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Abstract
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Reference

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Co-Ttrimoxazole Prophylaxis Is Associated with Reduced Risk of Incident Tuberculosis in Participants in the Swiss HIV Cohort Study

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Co-trimoxazole reduces mortality in HIV-infected adults with tuberculosis (TB), and in vitro data suggest potential antimycobacterial activity of co-trimoxazole. We aimed to evaluate whether prophylaxis with co-trimoxazole is associated with a decreased risk of incident TB in Swiss HIV Cohort Study (SHCS) participants. We determined the incidence of TB per 1,000 person-years from January 1992 to December 2012. Rates were analyzed separately in participants with current or no previous antiretroviral treatment (ART) using Poisson regression adjusted for CD4 cell count, sex, region of origin, injection drug use, and age. A total of 13,431 cohort participants contributed 107,549 person-years of follow-up: 182 patients had incident TB—132 (73%) before and 50 (27%) after ART initiation. The multivariable incidence rate ratios for cumulative co-trimoxazole exposure per year for persons with no previous ART and current ART were 0.70 (95% confidence interval [CI], 0.55 to 0.89) and 0.87 (95% CI, 0.74 to 1.0), respectively. Co-trimoxazole may prevent the development of TB among HIV-positive persons, especially among those with no previous ART.

Although tuberculosis (TB) can be successfully treated, it remains a leading cause of death among HIV-infected persons, particularly in low-income countries. A substantial proportion of deaths among patients with TB are caused by bacterial sepsis, and rates of bacterial pneumonia are several times higher among HIV-TB-coinfected patients than in the HIV-monoinfected population. Co-trimoxazole is a combination of trimethoprim and sulfamethoxazole that is widely used to treat bacterial infections, including lower respiratory, gastrointestinal, and urinary tract infections and Pneumocystis jirovecii pneumonia (PCP). A randomized controlled trial showed that co-trimoxazole prophylaxis significantly reduced mortality in HIV-infected adults receiving TB treatment in Côte d’Ivoire (1). Other studies confirmed the effect of co-trimoxazole prophylaxis on morbidity and mortality for combination antiretroviral treatment (ART)-naive HIV-TB-coinfected (2, 3) and ART-experienced (4) persons. Furthermore, co-trimoxazole is strongly recommended as prophylaxis against PCP pneumonia in HIV-infected persons with CD4 cell counts below 200 cells/µl.

Recent in vitro studies suggested a potential antimicrobial effect of co-trimoxazole on Mycobacterium tuberculosis (5–9), whereby sulfamethoxazole seems to be the active compound in the fixed-dose combination (6). Moreover, sulfamethoxazole together with rifampin appears to have a synergistic effect against M. tuberculosis (8). Whether co-trimoxazole prophylaxis may prevent TB is uncertain. We therefore studied cumulative co-trimoxazole exposure as a determinant of incident TB among participants in the Swiss HIV Cohort Study (SHCS). Additionally, we considered total mortality as an endpoint, where we expected to find a beneficial effect of co-trimoxazole, in order to confirm adequate adjustment for various confounders.

MATERIALS AND METHODS

HIV-infected adults (≥16 years of age) who attend outpatient clinics of seven cohort centers, affiliated regional hospitals, or private practitioners collaborating with the centers are continuously enrolled in the prospective observational SHCS. The enrollment of participants is independent of social status. Health care in Switzerland is universal, with mandatory health insurance (including for immigrants and marginalized groups). Demographic, psychosocial, clinical, laboratory (immunologic and virologic parameters), and treatment information is collected at enrollment and thereafter completed every 6 months by physicians and study nurses (10). Local ethical committees approved the SHCS protocol, and written informed consent was obtained from all participants.

HIV-associated opportunistic infections, including TB events, have been documented since 1988, and data on immune reconstitution inflammatory syndrome (IRIS [including TB IRIS]) have been collected since 2005. A TB event is diagnosed if there is culture-positive evidence of Mycobacterium tuberculosis in a symptomatic patient. As part of a recent SHCS project by Fenner et al., there was an endpoint validation of TB events (11). Purified protein derivate-based tuberculin skin testing (TST) is routinely performed in the SHCS, and latent TB treatment is initiated in TST-positive cases (defined as a skin induration of ≥5 mm) according to standard guidelines. We decided to exclude patients with previous TB treatment or latent TB treatment during follow-up, since latent TB treatment could be a major source of bias (if the hypothesis is correct that the cumulative co-trimoxazole effect is based on treatment of latent TB infection).

Controlled trials identified the effectiveness of co-trimoxazole as a secondary and primary PCP prophylaxis in 1992. Therefore, SHCS participants with at least two cohort visits between 1 January 1992 and 31 April 2014 were included. This endpoint was defined as the first death that was not caused by a documented or observed cause of death in the SHCS data base.
December 2012, without evidence of prevalent TB and no previous TB treatment, were included in the analyses. Incident TB and all-cause mortality, respectively, were calculated as the number of events divided by the number of person-years of follow-up (PYFU). Follow-up was counted from the first visit after 1 January 1992, the earliest event, the patient’s last cohort visit, or 31 December 2012.

Poisson regression was used to model the incidence of TB or all-cause mortality separately in HIV-infected persons who had never yet received or had ever previously received combination ART (subsequently denoted “no previous ART” or “current ART,” respectively). We decided to specify separate models for those with no previous ART or current ART, because of differences in who would have been prescribed co-trimoxazole, depending on ART status, and because of the potential for interactions between many covariates and ART in terms of effect on the outcomes. Because associations between co-trimoxazole intake and opportunistic infections or death are strongly confounded by CD4 cell count, which was the main determinant of prescription, we do not present univariable associations but instead present bivariable associations adjusted for the latent variables.

We used Stata (version 12; StataCorp, College Station, TX) for statistical analyses.

RESULTS

From 1992 to 2012, 14,589 SHCS participants contributed data. A total of 1,158 (8%) participants were excluded because of prevalent TB within 30 days of cohort registration (n = 339) or any prior treatment of active or latent TB (n = 819), leaving 13,431 SHCS participants in analyses. Baseline characteristics are shown in Table 1. Median age at the first visit during the study period (baseline) was 35 years (interquartile range [IQR], 30 to 42 years). A total of 3,815 (28%) individuals were women, 2,357 (18%) were from a region other than Europe, North America, or Australia, and 2,697 (20%) had prior clinical AIDS. The nadir CD4 cell count was 273 cells/µl (IQR, 129 to 448 cells/µl). TST results were available for 8,980/13,431 (67%) of subjects, and 365/8,980 (4%) had a positive test result. Participants with a positive test result were more likely to have a high CD4 cell count (median, 466 cells/µl [IQR, 310 to 637 cells/µl] versus 271 cells/µl [IQR, 131 to 440 cells/µl] in those without a positive test result). Median CD4 cell counts for Caucasians and for persons from other regions with a positive TST were 544 cells/µl (IQR, 343 to 695 cells/µl) and 336 cells/µl (IQR, 249 to 489 cells/µl), respectively. A total of 95 (2%) patients who received co-trimoxazole had positive TST results; bivariable logistic regression confirmed that this difference was fully explained by the CD4 levels at the time of TST of 207 cells/µl (IQR, 101 to 349 cells/µl) versus 437 cells/µl (IQR, 300 to 614 cells/µl), respectively (data not shown).

A total of 5,265 (39%) persons took co-trimoxazole at some time during the study period for median of 1.3 years (IQR, 0.50 to 2.8 years). Among participants with no previous ART, co-trimoxazole exposure was 41,891 person-years of follow-up (PYFU), and among those with current ART, co-trimoxazole exposure was 65,657 PYFU (Fig. 1). A total of 1,406/13,431 (10%) participants inhaled aerosolized pentamidine, and 639 (5%) used pyrimethamine-dapsone as second-line prophylaxis against PCP pneumonia.

We observed 182 incident cases of TB. Incidence rates (IRs) for TB among persons with current and no previous ART were 0.76 (95% confidence interval [CI], 0.58 to 1.00) and 3.2 (95% CI, 2.7 to 3.7) per 1,000 PYFU, respectively.

Bivariable incidence rate ratios (IRR) for cumulative co-trimoxazole exposure/year were 0.71 (95% CI, 0.56 to 0.90) for persons with no previous ART and 0.85 (95% CI, 0.72 to 1.00) for persons with current ART (Table 2). Associations remained unchanged after multivariable adjustment for CD4, region of origin, IDU, and age of >40 years at baseline, but the impact of cumulative co-trimoxazole was slightly attenuated by ART use. In a combined analysis, we included ART and its interaction with co-trimoxazole use in the multivariable model for TB incidence, also adjusted for square root CD4, region of origin, IDU, and age. There was a strong protective effect of ART (IRR, 0.31 [95% CI, 0.21 to 0.45]), and the associations with co-trimoxazole use were virtually unchanged (per year of co-trimoxazole use pre-ART, IRR, 0.69 [95% CI, 0.54 to 0.88]; during ART IRR, 0.89 [95% CI, 0.76 to 1.00]). We did not find an interaction between time since ART initiation and cumulative co-trimoxazole exposure (e.g., P = 0.66 comparing 0 to 12 months versus >12 months). Inclusion of calendar period (1992 to 1995, 1996 to 1999, 2000 to 2003, 2004 to 2007, and 2008 to 2012) in the multivariable models did not substantially change the estimate for cumulative co-trimoxazole exposure (no previous ART, IRR, 0.77 [95% CI, 0.60 to 0.98]; current ART, IRR, 0.87 [95% CI, 0.74 to 1.0]). Inclusion of both current and cumulative co-trimoxazole exposures suggested a similar protective effect of cumulative exposure (no previous ART, IRR, 0.55 [95% CI, 0.40 to 0.75]; current ART, IRR, 0.84 [95% CI, 0.70 to 0.99]) but increased risk with current co-trimoxazole use (no previous ART, IRR, 2.8 [95% CI, 1.7 to 4.4]; current ART, IRR, 1.3 [95% CI, 0.61 to 2.7]), supporting the concern about reverse causality.

In sensitivity analyses including exposure to pentamidine and/or dapsone as well as co-trimoxazole, there was an association of reduced TB incidence with cumulative co-trimoxazole use (no previous ART, IRR, 0.70 [95% CI, 0.55 to 0.87]; P = 0.003; current...
ART, IRR, 0.86 [95% CI, 0.73 to 1.0], P = 0.075), whereas no such evidence was present for cumulative aerosolized pentamidine (no previous ART, 0.86 [95% CI, 0.63 to 1.2], P = 0.36; current ART, 0.11 [95% CI, 0.04 to 3.3], P = 0.20) and for dapsone-pyrimethamine (no previous ART, 0.83 [95% CI, 0.45 to 1.5], P = 0.55; current ART, 0.80 [95% CI, 0.38 to 1.7], P = 0.57).

A total of 2,447 persons died, with IRs of 10 (9 to 11) and 42 (40 to 44) per 1,000 PYFU in participants with current and no previous ART, respectively. The SHCS introduced detailed causes of death with ICD10 codes in 1999. One of the 1,016 patients who died since 1999 had miliary tuberculosis as the contributing cause of death; no other patients had TB as the primary or secondary cause of death. Bi- and multivariable models showed lower death rates associated with current co-trimoxazole use irrespective of ART (all P values were < 0.05) (Table 3). Associations after multivariable adjustment remained unchanged in an analysis that included current co-trimoxazole and cumulative co-trimoxazole exposure (all P values were < 0.05).

We found several strong associations between covariables and TB and all-cause mortality in the respective multivariable models (Tables 2 and 3). Risk of incident TB (Table 2) and all-cause mortality (Table 3) decreased as current CD4 increased irrespective of ART status; persons from regions other than Europe, North America, or Australia had higher risks of incident TB and lower risks of all-cause mortality with current and no previous ART, and IDU and older age were associated with higher risks of all-cause mortality with current and no previous ART.

### DISCUSSION

We assessed incident TB and all-cause mortality and studied associations with cumulative and current co-trimoxazole exposure among 13,431 SHCS participants prospectively followed for a 20-year-period. Cumulative co-trimoxazole exposure reduced the risk for incident TB among ART-naïve persons and to a lesser extent in ART-experienced persons, and current co-trimoxazole exposure reduced all-cause mortality after multivariable adjustment for CD4 cell count, region of origin other than Europe, North America, or Australia, IDU, and age of >40 years at baseline, irrespective of antiretroviral treatment.

It is difficult to compare our results with those from other cohorts because the association between co-trimoxazole prophylaxis and incident TB does not appear to have been previously investigated. Other studies estimated either the effect of ART on TB incidence (12) or the effectiveness of co-trimoxazole prophylaxis...
laxis on morbidity and mortality in HIV-infected ART-naive persons (1–3) or those taking ART (4). A recent large collaboration from Europe and the United States (12) found that TB incidence decreased after ART initiation, except in older persons and those with low CD4 cell counts. In the SHCS, we also observed a marked decrease of TB incidence by year among persons on ART (13).

Based on studies showing that co-trimoxazole reduces morbidity and mortality at ART-naive persons with suspected or diagnosed TB (1–3), HIV-TB-coinfected persons should receive co-trimoxazole prophylaxis. However, the mechanism through which co-trimoxazole reduces mortality in these patients is unclear, and until now, many assumed that co-trimoxazole would reduce deaths due to other HIV-related opportunistic infections, invasive bacterial disease, or malaria. We found a protective effect of co-trimoxazole on all-cause mortality and incident TB among SHCS participants, suggesting that co-trimoxazole may have direct antituberculosis effects. Such speculation is supported by several in vitro studies suggesting potential activity of co-trimoxazole against M. tuberculosis (5–9) and one case report of improvement of a TB patient with co-trimoxazole treatment (5). Of note, the addition of co-trimoxazole in combination with either isoniazid or rifampin prevented the emergence of drug resistance in vitro (9).

A recently published trial with HIV-infected children receiving long-term ART in sub-Saharan Africa comparing continuing versus stopping co-trimoxazole prophylaxis found that continued co-trimoxazole prophylaxis was beneficial, with fewer hospitalizations and diagnostically confirmed malaria cases (14). Interestingly, fewer cases of other infections and also fewer cases of TB occurred in the continued co-trimoxazole group (5/376 and 15/382 TB events in the continued versus stopped co-trimoxazole group, respectively; hazard ratio, 0.33 [95% CI, 0.12 to 0.91]; P = 0.032). While most diagnoses were presumptive, reflecting challenges in pediatric TB diagnosis, and bacterial coinfections are relatively common, this adds epidemiological evidence of a protective effect of co-trimoxazole on the incidence of TB among HIV-positive persons on ART. The effect of co-trimoxazole prophylaxis was also investigated among African adults starting ART in the DART cohort (4). Current co-trimoxazole prophylaxis reduced overall mortality, but only for the first 72 weeks on ART. There were no overall or long-term benefits from co-trimoxazole for pulmonary or extrapulmonary TB (unpublished data). However, this setting is very different from that in our study: 25% of DART participants reported previous TB at enrollment, very few participants received isoniazid prophylaxis, and TB incidence was around 10-fold higher than in those on ART in the SHCS. Similar results were obtained in another trial investigating the effect of early chemoprophylaxis with co-trimoxazole on morbidity and mortality in treatment-naive HIV-infected persons in Cote d’Ivoire (15), where 11% of participants reported a history of TB at trial inclusion. Seventeen of 271 (6%) of the co-trimoxazole group and 19/270 (7%) of the placebo group were hospitalized or died from TB (P = 0.6, log rank test), but no information was available as to whether these hospitalizations/deaths were incident cases or not. Lastly, a recent study (16) found no evidence that

TABLE 2 Risk of incident tuberculosis in 13,431 cohort participants based on bivariable and multivariable Poisson regression analyses

<table>
<thead>
<tr>
<th>Covariable</th>
<th>No previous ART (132 events during 41,891 PYFU)</th>
<th>Current ART (50 events during 65,657 PYFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative co-trimoxazole use/yr</td>
<td>IRR bivariable models (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>0.71 (0.56–0.90)</td>
<td>0.005</td>
<td>0.70 (0.55–0.89)</td>
</tr>
<tr>
<td>Square root CD4 cells/μL</td>
<td>0.90 (0.88–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region of origin</td>
<td>3.4 (2.3–5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IDU</td>
<td>1.1 (0.77–1.6)</td>
<td>0.625</td>
</tr>
<tr>
<td>Age of &gt;40 yr</td>
<td>0.71 (0.46–1.1)</td>
<td>0.117</td>
</tr>
</tbody>
</table>

a Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ART, antiretroviral treatment; IDU, intravenous drug use.
b The IRR bivariable models were adjusted for time-updated CD4 cell count.
c Region of origin other than Europe, North America, or Australia.
d Age at baseline (1 January 1992 or at registration in the Swiss HIV Cohort Study, whichever is later).
There is a trend of a protective effect even among patients on ART-naive persons. Additionally, the use of co-trimoxazole prophylaxis may reduce the risk of TB in ART-naive persons. Our findings may, however, be more relevant in resource-limited settings. Further studies, especially in low-income countries with a high burden of TB and HIV, are needed to confirm our findings.

**ACKNOWLEDGMENTS**

We thank all involved physicians, study nurses, and most importantly the participants of the SHCS.


B.H. had full access to all data of the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. B.H., R.W., and B.L. designed the study. B.H. wrote the first draft, and B.H., S.W., R.W., and B.L. wrote the final version of the manuscript. B.L. analyzed the data. All investigators contributed to data collection and interpretation of the data, reviewed drafts of the manuscript, and approved the final manuscript.

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**TABLE 3 All-cause mortality in 13,431 cohort participants based on bivariable and multivariable Poisson regression analyses**

<table>
<thead>
<tr>
<th>Covariable</th>
<th>No previous ART (1,769 events during 42,229 PYFU)</th>
<th>Current ART (678 events during 66,419 PYFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR bivariable models (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Current co-trimoxazole use</td>
<td>0.05 (0.04–0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Square root CD4 cells/μl</td>
<td>0.79 (0.79–0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region of origin*</td>
<td>0.61 (0.50–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IDU</td>
<td>1.1 (0.97–1.2)</td>
<td>0.154</td>
</tr>
<tr>
<td>Age of &gt;40 yr†</td>
<td>1.4 (1.2–1.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a Abbreviations: CI, confidence intervals; IRR, incidence rate ratio; ART, antiretroviral treatment; IDU, intravenous drug use.
b The IRR bivariable models were adjusted for time-updated CD4 cell count.
c Region of origin other than Europe, North America, or Australia.
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REFERENCES


