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RESEARCH ARTICLE

Cotrimoxazole prophylaxis is associated with reduced risk of incident tuberculosis in participants in the Swiss HIV Cohort Study

Barbara Hasse[1#]; A. Sarah Walker [2]; Jan Fehr [1]; Hansjakob Furrer [3]; Matthias Hoffmann [4]; Manuel Battegay [5]; Alexandra Calmy [6]; Jacques Fellay [7], Caroline Di Benedetto [8]; Rainer Weber [1*]; Bruno Ledergerber [1*], and the Swiss HIV Cohort Study [9]

[1] *Division of Infectious Diseases and Hospital Epidemiology, University Hospital and University of Zurich, Zurich, Switzerland;*

[2] *MRC Clinical Trials Unit, London, United Kingdom*

[3] *Division of Infectious Diseases, Bern University Hospital and University of Bern, Berne, Switzerland;*

[4] *Division of Infectious Diseases, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland;*

[5] *Division of Infectious Diseases, University Hospital Basel, Basel, Switzerland;*

[6] *Division of Infectious Diseases, University Hospital Geneva, Geneva, Switzerland;*

[7] *Service of Infectious Diseases, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;*

[8] *Division of Infectious Diseases, Regional Hospital, Lugano, Switzerland;*

[9] *see acknowledgments*

* contributed equally

ABSTRACT

Cotrimoxazole reduces mortality in HIV-infected adults with tuberculosis (TB), and *in vitro* data suggest potential anti-mycobacterial activity of cotrimoxazole. We aimed to evaluate whether prophylaxis with cotrimoxazole is associated with a decreased risk of incident TB in SHCS participants. We determined the incidence of TB per 1000 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, injecting drug use, and age. 13,431 cohort participants contributed 107,549 person-years follow-up; 182 patients had incident TB; 132 (73%) before and 50 (27%) after ART initiation. The multivariable incidence rate ratios for cumulative cotrimoxazole exposure per year for persons with no previous and current ART were 0.70 (95% CI 0.55-0.89) and 0.87 (0.74-1.0) respectively. Cotrimoxazole may prevent the development of TB among HIV-positive persons, especially among those with no previous ART.

Key words: Cotrimoxazole prophylaxis**,** HIV-infection**,** tuberculosis

INTRODUCTION

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 co-infected patients than in the HIV mono-infected population. Cotrimoxazole is a combination of trimethoprim and sulfamethoxazole that is widely used to treat bacterial infections including lower respiratory, gastrointestinal, urinary tract infections and *P. jirovecii* pneumonia (PCP). A randomized controlled trial showed that cotrimoxazole prophylaxis significantly reduced mortality in HIV-infected adults receiving TB treatment in Côte d'Ivoire [1]. Other studies confirmed the effect of cotrimoxazole prophy-

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[Figure 1: Cumulative previous cotrimoxazole exposure with bars classifying PYFU by latest CD4 class among participants with no previous ART (A) and those on current ART (B).]

laxis on morbidity and mortality for combination antiretroviral treatment (ART)-naïve HIV-TB co-infected [2,3], and ART-experienced [4] persons. Furthermore, cotrimoxazole is strongly recommended as prophylaxis against PCP pneumonia in HIV-infected persons with CD4 cells counts below 200 cells/µL.

Recent *in vitro* studies suggested a potential antimicrobial effect of cotrimoxazole on *Mycobacterium tuberculosis* [5-9], whereby sulfamethoxazole seems to be the active compound in the fixed-dose combination [6]. Moreover, sulfamethoxazole together with rifampicin appears to have a synergistic effect against *M. tuberculosis* [8]. Whether

cotrimoxazole prophylaxis may prevent TB is uncertain. We therefore studied cumulative cotrimoxazole 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 cotrimoxazole, in order to confirm adequate adjustment for various confounders.

METHODS

HIV-infected adults, aged ≥16 years, who attend outpatient clinics of seven cohort centres, affiliated regional hospitals, or private practitioners collaborating with the centres, are continuously enrolled in the prospective observational SHCS. The enrolment of participants is independent of social status. Healthcare in Switzerland is universal with a mandatory health insurance (including for immigrants and marginalized groups). Demographic, psychosocial, clinical, laboratory (immunologic and virologic parameters), and treatment information are collected at enrolment and thereafter completed every six 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 are documented since 1988, and data on immune reconstitution inflammatory syndrome (including TB IRIS) are 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-positives (defined as a skin induration of ≥ 5 mm) according to guidelines. We decided to exclude patients with previous TB treatment or

also latent TB treatment during follow-up, since latent TB treatment could be a major source of bias (if hypothesis correct, that the cumulative cotrimoxazole effect is based on treating latent TB infection).

Controlled trials identified the effectiveness of cotrimoxazole as secondary and primary PCP prophylaxis in 1992. Therefore, SHCS participants with at least two cohort visits between 1 January 1992 and 31

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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 January 1, 1992, to the earliest of the first 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 on no previous ART or current ART, because of differences in who would have been prescribed cotrimoxazole 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 cotrimoxazole 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 but bivariable associations adjusted for latest, time-updated square root CD4 cell count. Multivariable Poisson models for incident TB were adjusted for time-

updated cumulative cotrimoxazole use, sex, region of origin, injecting drug use (IDU), and age >40 years. Cumulative cotrimoxazole was the primary exposure to avoid problems with reverse causality in patients prescribed cotrimoxazole for presumptive respiratory infection which was subsequently diagnosed as TB. We also considered ramp-functions in which the protective effect of cotrimoxazole increased over specified periods of time (1, 3, 6, 9, 12, 18 and 24 months) and then remained stable. Bivariable estimates of the protective effect for ramps up to 24 months did not indicate the presence of an inflection point (data not shown) which led us use cumulative cotrimoxazole use in the models. Interactions between cumulative cotrimoxazole exposure and CD4 categories were analyzed with a likelihood ratio test. Participants who stopped cotrimoxazole were analyzed based on the cumulative cotrimoxazole received. As an alternative, ART and its interaction with cotrimoxazole use were assessed in the multivariable model for TB incidence. In a sensitivity analysis we compared the TB incidence of patients who received cotrimoxazole with patients who received aerosolized pentamidine or dapsone assuming that they have similarly advanced HIV disease and that they can serve as a control group for the cotrimoxazole group. We calculated IRR for incident TB for cumulative pentamidine and cumulative dapsone use versus cumulative cotrimoxazole use.

Cumulative cotrimoxazole exposure, as a surrogate for the time being heavily immunosuppressed, is a confounding variable for death. Therefore we decided 1) to include current cotrimoxazole use, sex, region of origin, injecting drug use and age >40 years in multivariable Poisson models for all-cause mortality and 2) to fit a second Poisson model for all-cause mortality with adjustment for current and cumulative cotrimoxazole exposure.

We used Stata (Version 12, StataCorp, College Station, Texas) for analyses.

RESULTS

From 1992-2012, 14,589 SHCS participants contributed data. 1158 (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]: 30-42); 3,815 (28%) individuals were women; 2,357 (18%) were from a region other than Europe, North America, or Australia; 2,697 (20%) had prior clinical AIDS. Nadir CD4 cell count was 273 (IQR 129-448) 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 [IQR 310-637] versus 271 [131-440] cells/µL in those without). Median CD4 cell counts for Caucasians and for persons from other regions with a positive TST were 544 [343-695] and 336 cells/µL [249-489] cells/ µL, respectively. 95 (2%) patients who received cotrimoxazole vs. 270 (5%) who never received cotrimoxazole had positive TST results; bivariate logistic regression confirmed that this difference was fully explained by the CD4 levels at the time of TST of 207 cells/µL [101-349] versus 437/µL [300-614] respectively (data not shown).

5265 (39%) persons took cotrimoxazole at some time during the study period for median 1.3 [IQR 0.50-2.8] years. Among participants with no previous ART cotrimoxazole exposure was 41,891 person years of follow up (PYFU), and among those with current ART cotrimoxazole exposure was 65,657 PYFU (figure 1). 1,406/ 13,431 (10%) 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 (IR) for TB among persons with *current* and *no previous* ART were 0.76 (95% confidence intervals, CI [0.58-1.00]), and 3.2 [2.7-3.7] per 1000 PYFU respectively.

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

In sensitivity analyses including exposure to pentamidine and/or dapsone as well as cotrimoxazole, there was an association of reduced TB incidence with cumulative cotrimoxazole use (no previous ART: IRR 0.70 [0.55-0.87], P=0.003; current

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[Table 1: Baseline characteristics of 13,431 HIV-infected participants stratified by co-trimoxazole use]

ART: IRR 0.86 [0.73-1.0], P=0.075), whereas no such evidence was present for cumulative aerosolized pentamidine (no previous ART: 0.86 [0.63-1.2], P=0.36; current ART: 0.11 [0.04-3.3], P=0.20) and for dapsone/ pyrimethamine (no previous ART: 0.83 [0.45-1.5], P=0.55; current ART: 0.80 [0.38-1.7], P=57).

2,447 persons died, with IR 10 [9-11] and 42 [40-44] per 1000 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 1016 patients who died since 1999 had miliary tuberculosis as contributing cause of death; no other patients had TB as primary or secondary cause of death. Bi- and multivariable models showed lower death rates associated with current cotrimoxazole use irrespective of ART (all P<0.05) (table 2). Associations after multivariable adjustment remained unchanged in an analysis including current cotrimoxazole and cumulative cotrimoxazole exposure (all P<0.05).

We found several strong associations between co-variables and TB and all-cause mortality in the respective multivariable models (table 2). Risk of incident TB and all-cause mortality 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* cotrimoxazole exposure among 13,431 SHCS participants prospectively followed for a 20-year-period. *Cumulative* cotrimoxazole exposure reduced the risk for incident TB among ART naïve and to a lesser extent in ART-experienced persons, and *current* cotrimoxazole 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 >40 years at baseline, irrespective of antiretroviral treatment or not.

It is difficult to compare our results with other cohorts because the association between cotrimoxazole 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 cotrimoxazole prophylaxis on morbidity and mortality in HIV-infected ART-naïve 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 and among persons on ART [13].

Based on studies showing that cotrimoxazole reduces morbidity and mortality among ART-naïve persons with suspected or diagnosed TB [1-3], HIV-TB co-infected persons should receive cotrimoxazole prophylaxis. However, the mechanism through which cotrimoxazole reduces mortality in these patients is unclear, and until now, many assumed that cotrimoxazole would reduce deaths due to other HIV-related opportunistic infections, invasive bacterial disease, or malaria. We found a protective effect of cotrimoxazole on all-cause mortality and incident TB among SHCS participants,

suggesting that cotrimoxazole may have direct anti-tuberculosis effects. Such speculation is supported by several *in vitro* studies suggesting potential activity of cotrimoxazole against *M. tuberculosis* [5-9], and one case report of improvement of a TB patient with cotrimoxazole treatment [5]. Of note, the addition of Cotrimoxaozle in combination with either isoniazid or rifampin prevented the emergence of drug resistance *in vitro* [9].

A recently published trial in HIV-infected children receiving long-term ART in sub-Saharan Africa comparing continuing vs stopping cotrimoxazole prophylaxis found that continued cotrimoxazole 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 cotrimoxazole group (5/376 and 15/382 TB events in the continued versus stopped cotrimoxazole group, respectively; hazard ratio 0.33 (95%CI 0.12-0.91), P=0.032). Whilst most diagnoses were presumptive, reflecting challenges in pediatric TB diagnosis, and bacterial co-infections are relatively common, this adds epidemiological evidence of a protective effect of cotrimoxazole on the incidence of TB among HIV-positive persons on ART. The effect of cotrimoxazole prophylaxis was also investigated among African adults starting ART in the DART cohort [4]. Current cotrimoxazole prophylaxis reduced overall mortality, but only for the first 72 weeks on ART. There were no overall or long-term benefits from cotrimoxazole on pulmonary or extrapulmonary TB (data unpublished). However, this setting is very different from our study: 25% of DART participants reported previous TB at enrolment, 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 cotrimoxazole on morbidity and mortality in treatment naïve HIV-infected persons in

Cote d'Ivoire[15], where 11% of participants reported a history of TB at trial inclusion. 17/271 (6%) of the cotrimoxazole group and 19/270 (7%) of the placebo group were hospitalized or died from TB (log-rank test P=0.6), 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]

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[Table 3: All-cause mortality in 13,431 cohort participants based on bivariable and multivariable Poisson regression analyses]

cotrimoxazole reduced TB incidence in another high-incidence setting (South Africa). Whilst this study is directly comparable with ours, since it excluded prevalent cases and considered only laboratory confirmed diagnosis, it only investigated the impact of current cotrimoxazole, which both we and they suggested could be associated with residual confounding.

Strengths of our study include its statistical power because of the large number of patient-years, and the prospective collection of incident TB and death. Additionally, we controlled for several cofactors known to be associated with incident TB or death. Several limitations should also be noted. First, Switzerland is a low incidence country for TB and TB incidence declined during the study period, which may limit the generalizability of our findings. This is one reason that 4% of participants had a positive

TST test result but received no isoniazid prophylaxis (and hence were included in the analysis), because this was not routinely provided when lifetime risk of incident TB was categorized as very low (Swiss origin, high CD4 cells, potentially BCG vaccination in the past). We were not able to include TST test results in our multivariable model, because TST results were only reliably done in 8989/13,431 (67%) of our participants and time-updated TST results are not available in the SHCS. Second, cotrimoxazole is routinely used among SHCS participants with CD4 cells below 200 cells/ µl, and therefore the effect of cotrimoxazole and not being on ART is often confounded, which is why we conducted stratified analyses. Third, adherence to cotrimoxazole is not routinely assessed in the SHCS. Fourth, the SHCS does not collect information on homelessness and information on poverty, which are important social determinants of TB. However, only 0.5% of our patients were institutionalized in 2012, and the majority of IDUs in Switzerland, if still substance dependent, participate in opiate substitution programs and receive methadone or even heroin in healthcare settings. Fifth, microbiological isolates were not stored, so we could not perform susceptibility testing for cotrimoxazole among culture-positive TB samples among SHCS participants.

In conclusion, we found epidemiological evidence of a protective effect of cotrimoxazole prophylaxis on the incidence of manifest TB among SHCS participants. Cotrimoxazole prophylaxis may hence reduce the risk of TB in ART naïve persons. Additionally, there is a trend of a protective effect even among patients on ART. The clinical utility of our observation is uncertain for the developed world. In 2013 the liberal use of ART is promoted and clearly the higher priority than starting cotrimoxazole to reduce the risk of TB. It 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.

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AUTHORS' CONTRIBUTIONS STATEMENT

Barbara Hasse had full access to all the data of the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Barbara Hasse, Sarah Walker, Rainer Weber and Bruno Ledergerber designed the study; Barbara Hasse wrote the first draft; and Barbara Hasse, Sarah Walker, Rainer Weber and Bruno Ledergerber wrote the final version of the manuscript. Bruno Ledergerber analysed the data. All investigators contributed to data collection and interpretation of the data, reviewed drafts of the manuscript, and approved the final manuscript.

FINANCIAL DISCLOSURE

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CONFLICTS OF INTEREST STATEMENT

BH has received travel grants from Astra Zeneca, Essex Chemicals, Gilead Sciences, Janssen-Cilag and Wyeth. **ASW** has received grants or honoraria from Abbott, Gilead Sciences, GlaxoSmithKline/Viiv Healthcare, and Tibotec. **JF** has received grants, honoraria or travel grants from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Sharp & Dome. **HF** has participated in advisory boards of ViiVHealthcare, Bristol-Myers Squibb, Gilead, Merck Sharp & Dome, Boehringer-Ingelheim, Janssen Cilag. HF's institution has received unrestricted educational grants from Abbott, ViiV Healthcare, BMS, Roche, Gilead, Merck Sharp & Dome, Boehringer-Ingelheim, Janssen-Cilag. **MH** has received travel grants and speakers honoraria from Gilead, Roche, and Celestis (Quiagen). **MB** has received travel grants, speaker's honoraria and/or research grants from Abbott, Boehringer Ingelheim, Gilead Sciences, Hoffmann La Roche, Merck Sharp&Dome, Tibotec and ViiV. **AC** reports no conflicts of interest. **JFe** reports no conflicts of interest. **CdB reports** no conflicts of interest. **RW** has received travel grants or speakers honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dome, Pfizer, LaRoche, TRB Chemedica and Tibotec; and was a member of an endpoint adjudication panel of phase II and III antiretroviral treatment studies of Tibotec. **BL** has received travel grants, grants or honoraria from Abbott, Aventis, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Roche and Tibotec

REFERENCES

1. **Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maruice Ch, Djomand G, Ackah A, Domoua K, Kadio A, Yapi A, Combe P, Tossou, Roels TH, Lackritz EM, De Cock KM, Coluibaly IM, Greenberg AE**. 1999. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet. **353**:1469-1475.

2. **Nunn AJ, Mwaba P, Chintu C, Mwinga A, Darbyshire JH, Zumla Alimuddin.** 2008. Role of co-trimoxazole prophylaxis in reducing mortality in HIV infected adults being treated for tuberculosis: randomised clinical trial. BMJ. **337**:a257.

3. **Grimwade K, Sturm AW, Nunn AJ, Mbtha D, Zungu D, Gilks CF**. 2005. Effectiveness of cotrimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. AIDS.**19**:163-168.

4. **Walker AS, Ford D, Gilks CF, Munderi P, Ssali F, Reid A, Katabira E, Grosskurth H, Mugyenyi P, Hakim J, DArbyshire JH, Gibb DM, Babiker AG**. 2010. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. Lancet. **375**:1278-1286.

5. **Forgacs P, Wengenack NL, Hall L, Zimmermann SK, Silverman ML, Roberts GD.** 2009. Tuberculosis and Trimethoprim-Sulfamethoxazole. Antimicrob Agents Chemother. **53**:4789-4793.

6. **Ong W, Sievers A, Leslie DE**. 2010. Mycobacterium tuberculosis and sulfamethoxazole susceptibility. Antimicrob Agents Chemother. **54**:2748; author reply 2748-2749.

7. **Huang TS, Kunin CM, Yan BS, Yao-Shen C, Shin-Jung Lee S, Syu W**. 2012. Susceptibility of Mycobacterium tuberculosis to sulfamethoxazole, trimethoprim and their combination over a 12 year period in Taiwan. J Antimicrob Chemother. **67**:633-637.

8. **Macingwana L, Baker B, Ngwane AH, Harper C, Cotton MF, Hesseling A, Diacon AH, van Helden P, Wiid I**. 2012. Sulfamethoxazole enhances the antimycobacterial activity of rifampicin. J Antimicrob Chemother. **67**:2908-11.

9. **Vilcheze C, Jacobs WR, Jr**. 2012. The combination of sulfamethoxazole, trimethoprim, and isoniazid or rifampin is bactericidal and prevents the emergence of drug resistance in Mycobacterium tuberculosis. Antimicrob Agents Chemother. **56**:5142-5148.

10. **Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Gunthard HF, Telenti A, Furrer H, Yerly, S, Francioli P**. 2010. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol. **39**:1179-1189.

11. **Fenner L, Gagneux S, Helbling P, Battegay M, Rieder HL, Pfyffer GE, Zwahlen M, Furrer H, Siegrist HH, Fehr J, Dolina M, Calmy A, Stucki D, Jaton K, Janssens JP, Stalder JM, Bodmer T, Ninet B, Böttger EC, Egger M; Swiss HIV Cohort Study Group; Molecular Epidemiology of Tuberculosis Study group.** 2012**.** Mycobacterium tuberculosis transmission in a country with

low tuberculosis incidence: role of immigration and HIV infection. J Clin Microbiol. 50:388-395.

12. **HIV-Causal Collaboration**. 2012. Impact of antiretroviral therapy on tuberculosis incidence among HIV-positive patients in high-income countries. Clin Infect Dis. **54**:1364-1372.

13. Elzi L, Schlegel M, Weber R, Hirschel B, Cavassini M, Schmid P, Bernasconi E, Rickenbach M, Furrer H. 2007. Reducing tuberculosis incidence by tuberculin skin testing, preventive treatment, and antiretroviral therapy in an area of low tuberculosis transmission. Clin Infect Dis. **44**:94-102.

14. **Bwakura-Dangarembizi M, Kendall L, Bakeera-Kitaka S, Nahirya-Ntege P, Keishanyu R, Nathoo K, Spyer MJ, Kekitiinwa A, Lutaakome J, Tawanda Mhute CB, Kasirye P, Munderi P, Musiime V, Gibb DM, Walker AS, and Prendergast, AJ for the Antiretroviral Research for Watoto (ARROW) Trial Team**. 2014. A randomized trial of prolonged co-trimoxazole in HIV-infected children in Africa. N Engl J Med.**370**:41-53.

15. Anglaret X, Chene G, Attia A, Toure S, Lafont S, Combe P, Manlan K, D'Dri-Yoman T, Salamon R and the Cotrimo-CI Study Group. 1999. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Lancet. **353**(9163):1463-1468.

16. Hoffmann CJ, Chaisson RE, Martinson NA. 2014. Cotrimoxazole Prophylaxis and Tuberculosis Risk among People Living with HIV. PLoS One. **9**:e83750.

FIGURE 1

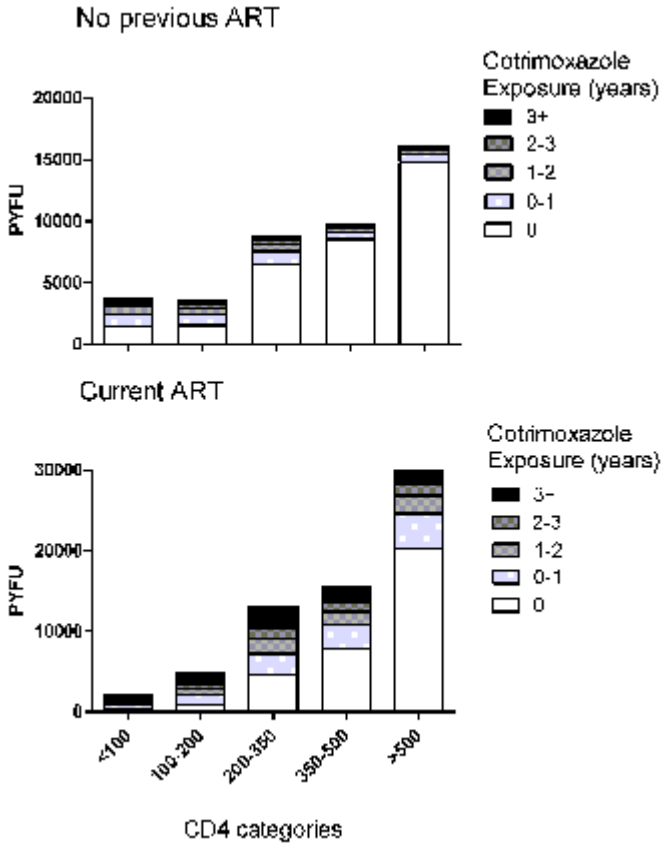

FIGURE LEGEND

Cumulative previous cotrimoxazole exposure with bars classifying PYFU by latest CD4 class among those with no previous (Panel A) and current ART (Panel B)

Abbreviations: PYFU, person years of follow up, ART, antiretroviral therapy

Table 1 Baseline characteristics of 13,431 HIV-infected participants stratified by cotrimoxazole use

	Participants	Never cotrimoxazole	Ever cotrimoxazole	P-value
Participants, n (%)	13,431 (100)	8,166 (61)	5,265 (39)	
Year of baseline visit, median (IQR)	1998 (1993-2005)	2000 (1995-2006)	1996 (1992-2001)	<0.001
Female, n (%)	3,815 (100)	2,293 (60)	1,522 (40)	0.299
Age, median years (IQR)	35 (30-42)	34 (29-41)	35 (30-43)	<0.001
Nadir CD4, cells/ µl, median (IQR)	273 (129-448)	355 (228-525)	150 (61-274)	<0.001
Nadir CD4 <200 cells/ µL, n (%)	4,602 (100)	1,510 (33)	3,092 (67)	<0.001
Riskgroups and respective percentage with nadir CD4 <200/ cells µL				
Heterosexuals, n (%)	4,521 (100)	2,292 (60)	1,829 (40)	<0.001
Nadir CD4 <200 cells/ µL, n (%)	1,697 (100)	510 (30)	1187 (70)	<0.001
IDU, n (%)	3,108 (100)	1,591 (51)	1,517 (49)	
Nadir CD4 <200 cells/ µL, n (%)	1,084 (100)	349 (32)	735 (68)	<0.001
MSM, n (%)	5,271 (100)	3,583 (68)	1,688 (32)	
Nadir CD4 <200 cells/ µL, n (%)	1,618 (100)	597 (37)	1021 (63)	<0.001
Other, n (%)	531 (100)	300 (57)	231 (44)	

Nadir CD4 <200 cells/ µL, n (%)	203 (100)	54 (27)	149 (73)	<0.001
Ethnicity				
Caucasian[1], n (%)	11,074 (100)	6,679 (60)	4,395 (40)	0.012
Other, n (%)	2,357 (100)	1,487 (64)	870 (37)	
CDC Stage				
A, n (%)	8,497 (100)	6,111 (72)	2,386 (29)	<0.001
B, n (%)	2,237 (100)	1,131 (51)	1,106 (49)	
C, n (%)	2,697 (100)	924 (34)	1,773 (66)	
Nadir CD4, cells/ µl, median (IQR)	273 (129-448)	355 (228-525)	150 (61-274)	<0.001
TST at enrollment				
Test performed, n (%)	8,989 (100)	5,088 (62)	3901 (74)	<0.001
TST positive, n (%)	365 (100)	270 (5)	95 (2)	<0.001

[1] "Caucasian" denotes SHCS participants from north-western Europe, North America and Australia

Abbrevations: IDU, intravenous drug use; MSM, men who have sex with men; TST, tuberculin skin test

Table 2 Risk of incident tuberculosis (Panel A) and all-cause mortality (Panel B): bivariable and multivariable poisson regression analyses in 13,431 cohort participants

Panel A

	No previous ART				Current ART			
	132 events during 41,891 person-years of follow-up				50 events during 65,657 person-years of follow-up			
Covariables	**IRR bivariable models (95% CI)[3]**	**P-value**	**IRR multivariable models (95% CI)**	**P-value**	**IRR bivariable models (95% CI)[4]**	**P-value**	**IRR multivariable models (95% CI)**	**P-value**
Cumulative Cotrimoxazole use per year	0.71 (0.56-0.90)	0.005	0.70 (0.55-0.89)	0.004	0.85 (0.72-1.00)	0.05	0.87 (0.74-1.0)	0.088
Square root CD4 [cells/µl]	0.90 (0.88-0.92)	<0.001	0.88 (0.86-0.90)	<0.001	0.85 (0.82-0.89)	<0.001	0.84 (0.80-0.87)	<0.001
Region of origin[1]	3.4 (2.3-5.0)	<0.001	3.8 (2.5-5.7)	<0.001	5.5 (3.1-9.6)	<0.001	4.2 (2.3-7.6)	<0.001
IDU	1.1 (0.77-1.6)	0.625	1.4 (0.95-2.1)	0.092	0.31 (0.12-0.78)	0.013	0.46 (0.17-1.2)	0.113
Age > 40 years[2]	0.71 (0.46-1.1)	0.117	0.85 (0.54-1.3)	0.480	0.54 (0.28-1.1)	0.074	0.61 (0.31-1.2)	0.155

Panel B

	No previous ART				Current ART			
	based on 1769 events and 42,229 person years of follow-up				based on 678 events and 66,419 person years of follow- up			
Covariables	**IRR bivariable models (95% CI)[3]**	***P*-value**	**IRR multivariable models (95% CI)**	***P*-value**	**IRR bivariable models (95% CI)[4]**	***P*-value**	**IRR multivariable models (95% CI)**	***P*-value**

Current cotrimoxazole use	0.05 (0.04-0.07)	<0.001	0.05 (0.04-0.07)	<0.001	0.18 (0.13-0.24)	<0.001	0.18 (0.13-0.23)	<0.001
Square root CD4 [cells/µl]	0.79 (0.79-0.80)	<0.001	0.78 (0.77-0.78)	<0.001	0.87 (0.86-0.88)	<0.001	0.84 (0.83-0.85)	<0.001
Region of origin[1]	0.61 (0.50-0.76)	<0.001	0.65 (0.52-0.80)	<0.001	0.35 (0.26-0.48)	<0.001	0.48 (0.35-0.66)	0.001
IDU	1.1 (0.97-1.2)	0.154	1.1 (1.0-1.3)	0.013	1.9 (1.6-2.2)	<0.001	2.1 (1.8-2.5)	<0.001
Age >40 years[2]	1.4 (1.2-1.5)	<0.001	1.6 (1.4-1.7)	<0.001	1.6 (1.4-1.9)	<0.001	2.0 (1.7-2.3)	<0.001

[1]Region of origin other than Europe, North America, or Australia

[2]Age at baseline (1. January 1992 or at registration in the Swiss HIV Cohort Study whichever is the later)

[3]The IRR bivariable models were adjusted for time-updated CD4 cell count**.**

Abbreviations: CI, confidence intervals; IRR, incidence rate ratio; ART, antiretroviral treatment. IDU, intravenous drug use