**Editorial comment: Dysbiosis and immune dysregulation: distilling the evidence**

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Globally, approximately 1.3 million women living with HIV gave birth in 2021 and 81% received antiretroviral therapy (ART) to prevent mother-to-child transmission (MTCT) [1]. While many countries have eliminated MTCT, countries with the largest epidemics, such as South Africa, are yet to reach this target. Consequently, ±160,000 new HIV infections occurred among children under the age of five years in 2021 [2]. Children living with HIV continue to have increased morbidity and mortality, despite the great advances that have been made in HIV care. In addition, many studies, although not all, have reported that children with perinatal exposure to HIV have suboptimal clinical and developmental outcomes, even when they themselves are HIV-uninfected [3]. The mechanisms regulating these poor outcomes are still poorly understood and are likely multi-factorial, including socio-economic conditions, greater exposure to co-pathogens, HIV- or ART-induced immunological and metabolic aberrations, and sub-optimal nutrition [3]. The importance of the microbiome in this context is gradually becoming clearer.

The microbiota (bacteria, archaea, fungi, and viruses) and their evolution in a particular habitat (collectively termed the microbiome) play essential roles as regulators of functional processes. However, very little is known regarding the precise mechanisms by which they exert these effects and whether the results may be directly applicable to human health. Recent studies suggest that the microbiome may play a pivotal role in regulating the health of people living with HIV [4]. Amongst other functions, gut microbiota are essential for immune homeostasis. Disruptions, such as those induced by HIV infection, may precipitate gut dysbiosis, chronic mucosal inflammation, and compromised epithelial integrity with subsequent microbial translocation and systemic inflammation [4]. Disruption of the gut microbiota and its consequences are, however, still poorly explored in the setting of perinatal HIV exposure.

In their article, *Gut-Dependent Inflammation and Alterations of the Intestinal Microbiota in Individuals with Perinatal HIV Exposure and Different HIV Serostatus*, Tincati *et al.* [5] compared the blood and faecal microbiome as well as markers of gut damage, microbial translocation, and immune activation/inflammation in infected (HEI) and exposed (HEU) children over the age of one year. Despite having similar microbiota profiles in plasma and faeces, differences were observed in faecal beta-diversity and relative abundance. HEI children appear to have an immunological profile indicative of higher monocyte activation and inflammation. One of the inflammatory biomarkers, interleukin-6 (IL-6), has been associated with an increased risk of mortality in HEI children, independently of $CD4^+$ T-cell count [6]. This profile was observed despite HEI having similar levels of markers of intestinal damage and microbial translocation than HEU children. The underlying causes of this inflammatory profile are therefore unclear.

Overall, this study provides some insights regarding the differential effects of HIV exposure on children who end up being HIV-infected or uninfected. The observation of a faecal microbiota profile with anti-inflammatory properties in the gut of HEI children is of particular interest, especially in conjunction with the finding of equivalent intestinal damage profiles to HEU. It is, however, important to note that this study primarily relied on 16S

rRNA gene amplicon sequence data and quantitative PCR and the results should therefore be interpreted with some caution. For instance, as evidenced by results in other systems, the functional roles of microbiota cannot be inferred based on 16S rRNA gene amplicons [7]. Moreover, without transcriptomic evidence, interpretations based on fluctuations in the abundances of certain phyla might lead to spurious conclusions. In this case, the differences may not necessarily be due to the disease state but could be due to other factors which are known to alter gut microbiota [8]. In addition, the lack of an HIV unexposed control group limits the interpretation of these findings and precludes speculation about 'normalisation' of the microbiota and gut epithelium in HEI children on ART.

Finally, given the differences observed in the faecal microbiota of developed and developing countries, as well as urban and rural areas [9], more work is needed to describe and assess the impact of different faecal microbiomes in children exposed to HIV, regardless of their serostatus. These datasets, together with additional longitudinal and mechanistic studies, will ultimately result in more accurate interpretations of the importance of gut microbiota.

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