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Management of diarrhea in HIV-affected infants and children

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Abstract

Globally, diarrhea is the second leading cause of death in children less than 5 years of age. HIV-infected and HIV-exposed uninfected (HEU) children are at high risk of dying from diarrhea and may be more susceptible to the highest risk enteric pathogens. This increased risk associated with HIV infection and HIV exposure is likely multifactorial. Factors such as immunosuppression, proximity to individuals more likely to be shedding pathogens, and exposure to antimicrobial prophylaxis may alter the risk profile in these children. Current international guidelines do not differentiate management strategies on the basis of whether children are infected or affected by HIV, despite likely differences in etiologies and consequences. Reducing diarrhea mortality in high HIV prevalence settings will require strengthening of HIV testing and treatment programs; improvements in water, sanitation and hygiene interventions targeted at HIV-affected households; and reconsideration of the use of empiric antimicrobial treatment of pathogens known to infect HIV-infected and HEU children disproportionately.

In sub-Saharan Africa, child mortality remains unacceptably high, with one in every 9 children dying before the age of 5.¹ Many of these deaths are due to preventable or treatable infectious diseases, with diarrhea ranking as the 2nd leading cause.² HIV infection and HIV exposure are important comorbidities in sub-Saharan Africa and there is substantial overlap between the highest diarrhea case-fatality and HIV burden countries.³ HIV infection and HIV exposure are associated with increased risk of developing diarrhea and with risk of poorer outcomes following each diarrheal episode.^{4,5} The largest study of infectious diarrhea etiology to date, the Global Enteric Multicenter Study (GEMS), identified three high-risk pathogens associated with death in children; typical enteropathogenic *Escherichia coli* (EPEC) and enterotoxigenic *Escherichia coli* (ETEC) in infants (0–11 months) and *Cryptosporidium* in toddlers (12–23 months).³ Notably, the sites with the highest mortality in the GEMS study were also those with highest adult HIV prevalence.⁶ HIV-infected children and HIV-exposed uninfected children (HEU) may be at higher risk of acquiring, and failing to recover from, infection with these pathogens.⁷ This increased risk associated

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with HIV infection and HIV exposure may occur as a result of proximity to individuals who are more likely to be shedding pathogens. Alternatively, exposure to antimicrobial prophylaxis, such as cotrimoxazole, may alter the risk profile for infection with certain pathogens. Finally, immunosuppression associated with both HIV infection and HIV exposure may result in reduced immunologic response and lack of protection from vaccines or prior exposure. Given the high burden of diarrhea-associated morbidity and mortality in sub-Saharan Africa, targeted management strategies of diarrhea in HIV-affected children, including children living in high HIV-prevalent settings, are needed.

HIV infection and HIV exposure increase risk through multiple overlapping pathways. HIV infection drives immune activation and immune suppression, both of which are associated with increased acquisition of pathogens and more severe disease.⁸ HIV-infected children also experience rapid disease progression and are at markedly higher risk of morbidity and mortality than HIV-uninfected children.^{9,10} HEU children, despite avoiding HIV-infection, appear to exhibit significant defects in immunity that may directly impact disease virulence.¹¹ In addition, exposure to passively acquired antibodies from breast-feeding may be reduced in HIV-infected and HEU children. As a consequence of maternal HIV infection, these children may receive reduced duration, frequency, and quality of breast-milk, may be less likely to be exclusively breastfed, or may wean earlier as a result of stigma or fear of mother-to-child HIV transmission.¹² Although debated, HIV infected and HEU children may not mount or sustain the same vaccine response as HIV-unexposed children and acquired immunity following pathogen challenge appears reduced.^{13–16} As the rotavirus vaccine is rolled-out throughout sub-Saharan Africa, suboptimal vaccine responses in HIV-infected and HEU children may need to be considered in anticipating gaps in effectiveness. Immune deficiency associated with both HIV infection and HIV exposure may substantially reduce the infective dose of enteric pathogens required to develop clinical symptoms and likely increases the severity of disease associated with infection.

The World Health Organization (WHO) recommends that all individuals with confirmed HIV infection be started on cotrimoxazole (CTX) prophylaxis.¹⁷ For HEU children, CTX prophylaxis is advised until HIV infection is ruled out and the child is no longer breastfeeding. Cotrimoxazole has activity against many enteric bacterial pathogens, including *Shigella* and pathogenic *E. Coli*, and has been shown to reduce mortality.^{18,19} Cotrimoxazole has also been shown to reduce diarrheal illness in both HIV infected and HEU children. However, exposure to cotrimoxazole may also create selective pressure at both the individual and the community level favoring either resistant bacteria or colonization of non-bacterial pathogens.^{20–22} As a result, individual, household and/or community use of cotrimoxazole in response to HIV may alter the risk of acquiring *Cryptosporidium* and CTX-resistant EPEC and ETEC.

Living in proximity to HIV-infected caregivers, HIV-infected and HEU children may also be exposed to a greater quantity and diversity of pathogens. Maternal HIV-associated immunosuppression is associated with increased infant mortality and infection-related hospital admissions, independent of maternal mortality.²³ The family members of antibiotic prophylaxis-treated HIV-infected adults experience less infection-related morbidity and mortality.²⁴ HIV-infected adults are also more susceptible to a variety of infections and

appear to shed pathogens, including *Cryptosporidium*, in greater quantities and for long periods of time.^{25–27} Children living with an HIV-infected household member are therefore likely to have greater exposure to enteric pathogens than children living in HIV-unaffected households. In high HIV-prevalence settings, the unique susceptibility of HIV-infected individuals to particular pathogens, the widespread use of cotrimoxazole for prophylaxis, and the potential for HIV-infected individuals to act as ‘super-spreaders’, may all result in increased risk to children in these communities.

The biological, environmental, and clinical factors contributing to higher risk in the HIV-affected child may be further compounded by reduced caregiving capacity, as a result of illness related to a caregiver’s own HIV infection, decreased access to healthcare, and lower socioeconomic status.^{11,23} HIV-infected caregivers are at high risk of mortality, and children orphaned by a caregiver are at a higher risk of death themselves, regardless of the child’s underlying HIV status.²⁸ In addition, HIV-infected caregivers may be coping with recurrent illness, stigma and discrimination, and/or increased health care costs associated with managing their HIV infection, all of which may contribute to reduced earning potential. Low socioeconomic status further contributes to increased pathogen exposure due to decreased access to water and sanitation, increased risk of underlying morbidities such as malnutrition, and poor access to health care services for appropriate management of illness.^{11,23}

Reducing diarrhea-related morbidity and mortality in sub-Saharan Africa will require improvements in the management of diarrhea among individual HIV-infected and HEU children and will also require improvements to household and community level conditions that compound risk. Coverage of HIV testing is steadily increasing across sub-Saharan Africa and HIV-infection and HIV-exposure status could be added as an important risk-stratifying variable in diarrhea management guidelines. For example, infections highly associated with death, such as EPEC, ETEC, and *Cryptosporidium*, could be targeted for prevention and treatment in these populations. Current management guidelines for diarrhea do not recommend antibiotics for children in non-cholera endemic areas unless there is evidence of dysentery.^{29–31} Targeted use of antibiotics may be of benefit in select groups of children at high risk of EPEC or other bacterial causes of diarrhea but will need to be weighed against the risk of increasing antimicrobial resistance. In addition, given the importance of *Cryptosporidium* as both a common cause of diarrhea and a leading contributor to diarrheal death in this region, the use of empiric Nitazoxanide or other anti-protozoals should be explored.

Preventative strategies targeting HIV-affected children and family members may also achieve high impact in reducing diarrhea mortality and morbidity in areas of high HIV-prevalence. Household members are a potential source of high-risk enteric infections in HIV-infected and HEU children and the diagnosis and treatment of infected household members can prevent household sources of pathogen exposure. Preventative tools, such as household water filters, have been shown to reduce diarrhea while also delaying HIV disease progression among infected adults.³² Targeted provision of household water, sanitation and hygiene (WASH) interventions, such as water filters, facilities for excreta disposal, and hand washing interventions to households in high HIV prevalence areas might

be a cost-effective prevention strategy. Breastfeeding, particularly exclusive breastfeeding in the first six months of life among reduces risk of diarrhea-related morbidity and mortality among HIV-infected and HEU children.^{12,33} Based on substantial evidence that the risk of HIV transmission is overshadowed by risk of dying from diarrhea, malnutrition, or other non-HIV infectious diseases, the WHO recommends exclusive breastfeeding for the first 6 months of life in children of HIV-infected mothers.³⁴ Identifying HIV-infected infants and children early, and enrolling them in care will have major effects on preventing morbidity and mortality, including from diarrhea, among children under five.³⁵ However, there is still debate about whether ART should be started immediately or based on immunologic markers in children aged 2 to 5.³⁶

In sub-Saharan Africa, children seeking care for diarrhea experience a 5 to 20-times higher risk of death in the subsequent 60 days than children without diarrhea and HIV-infected and HEU children are among the highest risk groups.^{3,37} Targeted treatment protocols and management guidelines based on HIV-status or underlying community HIV prevalence may significantly reduce risk of death in these children and ultimately reduce the number of diarrhea deaths worldwide. Additionally, the management of HIV in children and adults, and encouraging breastfeeding and WASH interventions in high HIV prevalent settings, will likely result in morbidity and mortality benefits extending above and beyond diarrhea.

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