Reviewing co-trimoxazole for HIV-exposed, uninfected infants

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Most of the 1·3 million infants born to pregnant women living with HIV annually avoid HIV acquisition through use of maternal antiretroviral therapy (ART) and infant ART prophylaxis.[1] Despite their HIV-free status, children who are HIV-exposed and HIV-uninfected have an increased risk of adverse birth, developmental, and growth outcomes and increased risks of infection-related morbidity and mortality that are not fully mitigated by breastfeeding.[2] In settings with a high burden of HIV, where the health-care infrastructure is overburdened and where up to one in four infants is HIV-exposed and HIV-uninfected, such as South Africa and Botswana, modelling studies[3] suggest that excess mortality in HIV-exposed, HIV-uninfected infants increases overall infant mortality rates by approximately five deaths per 1000 infants. Clearly, many HIV-exposed, HIV-uninfected infants are not surviving and thriving, and they need strategies to improve their outcomes.

Since 2000, WHO has recommended co-trimoxazole in breastfeeding HIV-exposed, HIV-uninfected infants from age 6 weeks until breastfeeding has stopped and the infants are confirmed not to be infected with HIV.[4] At the time, this approach targeted morbidity and mortality in HIV-infected infants, when HIV diagnostics (access to polymerase chain reaction) were poor, the risk of infant HIV acquisition was high and accompanied by rapid disease progression, early mortality from *Pneumocystis jirovecii* pneumonia was common, and there was evidence that co-trimoxazole prevented serious bacterial infections in HIV-infected infants and children.[5] However, there was no such evidence in HIV-exposed, HIV-uninfected infants. In this context, Brodie Daniels and colleagues[6] enrolled into their trial HIV-exposed, HIV-uninfected infants aged 6 weeks whose mothers were living with HIV, were actively involved in transmission prevention programmes in two clinics in South Africa, and were breastfeeding their infants. In this study, in *The Lancet Global Health*, Daniels and colleagues randomly assigned the infants to receive co-trimoxazole or no co-trimoxazole, and they assessed the difference in mortality and infectious complications, specifically severe diarrhoea and pneumonia.[6] Their finding that no co-trimoxazole was not inferior to daily co-trimoxazole among breastfed HIV-exposed, HIV-uninfected infants in South Africa supports the findings of the Mpepu study,[7] in which co-trimoxazole did not outperform placebo in breastfed and formula-fed HIV-exposed, HIV-uninfected infants in Botswana.

The study by Daniel and colleagues is not perfect: the most concerning of the study's limitations were the 15% loss to follow-up, as a result of which, the authors were unable to exclude mortality in these infants. The study also had no placebo group, and adherence to therapy was not monitored rigorously. Nonetheless, the low mortality (0·3% in the co-trimoxazole group and 0·2% in the no co-trimoxazole group) and relatively few reported cases of severe pneumonia and diarrhoea were notable. By contrast, in the Mpepu study, 2·4% HIV-exposed, HIV-uninfected infants in the co-trimoxazole group and 2·6% of these infants in the placebo group died, indicating no difference between the groups.[7] Daniels and colleagues attribute this disparity to more frequent breastfeeding and earlier access to conjugated pneumococcal and rotavirus vaccines in South Africa than in Botswana.[6] Additionally, most infants in the South African cohort had access to safe water and sanitation and, notably, the study excluded infants with a serious illness before age 6 weeks or those who received antibiotics before enrolment, who could represent a higher risk subgroup.

The findings in the study by Daniel and colleagues and the Mpepu study are context-specific, and a review of the current WHO recommendation for HIV-exposed, HIV-uninfected infants would need to consider access to early infant diagnosis, the strength of the public health and vaccination programmes, and the malarial status of the country. In the Malawian Breastfeeding, Antiretrovirals and Nutrition study,[8] which was done before the introduction of pneumococcal vaccination, co-trimoxazole protected against symptomatic and asymptomatic malaria parasitaemia, diarrhoea, and pneumonia; the authors postulate that malaria and asymptomatic malaria might be drivers of other infection-related morbidity and, clearly, the possible benefit of malaria prevention would be important.

In the study by Daniels and colleagues, eight infants acquired HIV, four of which infections were related to breastfeeding. In settings with low HIV transmission, each transmission should be analysed to identify opportunities for interventions to move to zero transmission. If programmes in malaria non-endemic areas stopped routine co-trimoxazole for HIV-exposed, HIV-uninfected infants and redirected those resources to ensure retention in care and viral suppression of nursing women living with HIV and to strengthen child health programmes, identification, and linkage to care for infants with HIV, some of the mortality of HIV-exposed, HIV-uninfected and HIV-infected infants might be addressed, and HIV transmission could be further reduced while minimising antimicrobial resistance. In malaria-endemic areas, similar studies are needed in HIV-exposed, HIV-uninfected infants who have access to insecticide-treated bed nets, seasonal malaria prevention strategies, or malaria vaccines. Although the magnitude of the reduction in child mortality achieved with community-wide dosing of azithromycin is also context-specific, its potential to reduce infant mortality and prevent malaria[9] through programmes that do not require specific resources to be targeted to HIV-exposed, HIV-uninfected infants is an interesting prospect. In settings with a high burden of HIV, future studies that assess strategies targeting universal child survival should consider HIV-exposed, HIV-uninfected infants in their study design and compare them to HIV-unexposed, HIV-uninfected infants from the same communities receiving the same health interventions.

Supporting women living with HIV to continue receiving effective ART, improving maternal health, breastfeeding, a comprehensive vaccination programme, safe water and sanitation, and nutrition support for older infants will always be more important than antibiotics to reduce child mortality in all children and HIV-exposed, HIV-uninfected infants.

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