

Christopher J. Gill et al.

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## Commentary

# Cotrimoxazole prophylaxis for infants exposed to HIV infection

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Uncertainty remains about the risks and benefits of implementing guidelines on the use of cotrimoxazole prophylaxis for prevention of HIV-related infections in Africa (1). Gill et al. focus on recommendations for prophylaxis made by the World Health Organization and the United Nations Programme on HIV/AIDS (UNAIDS) for infants born to mothers with HIV infection, most of whom will not have HIV infection. They examine evidence of benefit, highlight concerns about risk, and propose a model that might be helpful in determining policy in various circumstances. A useful approach in principle but — as the authors conclude — important data required for this model remain unavailable, most notably for the magnitude of risk. Other issues, such as national policies and priority setting also need to be considered further.

## Benefits

Around one-third of African infants with HIV infection die in the first year of life and *Pneumocystis carinii* (now called *Pneumocystis jirovecii*) pneumonia (PCP) is responsible for 30%-50% of deaths (2,3). This is the rationale for cotrimoxazole prophylaxis. Evidence of efficacy from controlled trials may not be available but such studies would be difficult to justify in this setting. Experience has shown that the introduction of routine cotrimoxazole prophylaxis for infants of HIV-infected

mothers has markedly reduced the incidence of hospitalization and death caused by PCP (3).

Cotrimoxazole prophylaxis may also prevent illnesses in addition to PCP, particularly bacterial disease and malaria, with potential benefit to uninfected infants as well as infants with HIV infection (4,5). In developing countries, incidence and case-fatality rate of bacterial pneumonia is high in infants, and passive immunity against pneumococcus may be less in children of mothers with HIV infection (6,7,8). Infants become more susceptible to severe malaria (with anaemia) around 4-6 months, when maternal passive immunity wanes.

Studies of cotrimoxazole prophylaxis in African adults, and a recent study of Zambian children aged 1-14 years, have shown improved survival in people with HIV infection (4,5,9). This benefit was not from prevention of PCP, which was rare, but from prevention of bacterial disease and malaria. The degree of protection, however, was variable between study groups and diseases. There have been no studies in infants of mothers with HIV infection.

The potential of preventing PCP will encourage mothers to overcome some of their reluctance to discover their HIV status, preferably as one element of a package of measures that includes prevention of mother-to-child transmission, and improved maternal care. Maternal death, we know, is a major risk factor for early death in infants of mothers with HIV infection (2).

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## Risks

The risk of toxicity from cotrimoxazole is negligible (9,10). Gill et al. outline the major potential risk of widespread cotrimoxazole prophylaxis: increasing antimicrobial resistance of common pathogens such as *Streptococcus pneumoniae* and of *Plasmodium falciparum*. There is a consequent risk to individuals receiving cotrimoxazole, who may be more vulnerable to resistant pathogens, and to public health more broadly through shortening the useful life span of current therapies. Data to help determine the magnitude of these risks, in different settings of background resistance, are critical.

An additional risk in low-resource countries is that translating this policy into practice may hamper or dilute the effectiveness of other programmes. A number of health care strategies are rolled out at any one time, and these must be prioritized to avoid over-burdening the health system, especially because of the human resource crisis in many African countries with HIV endemics. From a child health perspective, prolonging the survival of a child with HIV infection may not have the same priority as improving maternal health or preventing mother-to-child transmission with antiretroviral therapy. Another priority may be preventing malaria by distributing insecticide-treated bed-nets. Whatever the choice, decisions to adopt global policy are best made at national level.

## Improved diagnosis of HIV infection

Gill et al. highlight how the balance between risk and benefit will be altered by substantial reductions in rates of mother-to-

child transmission. They also justifiably argue that improved diagnosis of HIV infection in infants should reduce duration of prophylaxis. This would, however, also depend on a policy — that may not be desirable — of bottle-feeding infants exposed to HIV infection to avoid late post-natal infection. There is evidence that, in the African context, maternal HIV antibodies do not persist in infants for as long as elsewhere which means that an HIV antibody test could be highly specific for infection as early as 6 months (11). Analyses of data from past cohort studies of African infants exposed to maternal HIV infection might help answer this question.

## The way forward

Recognizing that PCP is a common but preventable cause of high mortality in African infants with HIV infection, an alternative strategy of cotrimoxazole prophylaxis until 6 months of age could prevent most cases of PCP while reducing the duration of prophylaxis and risk of antimicrobial resistance (12). Randomized-controlled trials of cotrimoxazole prophylaxis are difficult, but studies must be done that provide important data on risk in a number of settings with variable background resistance and HIV prevalence. Comparisons could be made between infants who are HIV negative (and receiving cotrimoxazole prophylaxis) but whose mothers are HIV positive and infants of who are HIV negative and whose mothers are HIV negative. Cost-effectiveness studies are required as well to evaluate a package of care that also includes antenatal testing, perinatal antiretroviral therapy, and care for the mother. ■

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