among Asian patients in our cohort, adding to existing clinical evidence supporting the use of CTX in HIV-infected patients for broader prevention purposes.

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COMPETING INTERESTS

The authors have none to declare.

AUTHORS' CONTRIBUTIONS

SWWK, KJ, MKP, AW, RC, SK, AA, PSL, NK, CDD, TPM, KVN, AK, FIZ, MPL, YJC, JT, SK, BLHS, OTN, WR and WWW were involved in data collection. SWWK, AJ, JM and WWW were involved in data analysis. SWWK, AJ, KJ, MKP, AW, RC, JM and WWW were involved in data interpretation and presentation of the results. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:
Table S1. Factors associated with TB diagnosis, stratified by both CD4 category and site
Table S2. Factors associated with Presumptive TB diagnosis
Table S3. Factors associated with Definitive TB diagnosis
Table S4. Factors associated with diagnosis in males
Table S5. Factors associated with TB diagnosis in females

APPENDIX

THE TREAT ASIA HIV OBSERVATIONAL DATABASE

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