

Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations

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Objective: To evaluate the proposed WHO/UNAIDS criteria for initiating co-trimoxazole prophylaxis in adult HIV-infected patients in Africa [WHO clinical stages 2–4 or CD4 count $< 500 \times 10^6/l$ or total lymphocyte count (TLC) equivalent].

Design: Observational cohort study of 5-year follow-up.

Setting: Adult HIV clinics, University of Cape Town, South Africa.

Methods: Effect of prophylactic low dose co-trimoxazole (480 mg per day or 960 mg three times per week) on survival and morbidity was assessed in patients stratified by WHO clinical stage, CD4 T-lymphocyte count or TLC. Patients receiving antiretroviral therapy were excluded.

Results: Co-trimoxazole reduced mortality [adjusted hazard ratio (AHR), 0.56; 95% confidence interval (CI), 0.33–0.85; $P > 0.001$] and the incidence of severe HIV-related illnesses (AHR, 0.52; 95% CI, 0.38–0.68; $P < 0.001$) in patients with evidence of advanced immune suppression on clinical (WHO stages 3 and 4) or laboratory assessment (TLC $< 1250 \times 10^6/l$ or CD4 count $< 200 \times 10^6/l$). No significant evidence of efficacy was found in patients with WHO stage 2 or CD4 count $200–500 \times 10^6/l$ /TLC $1250–2000 \times 10^6/l$. If we had applied the WHO/UNAIDS recommendations 88.3% of our patients would have received co-trimoxazole prophylaxis at their initial clinic visit.

Conclusion: Co-trimoxazole in HIV-infected adults from an area in which *Pneumocystis carinii* pneumonia is uncommon demonstrated a survival benefit consistent with previous randomized trials. Further studies are needed to assess the optimal time of commencement of prophylaxis, as widespread co-trimoxazole use will lead to increasing antimicrobial resistance to other major pathogens in Africa.

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Introduction

Pneumocystis carinii pneumonia (PCP) is the most common AIDS-defining illness in the industrialized countries [1–5]. Co-trimoxazole prophylaxis was shown to effectively prevent PCP in patients with clinical evidence of immune suppression [4]. Subsequent studies showed that the risk of PCP was largely confined to patients with a CD4 T-lymphocyte count of $< 200 \times 10^6/l$ [1,5]. Primary prophylaxis against

PCP became the standard of care in industrialized countries for patients with clinical evidence of immune suppression or with a CD4 T-lymphocyte count of $< 200 \times 10^6/l$.

The spectrum of opportunistic infections is different in sub-Saharan Africa [6]. In South Africa the initial HIV epidemic largely affected men who have sex with men, a population with a high risk of PCP [7]. PCP was noted to be much less common with the advent of the

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burgeoning heterosexual epidemic approximately a decade ago [8,9]. Because of this different incidence of PCP the practice in our HIV clinics was to offer primary PCP prophylaxis with co-trimoxazole only to men who have sex with men. However, evidence subsequently accumulated that prophylactic co-trimoxazole prevented other opportunistic infections such as toxoplasmosis [10], bacterial pneumonia [11], salmonellosis [12] and isosporiasis [13,14] which are collectively common in sub-Saharan African HIV-infected patients [6]. We thus offered co-trimoxazole to all of our patients. Recently two randomized studies in Cote d'Ivoire showed the benefits of prophylactic co-trimoxazole in HIV-infected patients [15,16].

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have recently recommended the use of co-trimoxazole prophylaxis for HIV-infected adults in Africa with symptomatic HIV disease (stage 2, 3 or 4 of the WHO classification of HIV infection and disease), and for asymptomatic individuals who have a CD4 T-lymphocyte count of $\leq 500 \times 10^6/l$ or total lymphocyte count (TLC) equivalent [17]. Wide-scale use of prophylactic co-trimoxazole may increase the spread of antimicrobial resistance in communities to other pathogens, notably *Plasmodium falciparum*, non-typhoidal salmonellae and *Streptococcus pneumoniae*. It would therefore be prudent to confine the use of this intervention only to those patients who will benefit most from it. Thus, further research for the optimal timing of initiation of cotrimoxazole prophylaxis in relation to stage of HIV infection and CD4 T-lymphocyte/TLC counts is paramount to refine the WHO/UNAIDS proposal.

We have previously reported significant reductions in morbidity and mortality in tuberculosis patients from our cohort who were given low dose co-trimoxazole prophylaxis [18]. In the present study we explore indications for initiating prophylaxis which are applicable in a resource-poor setting – namely the WHO clinical staging system and the total lymphocyte count (TLC).

Methods

An observational cohort of patients attending the adult HIV clinics of the University of Cape Town was commenced in 1992 and data entered prospectively until 1996. A standard computerized format was used for recording demographic, clinical and laboratory information. Follow-up was repeated 3–6 monthly or more frequently if indicated clinically. At each attendance, patients were examined for HIV-related manifestations and staged using the WHO clinical HIV staging system [19]. CD4 T-lymphocyte counts and

TLC were measured approximately 6 monthly by flow cytometry. Diagnosis of major morbid events were only accepted if they were definitively diagnosed or on standard presumptive grounds. Vital status was ascertained using in-patient records, notification by the family or general practitioner, or by reviewing local death registries.

Initially co-trimoxazole was administered only to men who have sex with men (because they had a high PCP risk [1]). The main indication for primary prophylaxis with co-trimoxazole was a CD4 T-lymphocyte count $< 200 \times 10^6/l$ or AIDS. At the end of 1993 when we became aware that co-trimoxazole prevented many other infections which were collectively common in our African heterosexual patients we offered this to all patients. A low dose of co-trimoxazole for primary prophylaxis was used throughout the study period: initially 960 mg three days per week, and subsequently 480 mg daily.

Patients using antiretroviral therapy were excluded. The frequency of newly diagnosed severe HIV-related illnesses (defined as AIDS-defining illnesses, or WHO clinical stage 4, together with serious bacterial infections and pulmonary tuberculosis) and survival in patients given co-trimoxazole was compared with a group of patients attending the clinics during the same period who had not used co-trimoxazole. TLC $< 1250 \times 10^6/l$ was used as an inexpensive surrogate for a CD4 T-lymphocyte count of $< 200 \times 10^6/l$ [20]. The incidence density rate of severe HIV-related illnesses in the two groups was defined as the number of new episodes occurring in each group per 100 patient-months of follow-up. Overall survival time was estimated using Kaplan–Meier method. The generalized log-rank test was used to compare the survival curves of the two groups.

A multivariate Cox regression hazards model was fitted to adjust for the possible confounding effect of age, year of presentation, WHO clinical stage, history of AIDS-defining illness, CD4 T-lymphocyte count, and socioeconomic status. Co-trimoxazole was fitted as a time-dependent variable. Observed survival distributions met the assumptions of proportionality of the hazard model [21].

The study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, South Africa.

Results

A total of 609 patients presented to the clinics between 1 January 1992 and 31 December 1996. The propor-

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tion of patients who fulfilled the proposed WHO/UNAIDS recommendations for starting co-trimoxazole prophylaxis at their initial clinic visit was 88.3%. Forty-seven (7.7%) patients used antiretroviral therapy and were excluded. Of the remaining 562 patients in the cohort, 155 received co-trimoxazole and 407 did not and were included in the study as a comparison group. There were 114 (73.5%) patients in the treatment group and 131 (32%) patients in the comparison group who presented at or after the end of 1993. Patients in the comparison group accrued at or after year 1993 generally presented with a CD4 cell count $> 200 \times 10^6/l$ until death/censoring and were thus not offered therapy. However 18 patients did develop a CD4 cell count $< 200 \times 10^6/l$ but were not given co-trimoxazole due either to allergy or an oversight by the clinic staff. The median follow-up time was 14.2 and 13.7 months in the co-trimoxazole group and the comparison group respectively ($P = 0.83$) and loss to follow-up was not significantly different (15.5% and 13.3% in treatment and comparison groups respectively; $P = 0.5$). Table 1 shows the distribution of the demographic and clinical parameters of the treatment and comparison groups.

A total of 124 cases of newly diagnosed severe HIV-related illnesses occurred; 23 in the co-trimoxazole group versus 101 in the comparison group. The incidence density rate in the two groups was 0.71 versus 1.49 per 100 patient-months respectively ($P < 0.001$). After adjusting for confounding using a Cox multivariate model, co-trimoxazole was protective against the hazard of severe HIV-related illnesses [adjusted hazard ratio (AHR), 0.52; 95% confidence

interval (CI), 0.38–0.68; $P < 0.001$]. A subanalysis was carried out on the 69 opportunistic infections potentially preventable by co-trimoxazole which occurred during follow-up: PCP [8], cerebral toxoplasmosis [17], non-typhoidal salmonellosis [15], and serious bacterial infections (mostly pneumonia) [22]. Twelve of these infections occurred in the co-trimoxazole group and 57 in the comparison group (incidence density, 0.48 versus 1.14 per 100 patient-months respectively; $P < 0.001$; AHR, 0.42; 95% CI, 0.29–0.71; $P < 0.001$).

During follow-up 108 patients died: 21 (13.5%) patients in the co-trimoxazole group compared with 87 (21.4%) patients in the comparison group: the mortality rate was significantly lower in the co-trimoxazole group (0.97 versus 1.76 per 100 patient-months respectively; $P < 0.05$).

In a stratified survival analysis, the median survival was significantly greater in the co-trimoxazole group than in the comparison group across strata of CD4 T-lymphocyte counts $< 200 \times 10^6/l$ ($P = 0.02$), TLC $< 1250 \times 10^6/l$ ($P = 0.02$), WHO clinical stage 3 ($P = 0.02$) and 4 ($P = 0.005$) (Fig. 1). However, median survival did not differ in patients presenting with CD4 T-lymphocyte counts of $200\text{--}500 \times 10^6/l$ ($P = 0.72$), TLC of $1250\text{--}2000 \times 10^6/l$ ($P = 0.69$), or WHO stage 2 ($P = 0.62$).

In a univariate Cox proportional hazards regression model, co-trimoxazole prophylaxis was protective against hazard of death (AHR, 0.40; 95% CI, 0.22–0.75; $P < 0.001$). The protective effect of co-trimoxazole prophylaxis persisted after adjusting for confound-

Table 1. Demographic and clinical characteristics of the co-trimoxazole prophylaxis and comparison groups.

Characteristic	Treatment group (n = 155)	Comparison group (n = 407)	<i>P</i> ^a
Mean age [years (SD)]	32 (3.4)	33 (5.7)	0.82
Male [n (%)]	72 (47)	208 (51)	0.39
Ethnicity [n (%)]			0.17
Asian	1 (0.65)	6 (1.5)	
Black	90 (58.1)	194 (47.4)	
Mixed race	30 (19.3)	132 (32.4)	
White	34 (21.9)	75 (18.7)	
Low socio-economic status [n (%)]	113 (73.5)	320 (78.6)	0.15
Exposure group [n (%)]			< 0.001
Men who have sex with men	41 (26.5)	12 (2.9)	
Heterosexual	114 (73.5)	395 (97.1)	
WHO clinical stage			< 0.01
Stage 1	22 (14.2)	140 (34.4)	
Stage 2	23 (14.8)	78 (19.2)	
Stage 3	69 (44.5)	120 (29.5)	
Stage 4	41 (26.5)	69 (16.9)	
CD4T-lymphocyte count [n (%)]			0.030
$< 200 \times 10^6/l$	134 (86.5)	265 (65)	
$200\text{--}500 \times 10^6/l$	21 (13.5)	94 (23)	
$> 500 \times 10^6/l$	-	48 (12)	

^aChi-square test.

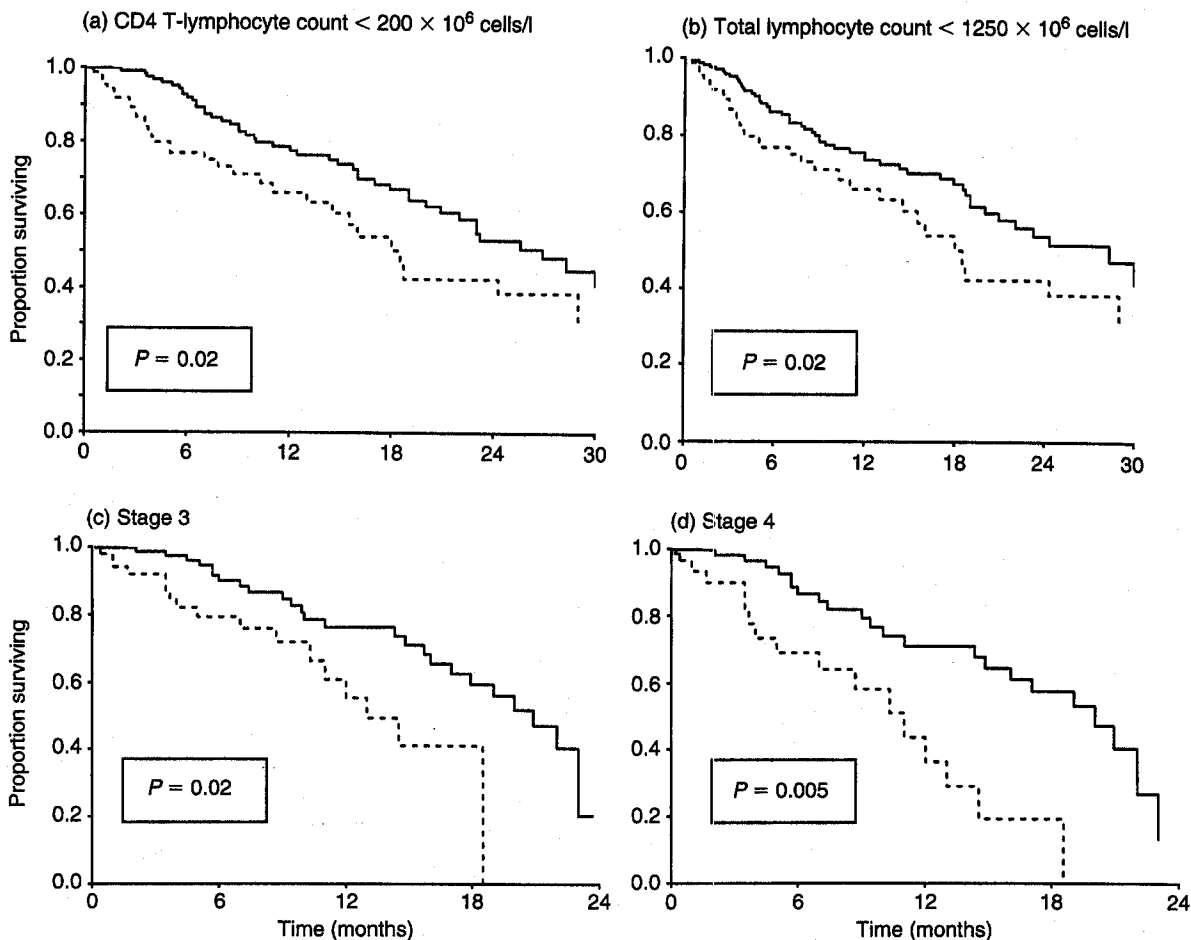


Fig. 1. Kaplan-Meier survival probabilities, according to CD4 T-lymphocyte count (a), total lymphocyte count (b), WHO Stage 3 (c) and WHO stage 4 (d) in patients with (solid line) and without (broken line) co-trimoxazole prophylaxis.

ing (AHR, 0.56; 95% CI, 0.33–0.85; $P < 0.001$). However, in stratified Cox proportional hazards regression analyses, the protective effect of co-trimoxazole was apparent only in subgroups of patients presenting with CD4 T-lymphocyte count $< 200 \times 10^6/l$, TLC $< 1250 \times 10^6/l$, WHO stage 3 or stage 4. No difference in the hazard of severe HIV-related illnesses or death was found in patients presenting with CD4 T-lymphocyte count $200\text{--}500 \times 10^6/l$, TLC $1250\text{--}2000 \times 10^6/l$ or WHO stage 2 (Table 2).

Because the spectrum of opportunistic infections in the White patients (nearly all of whom were men having sex with men) included in the above analyses has been shown to be different from that of other groups in South Africa [7,8] and because co-trimoxazole prophylaxis was used routinely in these patients, a subanalysis excluding White patients was conducted. The findings noted above were similar in this subgroup with significantly improved survival and reduced risk of severe HIV-related illnesses only in patients with CD4 T-lymphocyte count $< 200 \times 10^6/l$, TLC $< 1250 \times$

$10^6/l$ and WHO clinical stage 3 and 4 (Table 2). There was no significant difference in hazard of death or opportunistic infection when year of presentation was controlled for in the different models.

Discussion

This study has shown significant reductions in mortality and morbidity with low dose prophylactic co-trimoxazole in HIV-infected patients in sub-Saharan Africa where PCP is uncommon. These results are consistent with previous randomized studies carried out in different settings [2,4,15,16]. This study suggests that the beneficial effect of prophylactic co-trimoxazole in HIV-infected patients is limited to patients with clinical or laboratory evidence of significant immune suppression. Absence of beneficial effect in patients with WHO clinical stage 2 or CD4 T-lymphocyte count $200\text{--}500 \times 10^6/l$, suggests that the WHO/UNAIDS

Table 2. The effect of co-trimoxazole on severe HIV-related illnesses and death. Multivariate Cox proportional hazards regression analyses.

Category	AHR of opportunistic infection (95% CI)	AHR of death (95%CI)
General cohort		
CD4 count $\leq 200 \times 10^6/l$	0.47 (0.28–0.78)	0.52 (0.37–0.89)
CD4 count 200–500 $\times 10^6/l$	0.73 (0.43–1.54)	0.68 (0.39–1.25)
Stage 2	0.69 (0.37–1.67)	0.67 (0.41–1.08)
Stage 3	0.54 (0.38–0.79)	0.50 (0.31–0.85)
Stage 4	0.49 (0.24–0.86)	0.47 (0.29–0.79)
Subanalysis (excluding White patients) ^a		
CD4 count $\leq 200 \times 10^6/l$	0.37 (0.24–0.72)	0.49 (0.29–0.79)
CD4 count 200–500 $\times 10^6/l$	0.91 (0.43–2.68)	0.84 (0.34–2.53)
Stage 2	0.89 (0.21–2.85)	0.85 (0.37–2.01)
Stage 3	0.51 (0.20–0.81)	0.49 (0.28–0.76)
Stage 4	0.34 (0.19–0.89)	0.36 (0.25–0.81)

^aThe spectrum of opportunistic infections and use of co-trimoxazole was different in the White patients (see text). AHR, Adjusted hazard ratio; CI, confidence interval.

proposed indications for starting prophylactic co-trimoxazole are too early in the course of HIV disease.

A recent randomized, double-blind, placebo-controlled study of patients with WHO clinical stage 2 or 3 from Cote d'Ivoire found a significant reduction in hospitalization but no reduction in mortality [15]. Other studies which included patients with more advanced HIV disease showed significantly improved survival [5,16]. The morbidity reduction noted in the Cote d'Ivoire study may not be applicable to other areas in sub-Saharan Africa. Firstly, their rate of co-trimoxazole resistance among salmonellae and *S. pneumoniae* is lower than most other countries in the region [15]. Secondly, malaria was significantly reduced by co-trimoxazole – areas without malaria or with *P. falciparum* malaria resistant to sulfadoxine-pyrimethamine [23] would not benefit.

Of concern, the application of the proposed WHO/UNAIDS guidelines for the use of co-trimoxazole prophylaxis in HIV-infected adults in Africa will result in widespread use of co-trimoxazole in sub-Saharan Africa where 10–40% of adults are HIV seropositive. This will inevitably result in increasing antimicrobial resistance which will particularly affect pathogens such as non-typhoidal salmonellae, pneumococci and *P. falciparum* (increasing levels of resistance to sulfadoxine-pyrimethamine, which is now used as first line therapy in many African countries, have been reported [22]). Based on the findings of our study it may be more prudent to restrict co-trimoxazole prophylaxis to patients with more advanced disease.

Our study is the first to show that low dose co-trimoxazole is also effective in Africa. Several studies have shown that lower doses of co-trimoxazole, 480 mg daily or 960 mg three times per week, are as

effective as the standard dose of 960 mg daily and that lower doses reduce the risk of adverse reactions [3,22]. One study directly compared co-trimoxazole 480 mg daily with 960 mg daily and showed equal efficacy with delayed onset of adverse reactions [22]. A meta-analysis revealed that low dose compared with standard dose co-trimoxazole would result in a 43% decrease in severe side-effects prompting discontinuation of co-trimoxazole [3].

This study has important limitations. No information was available about adverse events or compliance. Cause of death was difficult to ascertain. Bias may have been introduced owing to the lack of randomization. The sample size of patients receiving co-trimoxazole with a CD4 T-lymphocyte count 200–500 $\times 10^6/l$ was small and a significant benefit in this group may have been missed. Despite the fact that groups were not strictly contemporaneous (i.e. the comparison group, by and large, preceded the treatment group), the management of patients, particularly use of antiretroviral therapy or interventions other than prophylactic co-trimoxazole, was not different throughout the study period. In addition, year of presentation was not a significant factor in the different regression models.

In conclusion, low dose prophylactic co-trimoxazole appears to reduce significantly death and opportunistic infections in South African HIV-infected adults, who have a relatively low incidence of PCP, with significant immune suppression. Patients qualifying for this intervention can be identified by simple clinical criteria or by using an affordable laboratory test (TLC). Further randomized studies are needed to assess the optimal time of commencing co-trimoxazole prophylaxis, and the impact of co-trimoxazole prophylaxis on microbial resistance patterns.

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