REVIEW ARTICLE

SPECIAL ISSUES AND MANAGEMENT OF HIV EXPOSED UNINFECTED INFANTS AND CHILDREN

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Abstract

New vertical HIV infections are declining and the numbers of HIV exposed but uninfected (HEU) infants and children are increasing. This positive trend is tempered by the realization that despite escaping HIV infection, the substantial population of HEU children bear consequences of being born to an HIV-infected mother. A structured approach to the care of these children may improve their long term health and well-being. We propose and discuss a 10-point care package for HEU infants centered on providing optimal basic child health management for all children both HIV-exposed and unexposed. Providing basic comprehensive child care interventions benefits all infants, both HIV-exposed and unexposed. For HEU infants, particular attention should be given to providing optimal vertical transmission prevention interventions and conducting appropriate HIV testing. Clinicians should be aware of the consequences of anti-retroviral (ARV) and HIV exposure on HEU infants. As vertical transmission prevention programs become more sophisticated there is a pressing need for the establishment of pharmacovigilance and long-term surveillance systems as well as affordable infant HIV diagnostic tests.

Keywords: HIV exposed uninfected, HEU, children, infants

Introduction

One of the public health successes of the last decade is the expansion of national programs for the prevention of vertical transmission of HIV from mothers to infants. Globally, new vertical HIV infections are declining and the numbers of HIV exposed but uninfected (HEU) infants and children are increasing. This extremely positive trend is tempered by the realization that despite escaping HIV infection, HEU children bear consequences of being born to an HIV-infected mother. Due to vulnerability for infectious diseases during infancy, HEU children experience greater mortality and morbidity in the first years of life than HIV unexposed (HU) children. (1–4) Universal infant risk factors that predispose to mortality in all infants, but that occur more often in HEU infants include being born preterm or small for gestational age, suboptimal breastfeeding, maternal mortality, exposure to infectious agents particularly tuberculosis (TB) and poverty. Additionally, risk factors unique to HIV-exposed infants may potentiate their vulnerability. These HEU unique factors include exposure in-utero to viral proteins and glycoproteins, a maternal pro-inflammatory and/or immune compromised state and exposure to antiretroviral (ARV) and other drugs both in utero and in breast milk.

The population of HEU children is substantial. In the high-burden country of South Africa for example, HIV prevalence in pregnant women is close to 30% and vertical transmission of HIV is now below 5%, resulting in more than 25% of the infant population in South Africa being HEU. A structured approach to the care of these children may improve their long term health and well-being. We propose and discuss a 10-point care package for HEU infants centered on providing optimal basic child health management for all children both HIV-exposed and unexposed.

Care package for HIV exposed infants (10-point check-list at each contact)

Optimal routine child health management:

1. Manage & treat acute problems
2. Provide feeding counselling & support
3. Monitor growth & development
4. Provide vaccinations, vitamin A, antihelminthics (deworming)
5. Screen for TB contacts and actively manage
6. Ask about mother's health, family planning
7. Provide social support and consider parental HIV disclosure

Optimal routine HIV-exposed infant management:

8. Provide vertical transmission prevention prophylaxis as appropriate (according to national guidelines)
9. Exclude HIV infection & perform HIV testing as appropriate (according to national guidelines) and maintain awareness of possibility of infection based on emerging information

Additional HEU infant management:

10. Identify high-risk HEU infants (poor birth outcomes, symptoms of anemia, impaired growth or neurodevelopment, history of hospitalization) & ensure more regular follow-up and monitoring

Optimal routine child health management

The majority of HEU infants live in settings with high child mortality where all benefit from comprehensive child health interventions such as the WHO integrated management of childhood diseases (IMCI). Management of acute problems is always paramount. HEU infants experience a greater severity of common childhood infections, particularly pneumonia, diarrhea and streptococcal infections specifically group B streptococcus and invasive pneumococcal disease (1,4–7). Active early management of these conditions is essential to prevent severe morbidity and mortality in HEU children.

Due to the risk of HIV transmission via breast milk many infants in less developed countries at high risk of infectious disease morbidity and mortality were denied the benefits of breastfeeding, either through complete replacement with infant formula milk or through an attenuated duration of breast milk exposure to lessen the risk of postnatal HIV transmission. There is a large body of evidence demonstrating how detrimental avoidance of breastfeeding has been to HEU infant health. The current recommendation is for HEU infants to receive exclusive breastfeeding with subsequent appropriate complimentary feeding in the first year of

life combined with prolonged infant or maternal ARV prophylaxis or maternal combination antiretroviral therapy (cART). (8) Clear, consistent infant feeding counseling and support from healthcare providers is essential to reduce postnatal HIV transmission while securing the nutritional and immunologic benefits of breast milk for HEU infants.

There is no clear evidence that HEU children experience impaired growth outside of the consequences of suboptimal infant feeding. However recent concern has developed regarding growth and neurodevelopmental consequences of in utero exposure to some ARVs that will be discussed further below. Being born to an HIV-infected mother increases risk for congenital cytomegalovirus (CMV) and it is important to be alert to the potential delayed neurologic sequelae of congenital CMV such as hearing impairment and neurodevelopmental delay. (9) Routine HEU infant hearing evaluations should be considered in addition to regular anthropometric and developmental milestone assessments.

As a result of deficient transplacental antibody transfer, HEU infants commence life with lower levels of maternally derived antibody than HU infants. (10) HEU infants respond robustly to vaccination though, and it should be ensured that HEU infants receive timeous administration of all routine infant vaccinations according to national schedules. In programs without routine pneumococcal conjugate vaccine, adding this vaccine for HEU and HIV-infected infants should be considered as there is strong evidence that both groups experience greater morbidity and mortality from invasive pneumococcal disease than HU infants. (7) Further routine child health interventions such as regular vitamin A supplementation and antihelminthics will benefit HEU infants and children. HEU infants may be more susceptible to measles infection in the first months of life due to inadequate maternal antibody transfer and measles morbidity as well as pneumonia and diarrhoea morbidity are exacerbated in vitamin A deficiency. Chronic worm infestation can result in stunting, anaemia and mild cognitive deficits in children already possibly at risk for growth and neurodevelopmental impairment due to HIV and ARV exposure.

HEU infants experience high rates of TB exposure in the home, with 10% of HEU infants already exposed to TB by three to four months of age in a South African study. (11) Primary isoniazid preventive therapy in the absence of a known TB contact however did not reduce the risk of TB infection or disease in HEU infants. (12) As in all infants, diligent screening for infectious TB contacts and active management of TB exposed infants at each care encounter is essential to reduce TB disease and its consequences in HEU infants.

Maternal well-being is a central component of improved child health for all children and this is even more so for infants born to an HIV-infected mother. The risk of morbidity and mortality in HEU infants is further increased for infants of mothers with severe immune compromise or who die during their child's infancy. (13) Active enquiry about mother's health, HIV disease and family planning desires should be performed at each child health visit.

Poverty is associated with poor child health outcomes and families living in poverty are more likely to be affected by HIV. Further, HIV affected families are more likely to experience additional vulnerabilities, including loss of earnings, greater expenditure on the direct and hidden costs of healthcare, food insecurity, stigma in the community and the responsibility of caring for children in the extended family or community orphaned by HIV. These circumstances may alter health seeking behaviour and can lead to economic, physical and emotional instability for HIV exposed children, even if HIV-uninfected. Assistance in accessing available social support programs should form part of the comprehensive care of all children and particularly HEU children. Structured disclosure of parental HIV-status to HIV-uninfected children must also be considered when age appropriate.

Optimal routine HIV-exposed infant management

It is vital that effective programs and systems are in place to prevent vertical HIV infection from occurring in utero, during labour and delivery and postnatally during breastfeeding. The WHO now recommends cART for all people diagnosed with HIV irrespective of disease stage. (14) Where this is not yet feasible, pregnant and breastfeeding women should be prioritized. Maternal cART is the most effective means of preventing vertical HIV infection and ensuring the safety of breastfeeding for HIV-exposed infants. (15) Irrespective of the specific local guidelines, at each child health encounter mothers and caregivers should be supported in maintaining optimal adherence to both maternal and infant ARVs through counseling on the need for the ARVs and joint problem-solving with healthcare professionals to overcome challenges with access to, administration of or side-effects experienced from the ARVs. Cotrimoxazole prophylaxis should be provided to all HIV-exposed infants until HIV-infection has been confidently excluded through age-appropriate testing and all HIV-exposure via breastfeeding has ceased. This is to ensure the prevention of pneumocystis pneumonia in infants already HIV-infected but not yet diagnosed with HIV-infection. Prolonged cotrimoxazole prophylaxis provides no additional benefit to HEU infants and should not be continued long-term in HEU infants. (16)

In addition to routine HIV-testing of HIV exposed infants according to national guidelines, HIV infection should be excluded in all HIV-exposed and HIV-unexposed infants with symptoms of HIV or any severe illness including severe pneumonia, diarrhoea, TB, severe acute malnutrition, neurodevelopmental delay and/or microcephaly. A new diagnosis of HIV in a parent or sibling should prompt further testing of all children in the family irrespective of age and the presence or absence of symptoms. In the case of a new diagnosis in a mother, HIV-infection should immediately be excluded in her infant and if breastfeeding postnatal prophylaxis can still be provided to either mother, infant or both. An HIV antibody test can be used to diagnose

HIV in all children over 18 months of age and is also a cost-effective screening test for children under 18 months of age, about 70% of whom would have lost all maternal HIV IgG antibodies by nine months of age. A diagnosis of HIV infection in a child under 18 months of age must be made using an HIV nucleic acid test such as the HIV-DNA-polymerase chain reaction (PCR) test.

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ARV exposure

Coupled with HIV exposure is the inevitable consequence of ARV drug exposure that may begin at conception in mothers already receiving cART or is introduced as soon as maternal HIV-infection is confirmed during pregnancy. (8) Infant ARV exposure continues postnatally by administration to the infants themselves or via breast milk. Although no ARVs used for vertical transmission prevention are clearly teratogenic, there are concerns of negative consequences regarding some drugs. Infants born to HIV-infected mothers compared to those born to HIV-uninfected mothers are more often preterm, small for gestational age (SGA) and of low birth weight (LBW). (17) These poor birth outcomes are associated with increased HEU neonatal and infant mortality. There is growing concern that in-utero ARV exposure, specifically triple cART and possibly protease-inhibitors, are additional determinants of adverse birth outcomes (preterm birth, SGA and LBW) in HEU infants. Women on cART at conception also have double the odds of pre-eclampsia/eclampsia compared to HIV-infected women not on cART at conception, an additional risk for adverse birth outcomes in HIV-exposed infants. (18)

Zidovudine (ZDV) and Tenofovir disoproxil fumarate (TDF) are widely used in vertical transmission prevention programs and clinicians should be aware of their potential consequences. ZDV causes a transient anemia in neonates after in-utero or postpartum exposure. (19) Other hematological aberrations associated with ZDV exposure, include altered neutrophil and platelet count. The clinical significance of these hematological alterations in HEU infants has not been determined. Looking for symptomatic anemia is advised and ZDV should be withdrawn in symptomatic HEU infants still receiving ZDV prophylaxis. Mitochondrial toxicity secondary to ZDV and other nucleoside reverse transcriptase inhibitor exposure has been observed. The clinical significance of these mitochondrial changes is again unclear but has potential for poorer neurodevelopmental outcomes, myocardial aberrations and oncogenic effects. Language and social-emotional development may be affected by in utero Atazanavir exposure, although this is seldom used to prevent vertical transmission. TDF has nephrotoxic effects that, through altered bone metabolism, can result in reduced bone mineral density when used in HIV-infected children. There is concern about in-utero exposure to TDF and its effects on the developing fetal skeletal structure. Reduced neonatal bone mineral density and impaired length growth at six to 12 months of age were observed in TDF exposed infants. (6,20) More recently Lopinavir/ritonavir was implicated in reduced neonatal bone mineral density in the PROMISE trial rather than TDF. (21)

Case reports and animal studies have described neural tube defects following first trimester efavirenz (EFV) exposure. A comprehensive systematic review and meta-analysis found no evidence of birth defects associated with first trimester EFV use, although the numbers were too small to comment specifically on neural-tube defects. (22) Prolonged postnatal nevirapine (NVP), widely used in vertical transmission prevention programs, was safe when used at prophylactic doses up to six months of age in breastfed infants. Although NVP associated rash or hepatotoxicity is infrequent in HEU infants exposed to prophylactic NVP, clinicians should be aware of these complications.

Although optimal prevention of vertical HIV infection is imperative, pharmacovigilance systems are urgently needed in high burden countries to understand the safety of ARV exposure as regimens become more complex and duration of exposure is extended both antenatally and postnatally.

Infectious morbidity

HEU infants are at greater risk for mortality and hospitalization in the first year of life than HU infants. This is largely due to an increased severity of common childhood infections. Studies have observed a greater severity of pneumonia in HEU compared to HU infants, represented by the severity of symptoms and inadequate response to empiric pneumonia treatment. (5,23) HEU infants are also more susceptible to late onset group B streptococcal infection and to a higher rate of mortality from invasive pneumococcal disease. (7,24) Although the neonatal period has the highest absolute risk for mortality for all infants, the greatest relative increase in infectious morbidity and mortality risk in HEU compared to HU infants is during mid-infancy between two to six months of age. (1,2,6) This vulnerability to infectious diseases wanes by two years of age. A small subset of HEU infants appear susceptible to opportunistic infections, occurring in the absence of an identifiable primary or other immune deficiency. Case reports have described HEU infants with pneumocystis pneumonia and CMV pneumonia and colitis.

Challenges in diagnosing infant HIV infection

With advancement of vertical transmission prevention programs and prolongation of infant ARV prophylaxis, establishing a diagnosis of HIV and the optimal timing of testing in infants is now more difficult. The WHO recommended first HIV-PCR test at six weeks of age for all HIV-exposed infants may no longer be appropriate. Twenty percent of perinatally HIV-infected infants die within the first three months of life, and waiting to make the diagnosis at six weeks of age is too late for these infants. Birth HIV-testing is now recommended where feasible to reduce this early mortality in HIV-infected infants. Prolonged infant ARV prophylaxis, even given as a single drug, can temporarily suppress HIV viral replication to give false negative HIV-PCR results during post-exposure

prophylaxis (25). Repeat testing at least four weeks after cessation of all ARV prophylaxis is advised in all HEU infants receiving postnatal prophylaxis. Correlation of the test result with the clinical picture of the infant is essential and HIV-infection should be excluded in all symptomatic HIV-exposed infants regardless of the results or timing of prior testing. There is an urgent need to expand access of affordable virologic HIV tests for early infant HIV diagnosis if the current WHO 90-90-90 (90% of HIV infections diagnosed, 90% of people diagnosed with HIV on sustained antiretroviral therapy and 90% of people on antiretroviral therapy with viral suppression) targets are to be met by 2020.

Conclusion

Providing basic comprehensive child care interventions benefits all HEU and HU infants. For HEU infants, particular attention should be given to preventing vertical transmission and conducting appropriate HIV testing. Clinicians should be aware of the consequences of ARV and HIV exposure on HEU infants. As vertical transmission prevention programs become more sophisticated, there is increasing need for pharmacovigilance and long-term surveillance systems and more affordable infant HIV diagnostic tests.

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