

Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial

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Summary

Background No trials of co-trimoxazole (trimethoprim-sulfamethoxazole) prophylaxis for HIV-infected adults or children have been done in areas with high levels of bacterial resistance to this antibiotic. We aimed to assess the efficacy of daily co-trimoxazole in such an area.

Methods We did a double-blind randomised placebo-controlled trial in children aged 1–14 years with clinical features of HIV infection in Zambia. Primary outcomes were mortality and adverse events possibly related to treatment. Analysis was by intention to treat.

Findings In October, 2003, the data and safety monitoring committee recommended early stopping of the trial. 541 children had been randomly assigned; seven were subsequently identified as HIV negative and excluded. After median follow-up of 19 months, 74 (28%) children in the co-trimoxazole group and 112 (42%) in the placebo group had died (hazard ratio [HR] 0.57 [95% CI 0.43–0.77], $p=0.0002$). This benefit applied in children followed up beyond 12 months ($n=320$, HR 0.48 [0.27–0.84], test for heterogeneity $p=0.60$) and across all ages (test for heterogeneity $p=0.82$) and baseline CD4 counts (test for heterogeneity $p=0.36$). 16 (6%) children in the co-trimoxazole group had grade 3 or 4 adverse events compared with 18 (7%) in the placebo group. These events included rash (one placebo), and a neutrophil count on one occasion less than $0.5 \times 10^9/L$ (16 [6%] co-trimoxazole vs seven [3%] placebo, $p=0.06$). *Pneumocystis carinii* was identified by immunofluorescence in only one (placebo) of 73 nasopharyngeal aspirates from children with pneumonia.

Interpretation Our results suggest that children of all ages with clinical features of HIV infection should receive co-trimoxazole prophylaxis in resource-poor settings, irrespective of local resistance to this drug.

Introduction

Co-trimoxazole (trimethoprim-sulfamethoxazole) is a widely available, low-cost antibiotic, which has been used worldwide for many years in treatment of community-acquired infections. In HIV infection, it is highly effective for treatment of, and prophylaxis against, *Pneumocystis carinii* pneumonia, one of the earliest opportunistic infections to arise with increasing immunosuppression in Europe and the USA.¹

Evidence suggesting that co-trimoxazole might reduce bacterial infections in HIV-infected children was first reported in a non-randomised subanalysis of a trial designed to measure the efficacy of intravenous immunoglobulin therapy in HIV-infected children in the USA in 1991.² In 1999, results from clinical trials in Côte d'Ivoire showed that co-trimoxazole prophylaxis reduced mortality in HIV-infected African adults with pulmonary tuberculosis,³ and lowered hospital admission rates in adults with high CD4 cell counts without tuberculosis.⁴ Benefit seemed to be due to reductions in bacterial infections, malaria, and isosporiasis; no cases of *P carinii* pneumonia were identified. Of note, the prevalence of bacterial resistance to co-trimoxazole was low in Côte d'Ivoire during the time of the trials, and the investigators commented that the findings might not be

generalisable to other areas with higher resistance rates.^{3,4} Although recommendations to give prophylaxis to infected people in Africa followed,⁵ concerns were expressed that it might not work in areas with high levels of bacterial resistance to co-trimoxazole, might substantially increase bacterial resistance in individuals and communities,^{6–9} and might lead to cross-resistance of bacteria to penicillin¹⁰ and to resistance of malaria parasites to sulfadoxine-pyrimethamine.¹¹

In children, findings from autopsy and clinical studies from various countries^{12–18} have shown that *P carinii* pneumonia is common in HIV-infected African infants, with median age of presentation of 3 months.¹⁹ Co-trimoxazole has therefore been recommended for primary prophylaxis against this infection in all infants born to HIV-infected women in industrialised and resource-poor countries, starting at 6 weeks of age and continuing until HIV-infection status is negative.^{5,20} In HIV-infected children after infancy, co-trimoxazole is recommended if CD4 counts are less than 15% of total lymphocyte count.²⁰

No trials of co-trimoxazole prophylaxis in adults or children have been reported from areas with high rates of bacterial resistance, such as Zambia.⁷ The aim of the Children with HIV Antibiotic Prophylaxis (CHAP) trial

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	Co-trimoxazole (n=265)	Placebo (n=269)	Total (n=534)
Male	126 (48%)	140 (52%)	266 (50%)
Primary carer mother	182 (69%)	179 (67%)	365 (68%)
Route of referral			
Children's clinic	201 (76%)	191 (71%)	392 (74%)
Other clinic	16 (6%)	27 (10%)	43 (8%)
Inpatient admission	19 (7%)	15 (6%)	34 (6%)
Referred from VCT/other study	27 (10%)	36 (13%)	63 (12%)
Age (years)			
Median (IQR)	4.2 (2.1–8.3)	4.5 (2.1–8.2)	4.4 (2.1–8.3)
<1 year	11 (4%)	9 (3%)	20 (4%)
1–2 years	86 (32%)	84 (31%)	170 (32%)
2–5 years	68 (26%)	81 (30%)	149 (28%)
6–9 years	61 (23%)	52 (19%)	113 (21%)
≥10 years or older	39 (15%)	43 (16%)	82 (15%)
One or more previous hospital admissions			
Ever	195 (74%)	202 (75%)	397 (74%)
For tuberculosis	85 (32%)	90 (33%)	175 (33%)
For pneumonia	73 (28%)	74 (28%)	147 (28%)
For failure to thrive or diarrhoea	52 (20%)	48 (18%)	100 (19%)
For malaria	25 (9%)	24 (9%)	49 (9%)
For septicaemia or meningitis	12 (5%)	12 (4%)	24 (4%)
Growth	(n=256)	(n=263)	(n=519)
Weight <3rd centile	166 (65%)	183 (70%)	349 (67%)
Height <3rd centile	201 (79%)	202 (77%)	403 (78%)
BMI <3rd centile	51 (20%)	65 (25%)	116 (22%)
CD4 %	(n=196)	(n=197)	(n=393)
Median (IQR)	11% (7–17%)	10% (5–16%)	11% (6–16%)
0–4%	27 (14%)	38 (19%)	65 (17%)
5–9%	59 (30%)	54 (27%)	113 (29%)
10–14%	46 (23%)	48 (24%)	94 (24%)
15–19%	28 (14%)	31 (16%)	59 (15%)
≥20% or higher	36 (18%)	26 (13%)	62 (16%)

Data are number (%) unless otherwise indicated. % are of non-missing values (1 child missing primary carer, 2 missing route of referral, other denominators as shown). VCT=voluntary counselling and testing centre.

Table 1: Characteristics at baseline

was to assess the efficacy of daily co-trimoxazole prophylaxis in reduction of mortality and morbidity in HIV-infected African children after infancy, in an area with high rates of bacterial resistance to this drug.

Methods

Trial design and participants

CHAP was a double-blind randomised placebo-controlled trial in HIV-infected children aged 6 months to 5 years at University Teaching Hospital, Lusaka, Zambia. In July, 2001, 4 months after the start of the trial, an amendment restricted trial entry to children older than 12 months, after recognition that *P carinii* pneumonia occurred in infants aged 6–12 months in Lusaka,¹⁴ and in line with UNAIDS recommendations that all infants should receive co-trimoxazole.⁵ Furthermore, as increasing numbers of children older than 5 years were being diagnosed with HIV at the hospital, inclusion criteria were extended to include children up to their 15th birthday. Children younger than 5 years received 240 mg (5 mL suspension) co-trimoxazole daily, and those older than 5 years 480 mg (10 mL), or matching placebo.

Most children were recruited from paediatric outpatient clinics at the hospital (table 1). Clinical criteria that were initially suggestive of HIV infection (such as lymphadenopathy, hepatosplenomegaly, failure to thrive, recurrent pneumonia, oral candida, parotitis) were used to identify children for HIV antibody testing. However, we also recruited asymptomatic children with known HIV infection, and also attempted to recruit asymptomatic children from primary care clinics in Lusaka to increase the generalisability of results. This attempt was largely unsuccessful because parents and caregivers were reluctant to allow healthy children to be tested for HIV. Children were eligible for randomisation if they had a positive HIV antibody test and, for those younger than 18 months, clinical features suggestive of HIV infection. Exclusion criteria at screening were presence of an opportunistic infection, life expectancy 4 weeks or less, current co-trimoxazole treatment, history of allergy to this drug, or a previous episode of *P carinii* pneumonia. We recognised that some children aged 6–18 months with positive HIV antibody status might subsequently prove negative for these antibodies, but that this situation would represent real life in Africa, where availability of diagnostic PCR tests for HIV DNA is restricted. Children younger than 18 months were to have antibody tests repeated at age 18 months, and if HIV negative, trial drug would be stopped and they would be excluded from the analysis.

Parents or main carers gave informed written consent for screening (including HIV antibody testing) and, if children were HIV positive and still eligible, additional written consent for randomisation into the trial. The trial was approved by the research ethics committees at University College London, UK, and University Teaching Hospital, Lusaka.

Procedures

Masked trial drug was labelled with sequential study numbers according to a prepared blocked randomisation list. Randomisation codes linking allocation to study number were held only at the UK Medical Research Council (MRC) Clinical Trials Unit by the trial statistician. Children were allocated study numbers sequentially, and thus randomly allocated trial drug, except for siblings who were allocated to the same group to avoid accidental mixing of drug—in these cases, study numbers were assigned manually from the Clinical Trials Unit and sent by fax. After the amendment, randomisation was stratified by age (younger than 5 years vs 5 years and older). In general, doctors enrolled children, and nurses gave the trial drug.

Children who were eligible at screening and whose caregivers consented to enrolment were assessed at baseline (week 0), when trial drugs were prescribed, then every 4 weeks for 16 weeks, and every 8 weeks thereafter. At every visit a clinical assessment was made, and at weeks 4, 12, 24, then every 24 weeks, full blood

count, white blood cell differential, malaria parasites in blood, were measured and plasma stored. CD4 cell count and percentage measurements became available and were included from the first protocol amendment (July, 2001) and from then onwards (for 393 children at baseline). Trial drug was prescribed monthly, and carers returned bottles at every visit. Special efforts were made to diagnose illnesses in children admitted to hospital. In particular, nasopharyngeal aspirates from children with respiratory illnesses were tested for the presence of *P carinii* by immunofluorescence in real-time and by PCR on retrospectively stored specimens.

The data and safety monitoring committee met every 6 months to review unmasked data. Guidelines for recommending modification of the trial included the statistical criterion that a difference in primary endpoint of at least 3 SD was necessary at an interim analysis.²¹ The original sample size of 700 children in total provided 80% power to detect a 35% reduction in mortality or admission rate at 18 months from 40% in the placebo group (two-sided $\alpha=0.05$), allowing for 15% complete loss to follow-up, 15% stopping masked trial drug, and 10% of randomly assigned children subsequently identified as HIV negative (because tested before age 18 months) and excluded.

In October, 2002, the data and safety monitoring committee advised that because of the higher event rate and lower loss to follow-up than expected, target recruitment should be decreased from 700 to 540, which would provide at least 80% power to detect the same 35% reduction in mortality alone (leading to a protocol amendment in October, 2002). In October, 2003, the committee recommended that the trial should be stopped prematurely because of substantial and sustained benefit in the co-trimoxazole group.

Eligibility, informed consent, baseline data, serious adverse events, deaths, and hospital admissions were validated against original hospital notes and clinic records by an independent senior trial manager from the Clinical Trials Unit, and a trained data monitor in Lusaka. A random sample of other data was similarly validated. Primary outcomes were mortality, and clinical or laboratory adverse events graded 3 or 4 according to a paediatric modification of the National Cancer Institute common toxicity criteria and thought to be probably or possibly related to trial drug. Hospital admission was a secondary outcome.

Statistical analysis

We used the Kaplan-Meier method to analyse all time-to-event outcomes, and comparisons were made with log-rank tests. Hazard ratios were estimated by Cox proportional hazards regression. Subgroup analyses by age, CD4 count, and time at risk were done to assess consistency of any effects. Heterogeneity across subgroups was assessed by interaction tests in Cox models.²² Median follow-up was calculated censoring

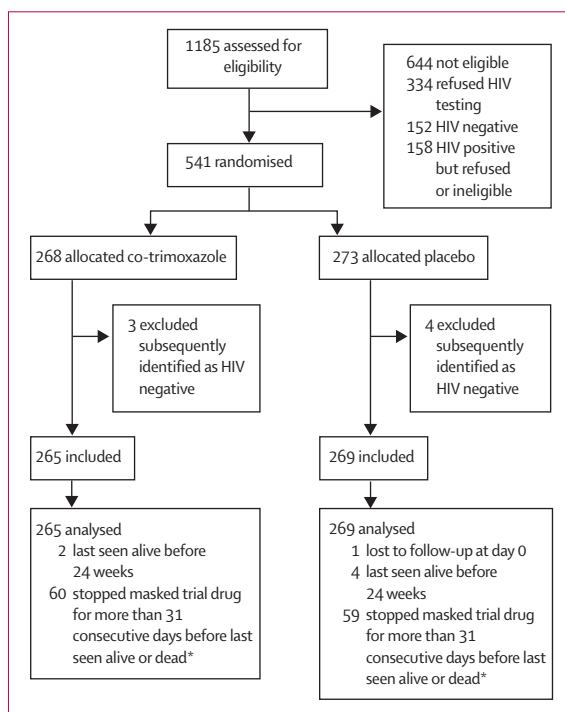


Figure 1: Trial profile

*Not including periods receiving open co-trimoxazole for intercurrent infections according to protocol.

deaths by the Kaplan-Meier method on the time to death or last known time alive. Categorical variables were compared across randomised group with exact tests, and medians and means with rank-sum and *t* tests, respectively.

All comparisons were by intention to treat. Analysis of adverse drug reactions was restricted to time on trial drug plus 31 days. Baseline values were those recorded nearest to randomisation, but before and within 6 weeks of it, except for CD4 count, for which values within 12 weeks of baseline were accepted. Where many tests happened to be available, the closest value to each scheduled visit week within equally spaced windows was used to calculate changes from baseline (with 4-week windows for assessment weeks 4, 8, 12, 16, 24, and 8-week windows subsequently).

CD4 results were expressed as percentage of total lymphocyte counts, since these are less variable with age than are absolute CD4 counts in uninfected children.²³ Height, weight, and weight-for-height were expressed as Z scores with reference to UK standards for uninfected children.²⁴

Role of the funding source

The funding sources of the trial had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

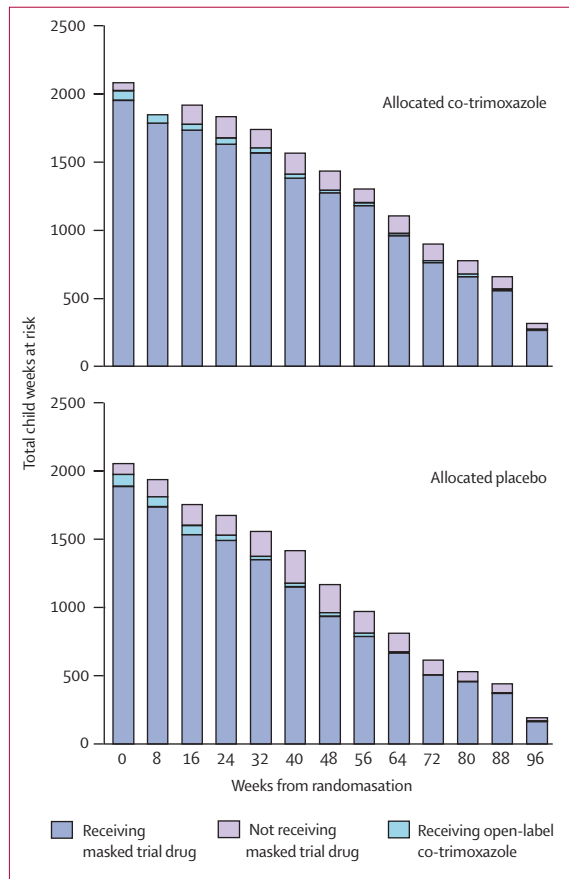


Figure 2: Time spent on treatment

Results

Of 1185 children assessed for eligibility, 851 were tested for HIV antibody. Consent was given for 541 of the 699 HIV-positive children to be enrolled and they were randomly allocated between March 14, 2001 and Jan 8,

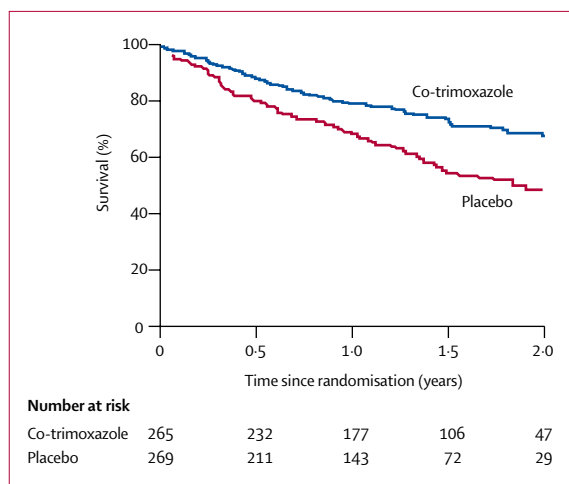


Figure 3: Survival in children on co-trimoxazole or placebo

2003 (figure 1). Seven were subsequently identified as HIV-negative and excluded from the analysis; three of them were younger than 18 months at initial screening visit, and four had false positive tests due to a faulty batch of testing kits. Once this faulty batch had been identified, results from these and all other children were repeated and no other false positive results were identified.

Table 1 shows baseline characteristics of children. 20 infants younger than 1 year were enrolled before the protocol amendment in July, 2001 (and continued in the trial since most were near or older than 12 months, or had died). Almost three-quarters of children had been in hospital at least once and most had some symptoms including previous or present oral candidosis (43%) and severe bacterial infections (28%). Height and weight were substantially impaired compared with UK reference standards.²⁴ Of 393 children whose T-cell subsets were measured, 272 (69%) had CD4 count less than 15% of total lymphocyte count. Median haemoglobin and neutrophil counts were 9.5 mg/dL (IQR 8.5–10.4) and $2.8 \times 10^9/L$ (1.6–4.1), respectively.

Median follow-up was 18.9 months (IQR 13.6–24.0); 19.4 months (14.7–24.1) in the co-trimoxazole group, and 17.7 months (12.9–23.9) in the placebo group, with 349 and 298 total child-years of follow-up, respectively. Vital status was known within the last 4 months of the trial (Oct 24, 2003) for all but 16 (3%) children. 98% of children not known to have died had been followed up in the trial for at least 24 weeks (figure 1). In total, 89% of scheduled clinic visits before death or last seen alive up to and including week 96 were attended (89.7% co-trimoxazole, 88.5% placebo). 245 (46%) children did not miss any scheduled clinic visits (122 co-trimoxazole, 123 placebo).

During follow-up, trial treatment was received during 89.1% of child-time at risk in the co-trimoxazole group, and during 86.4% of that time in the placebo group (figure 2). 193 (73%) children allocated co-trimoxazole and 184 (68%) allocated placebo spent more than 90% of their follow-up time supplied with trial drug. 60 (23%) and 59 (22%) children, respectively, had spent more than 31 consecutive days without being supplied such treatment at some stage during the trial.

Although 114 (43%) children in the co-trimoxazole group and 122 (46%) in the placebo group received open-label co-trimoxazole at some time for intercurrent infections during the trial, according to protocol, this proportion corresponded to only 2.1% and 2.4% of child-time at risk. If children received other antibiotics, trial drug was continued. One child (placebo group) was diagnosed with *P carinii* pneumonia 13 weeks after randomisation (diagnosis made by immunofluorescence done in real-time, although subsequent PCR was negative). The allocated treatment was unmasked and the child subsequently received open label co-trimoxazole.

	Co-trimoxazole	Placebo	HR (95% CI)
Age (years) (n=534)			
<1 year	8 (73%)	8 (89%)	0.68 (0.25–1.83)
1–2 years	25 (29%)	42 (50%)	0.43 (0.26–0.72)
2–5 years	16 (24%)	26 (32%)	0.68 (0.36–1.26)
6–9 years	15 (25%)	21 (40%)	0.54 (0.28–1.05)
≥10 years or older	10 (26%)	15 (35%)	0.63 (0.28–1.41)
Total (stratified HR)	74 (28%)	112 (42%)	0.55 (0.41–0.73)
CD4% (n=393)			
0–4%	14 (52%)	20 (53%)	0.87 (0.44–1.72)
5–9%	16 (27%)	24 (44%)	0.53 (0.28–0.99)
10–14%	7 (15%)	20 (42%)	0.29 (0.12–0.69)
15–19%	4 (14%)	8 (26%)	0.51 (0.15–1.70)
≥20% or higher	5 (14%)	4 (15%)	0.87 (0.23–3.24)
Total (stratified HR)	46 (23%)	76 (39%)	0.56 (0.38–0.80)

Data are number of deaths (%). HR estimated within subgroups.

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Table 2: Mortality by age and CD4% at randomisation

14 (5%) children on co-trimoxazole and 11 (4%) on placebo received antiretroviral therapy at some stage during the trial. Coformulated lamivudine, stavudine, and nevirapine (Triomune; Cipla, Mumbai, India) was the most frequently used combination. Overall, 3.6 and 1.9 child-years of follow-up were spent receiving antiretrovirals in the co-trimoxazole and placebo groups, respectively, corresponding to 1.1% and 0.6% of total follow-up time.

74 (28%) children died in the co-trimoxazole group and 112 (42%) died in the placebo group (hazard ratio [HR] 0.57 [95% CI 0.43–0.77] $p=0.0002$, figure 3). The effect was present during the first 6 months after randomisation ($n=534$, HR 0.56 [0.36–0.87]), 6–12 months ($n=444$, HR 0.7 [0.41–1.23]), and after 12 months ($n=320$, HR 0.48 [0.27–0.84], test for heterogeneity $p=0.60$). There was no evidence that the difference in mortality between the randomised groups varied significantly across age-groups (test for heterogeneity $p=0.82$, table 2), or across baseline CD4 count (test for heterogeneity $p=0.36$). In 272 children with CD4 count less than 15% of total lymphocyte count

(the criterion for initiation of co-trimoxazole prophylaxis in older children^{5,20}), the HR was 0.51 [0.34–0.77] compared with 0.62 [0.26–1.47] for those with CD4 count of 15% or greater ($n=121$, test for heterogeneity $p=0.73$).

Of 186 children who died, only 92 (49%) died in hospital; the rest died either at home (91 [49%]) or on the way to hospital (three [2%]). Cause of death could not be established in 28 children (15%), even in some who died in hospital. Median stay in hospital before death was 3 days (IQR 1–8). Pneumonia was the only clinical diagnosis that was more frequent in those allocated placebo than in those allocated co-trimoxazole (35 of 112 deaths in the placebo group vs 13 of 74 deaths in the co-trimoxazole group, $p=0.04$). In 73 nasopharyngeal aspirate samples from children admitted to hospital with respiratory symptoms, *P carinii* was identified in only one (diagnosed by immunofluorescence in real-time). Further molecular analysis with PCR showed all 73 samples to be negative for *P carinii*.

Hospital admission rate per child-year of follow-up was 0.48 in the co-trimoxazole group and 0.63 in the placebo group (table 3; rate ratio 0.77 [0.62–0.95]; $p=0.01$). 119 (45%) allocated co-trimoxazole and 159 (59%) allocated placebo were admitted to hospital or died (HR 0.64 [0.51–0.82] $p=0.0002$). This effect was present during the first 6 months after randomisation (HR 0.72 [0.53–0.99]), 6–12 months after randomisation ($n=367$, HR 0.48 [0.29–0.81]), and from 12 months onwards ($n=246$, HR 0.62 [0.37–1.05], test for heterogeneity $p=0.42$). Admission-free survival differed significantly between randomised groups across age-groups (test for heterogeneity $p=0.83$) and baseline CD4 count (test for heterogeneity $p=0.96$).

Similar numbers of children in each group had at least one grade 3 or 4 adverse drug reaction (table 4). Time to first such event possibly or probably related to trial drug did not differ between groups (HR 0.76 [0.39–1.50], $p=0.43$). Only one child (placebo group), who developed a grade 3 rash after 2 weeks, required permanent discontinuation of trial drug. 12 children (six co-trimoxazole, six placebo) had grade 3 or 4

	Co-trimoxazole (n=265)	Placebo (n=269)	p
New admissions			
0	176 (66%)	152 (57%)	0.02
1	51 (19%)	77 (29%)	
2	18 (7%)	27 (10%)	
≥3	20 (8%)	13 (5%)	
≥1	89 (34%)	117 (43%)	0.02
New admission rates per child-year at risk	0.48	0.63	0.01
Total days in hospital per child (median, IQR)			
All children	0 (0–3)	0 (0–7)	0.02
Children admitted	7 (3–15)	8 (3–15)	0.95
Total days in hospital	1147	1729	0.02

Data are number (%) unless otherwise indicated.

Table 3: Hospital admissions and inpatient days

	Co-trimoxazole (n=265)	Placebo (n=269)
Children with any event possibly or probably related to trial drug	16 (6%)	18 (7%)*
Rash (grade 3)	0	1
Anaemia (grade 4)	10	13*
Neutropenia (grade 3)†	0	2
Neutropenia (grade 4)†	6	4*

Data are number (%), and do not include conditions pre-existing at randomisation and are restricted to time at risk prescribed masked trial drug plus 31 days. *Two children had both grade 4 anaemia and neutropenia. †Neutropenia confirmed on second sample (as defined in protocol).

Table 4: Grade 3 and 4 adverse events possibly or probably related to masked trial drug

neutropenia, defined in the protocol as two consecutive neutrophil counts less than 0.75 (grade 3) or 0.5 (grade 4), possibly or probably related to trial drug. However, mean neutrophil count declined by $0.5 \times 10^9/L$ from baseline to week 4 in the co-trimoxazole group, compared with an increase of $0.4 \times 10^9/L$ in the placebo arm (t test $p=0.007$), and remained $0.6\text{--}1.2 \times 10^9/L$ below that in the placebo arm from weeks 12 to 72. In total, 16 (6%) children in the co-trimoxazole group and seven (3%) in the placebo group had a single neutrophil count less than $0.5 \times 10^9/L$ after baseline (Fisher's exact test $p=0.06$).

Discussion

Our results show that, in HIV-infected children living in Zambia, an area with high levels of in-vitro resistance of common bacteria to co-trimoxazole (60–80%, Mwansa J, personal communication⁷), this drug reduced mortality by 43% and hospital admission rates by 23% compared with matched placebo. Follow-up in the trial was excellent and few children stopped taking their medication. Mortality was improved in all ages, across the CD4 count range, and was sustained beyond at least 12 months. The results are very similar in magnitude to those in HIV-infected adults with WHO stage 2 or 3 participating in trials in west Africa.^{3,4} As in those trials, co-trimoxazole seemed to be well tolerated in our study with no allergic reactions. There were few reports of neutropenia, and rates of confirmed grade 3 or 4 neutropenia were similar in the two groups although, as expected, neutrophil counts were lower in the co-trimoxazole group than in the placebo group. Average follow-up time in our trial was almost double that in the west African trials,^{3,4} and provides reassurance that giving the drug over an extended period for prophylaxis, as would be necessary if initiated early in the course of HIV infection, seems not to decrease its effectiveness, at least over an average of 18 months.

The mechanism of action of co-trimoxazole prophylaxis in this trial is not entirely clear. Although there seemed to be a fall in the proportion of children dying of lung disease in the co-trimoxazole group, this effect did not seem to be related to *P carinii* pneumonia, since no cases of this infection could be confirmed by PCR analysis. Nasopharyngeal aspirates are not as sensitive as samples from bronchoscopy for diagnosing this form of pneumonia, although they have been used with some success in both industrialised²⁵ and African^{17,26} settings; however, bronchoscopy is not generally practical or safe for children in resource-poor settings. Furthermore, if the predominant cause of death were *P carinii* pneumonia, one might expect to see benefit confined to children with lower CD4 count, whereas we recorded similar magnitude of benefit in children with CD4 counts above and below 15% of total lymphocyte count. Further analyses of nasopharyngeal aspirates are being done to investigate causes of death in more detail,

and to assess development of resistance to respiratory bacteria by treatment group.

The substantial reduction in mortality in the co-trimoxazole group could challenge the relation between effectiveness and in-vitro laboratory resistance to this drug, which could be more complex than either all or nothing. Further molecular resistance studies are analysing bacteria isolated from nasopharyngeal aspirates and other samples taken during hospital admissions. Additionally, studies are examining molecular resistance patterns of *Streptococcus pneumoniae* carried per nasally in samples taken throughout the trial, and resistance of malaria parasites to sulfadoxine-pyrimethamine. However, most blood cultures were negative, and the prevalence of malaria in children in hospital was low. Although children who were followed up in our study had open access to a clinic where they could receive free medical treatment throughout the trial, families would have frequently consulted their local clinic before coming to hospital when a child was sick, and received treatment according to the integrated management of the sick child guidelines,²⁷ including treatment with antibiotics and antimalarials. This could be a reason for the low bacterial isolation rates from blood cultures and the low rates of malaria parasitaemia in children in the trial. Similar findings have come from children admitted to the University Teaching Hospital who were not enrolled in the CHAP trial (Mwansa J, personal communication).

Most children in the CHAP trial had symptoms of HIV infection at diagnosis, and our attempts to recruit asymptomatic children from peripheral clinics in Lusaka were largely unsuccessful. Nevertheless, over a third of children randomly allocated in the trial had CD4 count greater than the threshold at which current guidelines recommend initiation of antiretroviral therapy (15%^{5,20}). Findings from uninfected children from Zambia,²⁸ as well as from screened but HIV-negative children from our study (data not shown), suggest that values could be lower than in comparable uninfected children in Europe and North America. Therefore, thresholds for clinical care in industrialised countries might not necessarily be appropriate for children in resource-poor settings.

We believe, therefore, that our results can be generalised to a policy that could be applied universally to children with clinical features of HIV infection in Africa: all should receive co-trimoxazole prophylaxis irrespective of age and CD4 count. Economic analyses are planned to assess the costs and benefits of such an approach, which could be done in the community. Since antiretroviral treatment is being introduced more widely in Africa, many countries are considering how to provide care and such treatment to HIV-infected children as well as to adults. The results of this trial should provide an impetus to provide clinical care with co-trimoxazole prophylaxis and nutritional support, irrespective of levels of resistance to this drug. Whether it would continue to add benefit to

children also taking antiretroviral therapy in areas of high background rates of infection remains to be seen.

Contributors

D M Gibb and A J Nunn wrote the grant to obtain funding, in collaboration with G J Bhat, C Chintu, S H Gillespie, A Zumla, and I Chitsike. D M Gibb wrote the protocol, and with A J Nunn and L Farrelly, set-up the database and the trial with the Zambian team. V Mulenga, K Lishimpi, and F Sinyinza were trial physicians who coordinated the clinical team in Zambia, supervised by G J Bhat and C Chintu in Zambia and D M Gibb from London. L Farrelly, N Kaganson, and A J Nunn trained data managers in Zambia and checked and monitored data, and labelled drugs. A J Nunn did interim analyses for the data and safety monitoring committee. A S Walker did the main analysis. D M Gibb and A S Walker drafted the paper, which was commented on by the authors.

The CHAP trial team

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Conflict of interest statement

We declare that we have no conflict of interest.

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