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# Maternal HIV Infection Alters Antimicrobial Immunity in Exposed and Uninfected Infants

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The widespread use of antiretroviral therapy (ART) in pregnant women has markedly reduced the incidence of pediatric HIV infections worldwide. With the recent implementation of lifelong ART for all HIV-infected women, regardless of their CD4 T cell count, an increasing number of women conceive while receiving ART.<sup>1</sup> Specifically, 1.3 million women living with HIV become pregnant every year and about 80% of them receive ART. As a result, the number of children who are HIV-exposed but uninfected (CHEU) is steadily increasing to an esti-

mated 15 million, and 90% of them live in Sub-Saharan Africa.<sup>2</sup>

CHEU were initially considered to be at similar risk of medical complications than children not exposed to HIV in utero. However, during the past 15 years, studies have consistently revealed that maternal HIV infection is associated with an increased risk of infectious diseases, particularly during the first months of life (reviewed in references 3 and 4). CHEU present with more severe infections, are more often hospitalized for infections, have more frequent treatment failures, and in low- and middle-income countries (LMIC), have higher mortality due to infectious pathogens than infants born to mothers not infected with HIV. Severe infections are caused by a large diversity of infectious pathogens, including bacteria, viruses and parasites.<sup>3</sup>

The increased vulnerability of CHEU to infectious diseases could involve genetic risk factors, including prematurity, suboptimal breastfeeding, maternal mortality and poor socioeconomic conditions, and could also be related to risk factors unique to maternal HIV infection. In studies conducted in LMIC before ART was widely available for pregnant women, high maternal viral load and low CD4 counts were consistently associated with increased infectious morbidity and mortality in CHEU, supporting the notion that maternal HIV disease is a central determinant of infant susceptibility to infectious pathogens.<sup>3</sup> However, even after the implementation of ART during pregnancy in LMIC and high-income countries, CHEU

remained at a higher risk of severe infections as compared with unexposed children.<sup>3</sup>

The persistence of an increased risk could have been related to (1) inadequate control of maternal HIV infection by ART; (2) an adverse effect of infant exposure to ART during fetal life, or a combination of these factors. Recent studies suggest that the duration of maternal ART is a critical determinant of the health of CHEU. In a prospective study in Belgium, we observed that CHEU had a 2-fold increased risk of hospitalization for infections during the first months of life compared with infants who were HIV-unexposed.<sup>4</sup> Importantly, most of this increased risk could be attributed to the time of initiation of maternal ART. Specifically, compared with infants not exposed to HIV, the risk of hospitalization for infection of CHEU was 4-fold higher when mothers initiated ART during pregnancy but was not increased when ART was initiated before pregnancy.

Similar findings were reported from LMIC in a recent survey of 8 Sub-Saharan countries (<https://phia.icap.columbia.edu>). Saito<sup>5</sup> observed that CHEU born to women who initiated ARV before conception have a higher rate of survival during the first 3 years of life than those who are born to women who start on ARV during pregnancy. Together, these observations suggest that control of maternal HIV replication before conception positively impact the health of children born to women living with HIV beyond the prevention of vertical transmission.

The correlation between the control of maternal HIV replication and the vulnerability of CHEU to infectious diseases

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strongly suggests that HIV infection induces perturbations of the maternal environment that result in reduced antimicrobial immune defenses in the young infant. As severe infections in CHEU are caused by multiple pathogens, this likely affects a range of immune effector functions. Physiologically, multiple maternal immune factors are transferred across the placenta and in breast milk to provide passive immunity against a wide diversity of pathogens during the first months of life and to promote the development of innate immune defenses.<sup>6</sup>

The best characterized maternal immune factor transferred to the newborn is antibodies. From midgestation, maternal IgG is actively transferred across the placenta by receptors binding its crystallizable fragment. This process is selective and favors IgG carrying specific glycans at the crystallizable fragment and preferentially stimulating specific innate immune responses.<sup>7,8</sup> Multiple studies have shown that the transplacental transfer of maternal IgG is reduced by maternal HIV infection. The mechanism underlying this reduction is not established and could involve: (1) the saturation of placental receptors by the hypergammaglobulinemia that is commonly observed in pregnant women living with HIV; (2) alterations of IgG glycosylation profiles reducing their affinity for the placental receptors (3) alterations in the expression or function of the placental receptors, or a combination of these factors. Our recent studies indicate that time of initiation of ART significantly impact the transfer of maternal antibodies.<sup>4</sup> Pregnant women on preconception ART transferred antibodies to their newborn at higher rates than women who initiated ART during pregnancy. A second important immune perturbation induced by maternal HIV infection in CHEU is activation of innate immune cells.<sup>9,10</sup> Several studies conducted in different populations of CHEU detected high levels of soluble and cellular markers of innate immune activation at birth and during the first weeks of life. The mechanism underlying this state of immune activation is still unclear. Similar to the reduction in maternal antibody transfer, we observed that

immune activation was highest in newborns of mothers who initiated ART during pregnancy as compared with before pregnancy.<sup>4</sup> The level of activated innate immune cells in the newborns correlated with that of their mother, suggesting transplacental transfer of molecules promoting inflammatory responses across the placenta. The nature of these stimuli remains to be elucidated but may include maternal metabolites and/or microbial products derived from the maternal microbiome altered by HIV infection.<sup>11</sup>

Most studies documenting immune perturbations in CHEU included relatively small sample sizes and did not include clinical outcomes.<sup>3,9</sup> In CHEU born in Belgium, the most intense immune perturbations, that is, reduced maternal antibody transfer and innate immune activation, were observed in CHEU who were at highest risk of severe infections.<sup>4</sup> Data modeling revealed that immune parameters measured at birth were highly predictive of the risk of hospitalization for infection during the first months of life. In a recent study of CHEU in Brazil, a significant association was also observed between higher levels of soluble tumor necrosis factor receptor II at birth and the risk of lower respiratory infections in the first 6 months of life.<sup>10</sup> These observations support the notion that maternal HIV infection induces immune perturbations in the uninfected newborn that could be causally related to an increased susceptibility to severe infections during the first months of life. Furthermore, they suggest that implementation of lifelong ART of all HIV-infected women, regardless of their CD4 T cell count, has the potential to improve maternal determinants of protective immunity in the young infant.<sup>1</sup> Given the tremendous implications of these notions for the health of millions of infants worldwide, studies should be conducted to assess whether initiation of ART before conception has the same impact on the immune fitness of CHEU born in countries with high rates of maternal HIV infection and pediatric infectious diseases and where breast-feeding is promoted.<sup>3,12</sup> Addressing these knowledge gaps in multiple populations would take us

one step further in reducing the burden of the HIV epidemic on pediatric populations. This knowledge likely will also increase insight into the basic mechanisms of host protection from infection in early life beyond HIV.

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