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Routinely available cotrimoxazole prophylaxis and occurrence of respiratory and diarrhoeal morbidity in infants born to HIV-infected mothers in South Africa

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Objectives. To examine the influence of cotrimoxazole (CTM) prophylaxis on incidence of lower respiratory tract infections (LRTIs) and diarrhoea.

Design. A prospective observational cohort study. Morbidity and feeding data on infants born to HIV-infected mothers were collected routinely at clinic visits at 1 week, 6 weeks and 3 months, and 3-monthly thereafter, with blood drawn for determining HIV status.

Setting. Two hospitals in Durban, South Africa. In one hospital (King Edward VIII Hospital), infants born to HIV-infected mothers recieved CTM prophylaxis and in the other (McCord Hospital) infants did not receive CTM prophylaxis.

Subjects. Infants born to HIV-infected mothers.

Outcome measures. Incidence of LRTI and diarrhoea.

Results. In multivariate analysis controlling for breast-feeding status, number of clinic visits and HIV infection status, HIV-infected infants with access to CTM prophylaxis had a significantly lower incidence of LRTI (82%) than those without access to prophylaxis. However in HIV-uninfected infants, this was not the case. CTM prophylaxis was associated with a non-significant increased risk for diarrhoea in both infected (odds ratio (OR) 1.58, $p = 0.45$) and uninfected infants (OR 1.52, $p = 0.10$).

Conclusions. This observational study confirms current thinking that CTM prophylaxis is protective against LRTIs in HIV-infected children. However, because of a possible association between CTM prophylaxis and an increased risk of diarrhoea, HIV status of infants should be determined as early as possible in order to prevent unnecessary exposure of uninfected infants to CTM prophylaxis, while further studies to quantify both beneficial and adverse effects of CTM prophylaxis are undertaken.

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Cotrimoxazole (CTM) is recommended as standard-of-care for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) in all infants born to HIV-infected mothers in industrialised countries.[1] Primary prophylaxis with CTM is effective in decreasing the frequency of PCP and early death in infants with perinatal HIV infection.[2] The high morbidity and mortality of HIV-infected infants in developing countries,[3] and the demonstration that much of this is due to *P. carinii*[4-7] and acute bacterial infections,[8] has led to increasing support for the incorporation of CTM into prevention and care programmes for infected children.[9] However, to date the effectiveness of CTM prophylaxis in HIV-infected infants and children has not been proved in randomised controlled trials. The drug is not routinely employed for prophylaxis against infections in Africa, as clinicians and policy makers remain sceptical of any putative benefit and wary of adding unjustifiable costs. Four issues, which are of particular relevance to resource-constrained environments, provide an incentive for more data.

Firstly, the recent global expansion of programmes for the prevention of mother-to-child transmission (PMTCT) of HIV has led to increased rates of diagnosis of HIV-infected and HIV-exposed infants, especially in developing countries. Fifteen African countries have instituted PMTCT programmes and it is estimated that about 250 000 pregnant African women will have access to voluntary counselling and testing (VCT) within 2 years.[3] Secondly, adherence to frequent use of the drug can be anticipated to be sub-optimal. The common practice in many African countries of recommending CTM for all HIV-exposed infants (because of the expense of diagnosing HIV at this age) means that the number of infants subjected to CTM will increase. This will compound the substantial problem of bacterial resistance to CTM in many African countries and render a useful and affordable drug ineffective.[10,11] Thirdly, there is real concern that treating the large number of HIV-uninfected infants will increase service delivery burdens of already fragile systems. Adverse effects of CTM have been reported, ranging from skin reactions and gastrointestinal disturbances to blood dyscrasias, and from mild to lethal.[12] Lastly, there are no reliable data on outcomes of CTM prophylaxis in children in developing countries, although some information has been obtained from observational studies in Thailand[13] which showed that CTM reduced the risk of pneumonia in HIV-infected children. Moreover, it is not known whether CTM exerts any benefit in breast-fed HIV-infected infants. Breast-feeding is known to be protective, reducing lower respiratory tract infections (LRTIs) and diarrhoea in particular, and this effect is especially pronounced in the first 6 months of life.[14] Therefore CTM prophylaxis may either not add any further benefit or its prophylactic effects may become undetectable.

A randomised controlled trial of CTM prophylaxis in HIV-exposed infants is currently being conducted in Zambia and Tanzania but results are not expected for some time because of the large numbers of HIV-infected children needed. However, in the absence of trial results our observational data provide an opportunity to inform the debate and to assess the benefit of routine provision of CTM prophylaxis to all infants born to HIV-infected women. We have data collected within a previously reported vitamin A intervention trial[15] conducted in two clinics in Durban; in one clinic CTM was routinely provided to all children born to HIV-infected women and in the other it was not. In all other respects the enrolled infants were treated similarly, according to protocol requirements. In the first clinic the clinician in charge (KP) followed international guidelines, i.e. prophylaxis was provided for all HIV-exposed infants, and in the second the clinician in charge (ES) followed the South African guidelines at that time (1995 - 1998) which did not advocate routine prophylaxis. We investigated whether provision of routine CTM prophylaxis reduced the risk of LRTI and/or diarrhoea episodes in children of HIV-infected mothers and analysed the data according to infant feeding patterns.

Methods

Details of the study population and data collection have been described previously.[15] Briefly, the mother/infant pairs in the study were participating in a vitamin A intervention trial to reduce MTCT of HIV-1. The study was conducted at antenatal clinics at 2 hospitals in Durban: King Edward VIII Hospital (KEH) and McCord Hospital (MH). Women were recruited between July 1995 and April 1998 and were randomised to vitamin A or placebo. No women in the study received any antiretroviral therapy, which was not available at the time the study was conducted. The study was approved by the Ethics Committee of the University of Natal. Written informed consent was obtained from all women who participated in the trial.

Mothers were asked to attend a follow-up clinic when their infants were 1 week, 6 weeks and 3 months of age, and thereafter every 3 months. At each paediatric follow-up visit mothers were asked about breast-feeding and other infant feeding practices; infants were examined by a clinician and morbidity was recorded according to the study protocol. In addition, history of morbidity since the last visit was collected and anthropometric measurements were taken at each visit. Diarrhoea was defined as 4 or more watery, loose stools per day and LRTI was defined as cough and tachypnoea.

Infant venous blood was drawn on the first day after birth and again at 1 week, 6 weeks and 3 months of age, and 3-monthly thereafter until 15 months of age. If children were breast-fed beyond 15 months an additional sample was drawn at least 6 weeks after complete cessation of breast-feeding. Plasma samples collected from children before 9 months of age were tested using a quantitative assay of HIV viral RNA using polymerase chain reaction (PCR, Roche Molecular Systems,

Branchburg, New Jersey, USA). A sample with more than 400 HIV viral copies per millilitre was designated as a positive test. Samples collected from children after 9 months of age were tested for HIV antibodies (Abbott Laboratories, Chicago). Children were diagnosed as HIV-infected if they had 2 or more positive PCRs and/or were antibody-positive at 15 months of age. They were confirmed HIV-uninfected if they had never had a positive PCR and had at least 1 negative PCR 1 month after cessation of breast-feeding, or if they were antibody-negative 6 weeks after cessation of breast-feeding. Two children were presumed to be uninfected because they had at least 1 negative PCR, no positive PCRs and at least 1 negative enzyme-linked immunosorbent assay (ELISA), but the last negative ELISA was less than 6 weeks after cessation of breast-feeding.

Statistical analyses

Analyses were performed using Stata 7.0 (Stata Corporation, Texas, USA). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and logistical regression was used to adjust for potential confounding factors. Breast-feeding status was categorised as 'ever' or 'never'. Breast-feeding, HIV infection status and clinic (provision of CTM or not) were included in the models as these factors were considered to be associated with morbidity *a priori*. The number of visits was also included to allow for the fact that children who attended the clinic less frequently were less likely to be diagnosed as having illnesses.

Results

Women participating in this study had been randomly assigned to receive vitamin A or placebo during the last trimester of pregnancy. As there was no effect of vitamin A supplementation on the risk of MTCT of HIV-1 infection,[15] the two treatment groups were combined for analysis. Furthermore it is unlikely that vitamin A supplementation given to the mother during the last trimester of pregnancy would have any impact on long-term morbidity of infants. Information was available on a total of 738 mother/child pairs (second twins excluded). Of these, 15 mothers defaulted before delivery and 6 at delivery (20 were recruited at MH and 1 at KEH). Forty-nine children died during follow-up at a median age of 3 months (range 0 - 20 months); 305 children were lost to follow-up, 70% (N = 213) before 3 months of age; leaving 363 children with complete and prolonged follow-up (completers). The proportion of completers and non-completers was similar at each of the two clinic sites, suggesting equal access to CTM prophylaxis. There were no major differences in socio-demographic characteristics of completers and non-completers. Neither were there any differences in socio-demographic characteristics between the mothers enrolled in the 2 different hospitals.

Of the 363 children with complete follow-up information, 181 were male and 182 were female. Two-thirds (N = 238) were breast-fed and one-third (N = 125) were known to have never been breast-fed. Sixty-two children (17%) were HIV-infected, 299 (82%) were uninfected and 2 (0.5%) were presumed to be uninfected. One hundred and fifty-four children were seen at KEH and 209 at MH.

Most children (N = 334, 92%) had information available from 5 or 6 follow-up visits (range 2 - 6 visits). One-third of children (N = 118) had no illness episodes at all during follow-up and another third (N = 122) had 2 or more episodes of illness.

Mortality

Of the 49 children who died, 19 died at KEH and 30 at MH. HIV infection status was determined for 39 children and cause

Table I. Univariate and multivariate analyses — risk factors for ever having an illness episode

	No. of children					
	Ever ill (N = 245)	Never ill (N = 118)	Unadjusted odds ratio (95% CI)	p-value	Odds ratio adjusted for all other variables (95% CI)	p-value
Breast-fed (%)						
Ever	157 (66.0)	81	0.81 (0.51 - 1.30)	0.39	0.84 (0.51 - 1.38)	0.49
Never	88 (70.4)	37				
HIV status (%)						
Infected	55 (88.7)	7	4.59 (2.02 - 10.43)	< 0.001	4.56 (1.98 - 10.49)	< 0.001
Uninfected	190 (63.1)	111				
CTM (%)						
Provided	93 (60.4)	61	0.57 (0.37 - 0.89)	0.01	0.66 (0.41 - 1.05)	0.08
Not provided	152 (72.7)	57				
No. of visits (%)						
2 - 4	13 (44.8)	16	0.36 (0.17 - 0.77)	0.009	0.38 (0.17 - 0.85)	0.02
5 or 6	232 (69.5)	102				

CTM = cotrimoxazole.

of death was known for 44 of 49. Among 29 HIV-infected infants with known cause of death, pneumonia was the sole or contributing cause of death in 6 of 13 children (46%) at KEH where CTM is routinely provided compared with 11 of 16 children (69%) at MH where CTM was not provided; however this difference was not statistically significant. There were no pneumonia-related deaths among HIV-uninfected infants at either clinic. Grouping sepsis and septicaemia with pneumonia, 7 of 13 deaths (54%) among HIV-infected infants at KEH were due to these causes compared with 11 of 16 deaths (69%) among HIV-infected infants at MH (not a statistically significant difference). Serious bacterial infection was the cause of the only death at KEH in an uninfected child, and the cause of 2 of 5 deaths among uninfected infants at MH.

Overall morbidity

A total of 245 of 363 children had at least 1 illness episode, with HIV-infected children being significantly more likely to have had any morbidity than uninfected children (adjusted OR 4.56, $p < 0.001$). Table I shows the effect of breast-feeding, HIV infection status, access to CTM and number of visits on the risk of ever having an illness episode, both in univariate and multivariate analyses.

In univariate analysis, children with access to CTM were significantly less likely to have ever had an illness episode than children seen where CTM prophylaxis was not routinely provided, but the OR increased slightly and was of borderline significance when HIV infection status, breast-feeding and number of visits were taken into account (Table I).

Given the dominant effect of HIV infection status on morbidity, we also analysed morbidity in the 2 infection groups separately. Among the 62 HIV-infected children, 80% (16/20) of those with access to CTM were ever ill compared with 93% (39/42) of those who did not have access to CTM (unadjusted OR = 0.31, 95% CI: 0.06 - 1.60, $p = 0.14$). The apparently protective effect of CTM was not statistically significant owing to the small numbers ($N = 7$) of infected children who were never ill. A borderline significant association in the same direction was seen among uninfected children — 57% (77/135) of those with access to CTM were ever ill compared with 68% (113/166) of those who did not (unadjusted OR = 0.65, 95% CI: 0.40 - 1.04, $p = 0.07$). HIV infection was associated with breast-feeding ($x^2 = 3.47$, $p = 0.06$), but never breast-feeding did not significantly increase the likelihood of being ill among either the HIV-infected or the uninfected children.

As the effect of CTM prophylaxis may vary by type of morbidity, we also analysed the data for LRTI (68 children with at least 1 episode) and diarrhoea (113 children with at least 1 episode) separately.

LRTI

The results of univariate and multivariate analyses of the risk of ever having a LRTI are presented in Table II. Children provided with CTM were significantly less likely to have ever had a LRTI episode than children without access to CTM, even when adjusting for breast-feeding, HIV infection status and number of visits (adjusted OR = 0.41, $p = 0.005$). As expected, infected children were significantly more likely to ever have an LRTI episode than uninfected children (adjusted OR 3.01, $p = 0.001$). There was no significant difference in risk of LRTI by breast-feeding status (Table II).

CTM was apparently associated with a protective effect against LRTI among both HIV-infected and uninfected children, with the strongest effect observed for the infected children. Among the HIV-infected children, only 15% (3/20) of those who were provided with CTM had a LRTI compared with 45% (19/42) of those who were not (OR 0.21, 95% CI: 0.05 - 0.91, $p = 0.02$). Similarly, 10% (13/130) of the uninfected children with access to CTM had a LRTI compared with 20%

Table II. Univariate and multivariate analyses – risk factors for ever having a LRTI

	No. of children					
	Ever had a LRTI ($N = 68$)	Never had a LRTI ($N = 295$)	Odds ratio (95% CI)	p-value	Odds ratio adjusted for all other variables, (95% CI)	p-value
Breast-fed (%)						
Ever	39 (16.4)	199	0.65 (0.38 - 1.11)	0.12	0.68 (0.38 - 1.21)	0.19
Never	29 (23.2)	96				
HIV status (%)						
Infected	22 (35.5)	40	3.05 (1.66 - 5.60)	< 0.001	3.01 (1.60 - 5.67)	< 0.001
Uninfected	46 (15.3)	255				
CTM (%)						
Provided	16 (10.4)	138	0.35 (0.19 - 0.64)	< 0.001	0.41 (0.22 - 0.77)	0.05
Not provided	52 (24.9)	157				
No. of visits (%)						
2 - 4	3 (10.3)	26	0.48 (0.14 - 1.63)	0.24	0.61 (0.17 - 2.14)	0.44
5 or 6	65(19.5)	269				

Table III. Univariate and multivariate analyses — risk factors for ever having an episode of diarrhoea

	No. of children					
	Ever had diarrhoea (N = 113)	Never had diarrhoea (N = 250)	Odds ratio (95% CI)	p-value	Odds ratio adjusted for all other variables (95% CI)	p-value
Breast-fed (%)						
Ever	75 (31.5)	163	1.05 (0.66 - 1.68)	0.83	0.948 (0.58 - 1.52)	0.79
Never	38 (30.4)	87				
HIV status (%)						
Infected	21 (35.6)	41	1.16 (0.65 - 2.08)	0.61	1.25 (0.69 - 2.25)	0.47
Uninfected	92 (30.8)	209				
CTM (%)						
Provided	56 (36.4)	98	1.52 (0.97 - 2.38)	0.07	1.55 (0.97 - 2.46)	0.07
Not provided	57 (27.3)	152				
No. of visits (%)						
2 - 4	11 (37.9)	18	1.39 (0.63 - 3.05)	0.41	1.31 (0.59 - 2.90)	0.51
5 or 6	102(30.5)	232				

(33/165) of those without (OR 0.44, 95% CI: 0.22 - 0.87, p = 0.02).

Breast-feeding is a route of transmission of HIV infection and is also known to be associated with decreased risk of LRTI, especially early in life, and it was therefore important to examine the relationship between these factors more closely for possible interactions. The effect of breast-feeding on risk of LRTI was shown to depend on HIV infection status. Among uninfected children breast-feeding was associated with a significantly reduced risk of LRTI: 11% (21/191) of uninfected breast-fed children had a LRTI compared with 23% (25/110) of children who had never been breast-fed (OR 0.42, 95% CI: 0.22 - 0.80, p = 0.007). In the HIV-infected group, 38% (18/47) of those who were breast-fed had a LRTI compared with 27% (4/15) of those who were never breast-fed (OR 1.71, 95% CI: 0.46 - 6.29, p = 0.42).

Diarrhoea

Table III shows the results of analyses relating to the risk of ever having an episode of diarrhoea. In univariate and multivariate analyses breast-feeding, HIV infection status and number of visits were not associated with ever having had a diarrhoea episode. However, children seen where CTM is routinely provided were more likely to have ever had an episode of diarrhoea than children not receiving CTM although this association was only of borderline significance in both univariate and multivariate analyses (adjusted OR 1.55, p = 0.07).

Among HIV-infected children, 40% (8/20) of those with access to CTM had diarrhoea compared with 31% (13/42) of those who did not receive CTM (OR 1.49, 95% CI: 0.48 - 4.57, p = 0.49). Among the uninfected children, 36% (48/132) of those receiving CTM had diarrhoea compared with 26%

Table IV. Multivariate analyses stratified by HIV infection status

	HIV-infected children (N = 62)		Uninfected children (N = 301)	
	OR adjusted for other variables (95% CI)	p-value	OR adjusted for other variables (95% CI)	p-value
Ever ill				
Breast-fed*	1.71 (0.25 - 11.59)	0.58	0.79 (0.47 - 1.32)	0.37
CTM†	0.38 (0.06 - 2.28)	0.29	0.70 (0.43 - 0.13)	0.14
No. of visits‡	0.13 (0.01 - 1.25)	0.08	0.46 (0.20 - 1.05)	0.06
LRTI				
Breast-fed*	2.31 (0.59 - 8.98)	0.23	0.49 (0.26 - 0.95)	0.03
CTM†	0.18 (0.04 - 0.77)	0.02	0.52 (0.26 - 1.05)	0.07
No. of visits‡	1.41 (0.12 - 17.08)	0.79	0.56 (0.13 - 2.50)	0.45
Diarrhoea				
Breast-fed*	0.44 (0.13 - 1.51)	0.19	1.08 (0.63 - 1.83)	0.79
CTM†	1.58 (0.49 - 5.16)	0.45	1.52 (0.92 - 2.53)	0.10
No. of visits‡	1.69 (0.21 - 13.89)	0.63	1.23 (0.52 - 2.92)	0.64

*Ever v. never (never as the reference category).
†Provided v. not provided (not provided as the reference category).
‡2 - 4 visits v. 5 or 6 visits (5 or 6 visits as the reference category).
CTM = cotrimoxazole.

(44/169) of those who did not receive CTM (OR 1.56, 95% CI: 0.95 - 2.56, $p = 0.08$).

Thirty per cent (14/47) of the infected children who were breast-fed had diarrhoea compared with 47% (7/15) of those who were never breast-fed (OR 0.48, 95% CI: 0.14 - 1.63, $p = 0.23$). Among the uninfected children 32% (61/191) of those who were breast-fed had diarrhoea and 28% (31/110) of those who were never breast-fed had diarrhoea (OR 1.20, 95% CI: 0.71 - 2.00, $p = 0.50$).

Morbidity, LRTI and diarrhoea in infected and uninfected children

Because of the complex nature of the relationships between HIV infection, breast-feeding and morbidity, multivariate analyses were also performed separately for HIV-infected and uninfected children (Table IV). The protective effect of CTM against LRTI was strongest among HIV-infected children and only of borderline significance in the uninfected group. Although breast-feeding was not significantly associated with a reduced risk of LRTI overall, a significant protective effect was observed among the uninfected children.

Possible difference between the two clinics

The provision of CTM was clinic based and an assessment of the effect of CTM must therefore take into account other factors, which may have differed between the clinics. CTM was provided routinely at KEH but not at MH. Interaction between breast-feeding (ever/never) and clinic was investigated by adding an interaction term to the full multivariate models but none of the likelihood ratio test results were significant (all morbidity $x^2(1) = 0.15$, $p = 0.70$; LRTI $x^2(1) = 1.42$, $p = 0.23$; diarrhoea $x^2(1) = 0.63$, $p = 0.43$).

Discussion

Children seen in clinics with routine provision of CTM prophylaxis and who were subsequently shown to be HIV-infected had a significantly lower incidence of LRTI than children without access to prophylaxis. However, in infants who were HIV-uninfected, the lower incidence of LRTI associated with CTM prophylaxis was not significant. CTM prophylaxis in children was associated with a non-significant increased risk for diarrhoea in both infected and uninfected children.

These findings have important implications as they confirm that providing HIV-infected children with CTM prophylaxis is likely to protect them from LRTIs, probably including PCP. For the HIV-infected child the possibly increased risk of diarrhoea is outweighed by the benefits of protection against LRTI. However, for HIV-uninfected infants this may not be the case, and there is the additional public health risk that unnecessary treatment in this much larger group of HIV-exposed children will increase resistance to the drug. We therefore recommend that ideally all HIV-exposed children be tested at 6 weeks of age, and only infected children be provided with CTM prophylaxis. Although the cost of a PCR test for HIV is currently prohibitive in developing countries, in South Africa a PCR test is now available for R150 in some laboratories. It is likely that for most developing countries the costs of tests will become affordable. An affordable PCR test at 6 weeks is an attractive option because the cost will probably equate to the financial and other consequences of increasing the prevalence of resistance to CTM, one of the mainstays of antibiotic treatment in developing countries. Testing infants at 6 weeks also provides the additional advantage of using this information to inform mothers' decisions on continuation or cessation of breast-feeding.

Although our study had obvious shortcomings as it was not a randomised controlled trial, it is the first study in Africa to examine the effect of CTM prophylaxis on LRTI and diarrhoea incidence in HIV-exposed children. The results therefore provide valuable information to inform policy on CTM prophylaxis for all HIV-exposed infants in developing countries. A further limitation of our study is that children presenting with LRTIs were not investigated for causal agents and it can only be assumed from previous and current studies in South African hospitals that a large burden of this disease is PCP-related.[16]

The strength of the study is that morbidity data were collected prospectively for a large number of infants (with similar background profiles) who received similar management in all aspects except with regard to CTM prophylaxis. In addition the control group was not a historical control as both groups of infants were managed during the same time period. The analysis controlling for several variables further strengthens the inferences made.

A recent study in South Africa[16] retrospectively examined whether HIV-infected children presenting with pneumonia had been exposed to CTM prophylaxis. *P. carinii* was isolated less frequently in children receiving CTM prophylaxis, and none of the children with confirmed PCP who died had received CTM prophylaxis. However, at least one-quarter of children in whom PCP was diagnosed were receiving prophylaxis at the time of their presentation. This may suggest that CTM prophylaxis is obviously not 100% effective and *P. carinii* strains resistant to sulfa drugs may be emerging.[17] There is also the probability of non-adherence to treatment. These findings are similar to those reported here in our study.

We therefore recommend that developing countries continue providing CTM prophylaxis to HIV-exposed infants. However, serious consideration should be given to developing affordable tests for HIV and determining HIV status early so that those infants who are HIV-negative are not unnecessarily exposed to the unwanted side-effects of unnecessary treatment.

A Coutsoudis was the principal investigator, wrote the protocol, supervised the study, and wrote the manuscript. K Pillay and E Spooner assisted with study design, were responsible for clinical management of the mothers and children and edited the final manuscript. M-L Newell and L Pembrey were responsible for all the statistical analysis and contributed to the writing of the manuscript. H M Coovadia assisted with the writing of the manuscript.

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