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Mini-Symposium: Maternal Diseases effecting the newborn

# Maternal HIV and Paediatric Lung Health

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## EDUCATIONAL AIMS

- To emphasize the growing number of HIV exposed and uninfected infants (HEU) and the potential impact of HIV exposure on respiratory health in these children.
- To discuss possible mechanisms of lung injury in HEU infants.
- To summarize current knowledge of the impact of maternal HIV on the respiratory health of HEU infants.
- To help the reader appreciate the respiratory health risks of HEU infants in order to inform optimal management and preventive strategies.

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SUMMARY

With improved prevention of mother to child transmission of HIV, paediatric HIV disease is less common. However, the number of HIV exposed but uninfected infants is growing. Exposure to maternal HIV impacts infant respiratory health through an increase in known risk factors such as increased preterm birth and low birth weight, suboptimal breastfeeding, increased psychosocial stressors and increased exposure to infective pathogens. Exposure to the HIV virus and altered maternal immune environment result in immunologic changes in the infant that may contribute to respiratory disease risk. HIV exposed infants are at increased risk for severe pneumonia with poorer outcomes compared to unexposed infants. Maternal ART and optimal nutrition, including breastfeeding in high infective disease burden settings, reduce morbidity and mortality in HIV exposed infants and should be prioritized. The impact of exposure to maternal HIV on normal lung growth and risk for chronic respiratory disease is unknown and warrants further investigation.



## INTRODUCTION

Pregnancy and early life are a critical time for lung development. During this period the lungs are vulnerable to factors that could impair normal lung growth and function with lifelong implications on respiratory health for the individual [1]. Understanding the impact of the antenatal and early life environment on the developing lung is hence key to optimizing respiratory health in childhood through to adulthood. Maternal health is an important factor in healthy fetal development. Maternal HIV infection poses a number of risks for healthy fetal and early life lung development. These include exposure of the fetus to HIV viral proteins, alterations in maternal immunology and exposure to antiretroviral therapy (ART) and other drugs *in utero* and postnatally. In addition, families living with HIV are often challenged with social and environmental factors that further affect lung health. Each year approximately 1.4 million HIV-infected women become pregnant globally [2]. Expanding prevention of mother to child transmission (PMTCT) programs has resulted in marked reductions in the numbers of HIV-infected children born [2]. In the high burden country of South Africa for

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example, 30% of pregnant women are HIV-infected but as a result of a large effective public PMTCT program less than 3% of the 300,000 HIV-exposed South African infants born annually are HIV-infected, 97% being HIV exposed but HIV-uninfected (HEU) [3]. There is growing awareness that this large and expanding population of HEU infants and children may not achieve equivalent child health outcomes to their HIV unexposed (HU) peers, including increased risk of respiratory disease [4]. Moreover childhood respiratory disease remains a major contributor to morbidity and mortality globally, with lower respiratory tract infections (LRTI) a leading cause of death in children under five years [5]. The burden of respiratory illness is particularly high in low-middle income countries, with more than 90% of LRTI related deaths occurring in these areas [6]. Hence understanding the impact of maternal HIV on infant lung health is important if we are to maximize the lung health of this substantial population of HEU infants and reduce the burden of respiratory disease in high prevalence settings. This review summarizes possible mechanisms of lung injury in HEU infants, current knowledge of effects of HIV exposure on infant respiratory health and identifies priority areas for future research. This review does not consider the impact of pediatric HIV infection itself on infant lung health, detailed extensively in previous reviews [7,8].

## POSSIBLE MECHANISMS FOR LUNG INJURY IN HIV EXPOSED BUT UNINFECTED INFANTS

There are numerous potential pathways, particularly antenatally and during infancy, through which greater risk for both infectious and non-infectious lung morbidity could be mediated in HEU infants (Figure 1). These include an increase in factors known to impact lung health in all infants, irrespective of HIV exposure, such as poor birth outcomes (i.e. preterm birth, low birth weight and small for gestational age), suboptimal or no breastfeeding, compromised growth and nutrition, exposure to *Mycobacterium tuberculosis* (M.tb) and other infectious diseases, maternal ill health or death and poverty [4]. Risk factors unique to HIV-exposure may further impact infant respiratory health, including exposure *in-utero* to HIV viral proteins, a maternal pro-inflammatory and/or immune compromised state and exposure to antiretroviral and other drugs both *in utero* and in breast milk [9,10].

## PREMATURITY AND LOW BIRTH WEIGHT

Infants born to HIV-infected mothers are 30% more likely to be preterm and 80% more likely to be small for gestational age (SGA) compared to those born to HIV-uninfected mothers [11]. It is not clear whether these poor birth outcomes are due to direct HIV exposure, *in utero* ART exposure or the effect of additional non-infectious HIV comorbidities such as gestational hypertensive disorders, chronic hypertension and cardiovascular disease, all becoming increasingly important as ART access expands and the infectious complications of HIV are reduced. Being born preterm is associated with decreased lung function at birth that persists through early life and is associated with low lung function and chronic respiratory illness in older children and adults [12]. Even late preterm infants (33-36 weeks gestation) may have reduced early life lung function compared to full term infants [13]. Children and adults who were small at birth have lower lung function and increased risk of respiratory disease and death in later life [14,15]. Given the substantially higher rates of prematurity and impaired fetal growth in HIV-exposed infants, the long term consequences on lung health are of great concern in this population.

## SUBOPTIMAL BREASTFEEDING

Breastfeeding provides important protection against infectious respiratory disease mortality in all children. Suboptimal breastfeeding practice doubles the risk of infant mortality in the first six months of life and increases infant lower respiratory tract infection

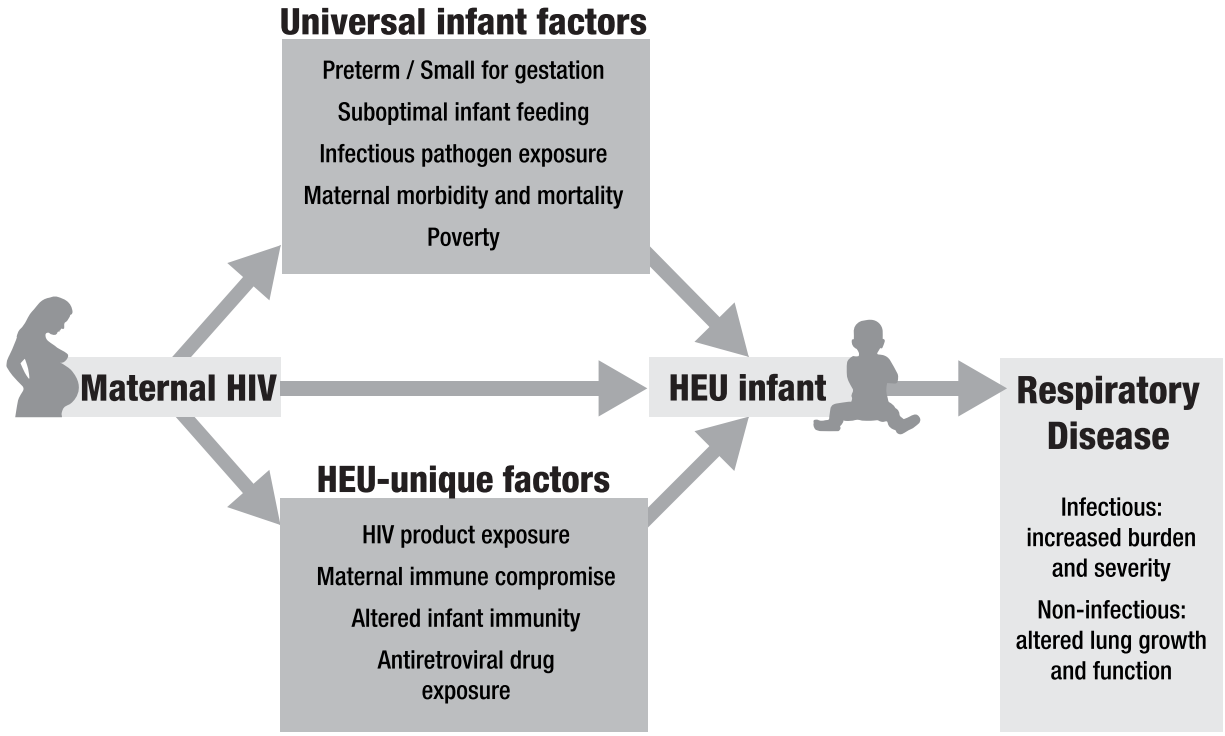


**Figure 1.** Mechanisms of lung injury and vulnerability in HIV exposed uninfected infants.