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

Motasim Badri, Rodney Ehrlich*, Robin Wood and Gary Maartens

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 × 10⁶/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 × 10⁶/l or CD4 count < 200 × 10⁶/l). No significant evidence of efficacy was found in patients with WHO stage 2 or CD4 count 200–500 × 10⁶/l/TLC 1250–2000 × 10⁶/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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Keywords: co-trimoxazole, prophylaxis, HIV infection, AIDS, Africa

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 × 10⁶/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 × 10⁶/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-trimox-
azo prevented other opportunistic infections such as
toxoplasmosis [10], bacterial pneumonia [11], salmo-
nellosis [12] and isosporiasis [13,14] which are collec-
tively 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-tri-
moxazole 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-lymphy-
cyte count of < 500 × 10⁶/l or total lymphocyte count
(TLC) equivalent [17]. Wide-scale use of prophylactic
co-trimoxazole may increase the spread of antimicro-
bial resistance in communities to other pathogens,
notably *Plasmodium falciparum*, non-tuboidal salmonel-
lae 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 para-
mount 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
indicators for initiating prophylaxis which are applic-
able 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 attend-
dance, patients were examined for HIV-related mani-
festations 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 morbidity events were
only accepted if they were definitively diagnosed or on
standard presumptive grounds. VITAL status was ascer-
tained 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 × 10⁶/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 infec-
tions and pulmonary tuberculosis) and survival in pa-

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480 mg daily.

The study was approved by the Research Ethics
Committee of the Faculty of Health Sciences, Uni-
versity 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-
ibly by flow vents were used or on was ascertainment by the wing local

only to men a high PCP prophylaxis cell count 3 when we met many common in this to all or primary dy period subsequently

excluded - HIV-related, or WHO-criteria sera as a surrogate 10^6 /l [20]. related illness number of 00 patients was estimated generalized survival curves 

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 × 10^6/l (P = 0.02), TLC < 1250 × 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 200–500 × 10^6/l (P = 0.72), TLC of 1250–2000 × 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>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group (n = 155)</th>
<th>Comparison group (n = 407)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age [years (SD)]</td>
<td>32 (3.4)</td>
<td>33 (5.7)</td>
<td>0.82</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>72 (47)</td>
<td>208 (51)</td>
<td>0.39</td>
</tr>
<tr>
<td>Ethnicity [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.65)</td>
<td>6 (1.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Black</td>
<td>90 (58.1)</td>
<td>194 (47.4)</td>
<td></td>
</tr>
<tr>
<td>Mixed race</td>
<td>30 (19.3)</td>
<td>132 (32.4)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>34 (21.9)</td>
<td>75 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Low socio-economic status [n (%)]</td>
<td>113 (73.5)</td>
<td>320 (78.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Exposure group [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>41 (26.5)</td>
<td>12 (2.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>114 (73.5)</td>
<td>395 (97.1)</td>
<td></td>
</tr>
<tr>
<td>WHO clinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>22 (14.2)</td>
<td>140 (34.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Stage 2</td>
<td>23 (14.8)</td>
<td>78 (19.2)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>69 (44.5)</td>
<td>120 (29.5)</td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td>41 (26.5)</td>
<td>69 (16.9)</td>
<td></td>
</tr>
<tr>
<td>CD4 T-lymphocyte count [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200 × 10^6/l</td>
<td>134 (86.5)</td>
<td>265 (65)</td>
<td>0.030</td>
</tr>
<tr>
<td>200–500 × 10^6/l</td>
<td>27 (17.5)</td>
<td>94 (23)</td>
<td></td>
</tr>
<tr>
<td>&gt; 500 × 10^6/l</td>
<td>–</td>
<td>48 (12)</td>
<td></td>
</tr>
</tbody>
</table>

*Chi-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.

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 × 10^6/l, TLI < 1250 × 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 200–500 × 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.

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

²The 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-tuboidal 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 × 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.
Acknowledgements

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References


