

Co-trimoxazole in HIV-exposed but uninfected infants may undermine benefits of breastfeeding – trial needed, say paediatricians

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Co-trimoxazole prophylaxis (CTXP) may not provide significant protection against bacterial infections in HIV-exposed but uninfected infants, and may even undermine the health benefits of breastfeeding, according to research from South Africa.

Optimal use of CTXP in breastfed HIV-exposed negative infants in a community programme in Durban, South Africa, was associated with an increased risk of diarrhoea (incidence rate ratio (IRR) = 1.38, 95% CI: 0.98 - 1.94, $p=0.065$) according to an analysis by Anna Coutsooudis and colleagues published in a research letter in the advance online edition of *AIDS*.

There was no consistent evidence to show that CTXP had any increased benefit in the prevention of lower respiratory tract infection (LRTI).

CTXP is recommended for all HIV-infected infants and children, following results of the CHAP trial, which showed that CTXP halved the risk of death for children and infants.

The World Health Organization (WHO) guidelines also recommend CTXP in breastfed HIV-exposed negative infants. However, these guidelines are based on evidence of efficacy in HIV-infected infants. Anna Coutsooudis and colleagues noted limited evidence of CTXP benefits in HIV-exposed but negative infants.

They note that studies in Mali and Uganda have shown CTXP to be effective in reducing the incidence of malaria in HIV-negative children. However, in Uganda reduction of malaria incidence in HIV-exposed but negative children was seen after breastfeeding stopped, but CTXP had no effect on bacterial infections.

The authors raise the concern that, despite a lack of evidence of the efficacy of CTXP in HIV-exposed breastfed infants, the guidelines continue to be followed. Breastmilk provides immune protection against diarrhoea and pneumonia. While breastfed infants have a strong gastrointestinal system, continued use of antibiotics (of which co-trimoxazole is one) will destroy the normal (healthy) gut bacteria, so allowing disease-forming bacteria to grow.

A recent commentary in the WHO Bulletin questioned the necessity of giving CTXP to HIV-exposed negative infants who are already protected from infections through breastmilk, and called for a re-examination of these guidelines.

With this in mind, the authors chose to review data from a cohort of breastfed HIV-exposed negative infants where they were able to compare the optimal (more than 60 days) to the minimal (under 60 days) use of CTXP to see if CTXP was beneficial to these infants during the first year of life.

The MTCT Plus Programme is in a municipal clinic in a poor community in Durban. Pregnant women testing positive at the clinic are referred to the programme where the aim is to reduce mother-to-child transmission and improve child health.

Infants testing HIV negative at 6 weeks of age were given CTXP in accordance with WHO guidelines.

Infants were seen at 6, 10 and 14 weeks and at 6, 9 and 12 months; growth and disease data and information on co-trimoxazole and other medications taken since the last visit were noted.

Drug stock-out and caregivers forgetting to pick up medicines, among other reasons, meant not all infants received the optimal (60 day) dose of co-trimoxazole.

Among 480 infants testing HIV-negative at 6 weeks of age between March 2003 and April 2010 approximately half (244) received CTXP for more than 60 days and the remainder for under 60 days. Median time of breastfeeding was 181 days, ranging from 1 day to 365 days.

Taking into account maternal socio-economic factors as well as CD4 cell count the analysis supported similar findings in an earlier retrospective study in South Africa: a trend toward increased risk of diarrhoea in infants on optimal CTXP and no significant reduction in the incidence of respiratory infections.

While the difference was not significant and the study was not designed to look at death and hospitalisation, the CTXP group nonetheless had a higher rate than the control group, 10.2% and 5.7%, respectively.

The authors believe their findings justify a randomised trial to ensure that the current WHO-recommended guidelines for the use of CTXP are appropriate.

A randomised controlled trial would determine if the benefits of CTXP in HIV-



exposed breastfed infants in protecting against bacterial infections outweigh the benefits of protection provided by breastfeeding.

'Our findings also suggest there is a need to determine whether the potential negative factors such as side effects, health system costs and drug costs justify the benefit which is now being called into question,' the authors add.

And, they conclude, 'such a study is vital in cognisance of the recent WHO World Health Day call for renewed attention to appropriate use of antibiotics in order to contain antimicrobial resistance'.

Coutsooudis A, et al. Impact of cotrimoxazole prophylaxis on the health of breastfed HIV exposed negative infants in a resource-limited setting. *Advance online edition AIDS* 25, doi: 10.1097/QAD.0b013e32834ad699, 2011.

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