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EDITORIAL COMMENTARY

BCG Vaccination and Mother-to-Infant Transmission of HIV

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(See the Major Article by Wood et al., on pages 44–53.)

Children born to human immunodeficiency virus (HIV)–infected mothers have a 15%–45% risk of becoming HIV infected [1]. Mother-to-infant transmission (MTIT) of HIV may occur in utero, during the intrapartum period, or during the postpartum period (through breastfeeding) [2]. In recent years, with an increasing number of HIV-infected women gaining access to antiretroviral therapy (ART), breastfeeding has become the key contributor to MTIT [3]. In 2017, 180 000 new cases of HIV infection were reported to occur in children born to HIV-infected mothers worldwide [4].

The United States has virtually eradicated breastfeeding-associated HIV transmission (ie, rates of breastfeeding-associated transmission have decreased to <5%) through multiple interventions, including administration of ART to HIV-infected mothers and their infants, elective cesarean section for women at term with persistent plasma viral loads, and complete replacement of breastfeeding regardless of ART use and maternal plasma viral suppression [2]. The World Health Organization (WHO) estimates that using similar interventions on a global scale will result in the virtual eradication of breastfeeding-associated HIV transmission. Yet in resource-limited settings with limited access to clean water and affordable infant feeding replacement formula, it is considered that the benefits of breastfeeding for children born to HIV-infected mothers outweigh the risks of HIV transmission, and as such, the WHO recommends that HIV-infected mothers breastfeed their infants for 12 months, with exclusive breastfeeding for the first 6 months [5]. This approach would demonstrably reduce malnutrition, diarrhea, and respiratory illnesses that frequently occur in infants with replacement feeding, owing to contaminated water and a lack of receipt of protective maternal antibodies through breast milk [5].

In these situations, in which HIV-infected mothers receiving ART are allowed to breastfeed, it is imperative that the risks of HIV transmission are minimized. ART administration to lactating mothers will suppress the virus and dramatically reduce the risk of transmission. Conversely, increased transmission may occur in the context of oral infections of the infant that alter the integrity of the oral mucosal barrier [6]. Furthermore, increased oral inflammation may also increase transmission, through either induction of lesions and/or an increased frequency of target cells (ie, activated memory $CD4^+$ T cells expressing the HIV coreceptor CCR5) at the mucosal sites. This aspect is particularly important, as suggested by the study of the natural hosts of simian immunodeficiency virus (SIV; African green monkeys, sooty mangabeys, and mandrills). In these species, a virtually nonexistent MTIT associates and appears to be determined by a very low expression of CCR5 on memory $CD4^+$ T cells, as well as an overall low frequency of memory $CD4^+$ T cells themselves at the mucosal sites [7–9]. Additionally, target cell availability at the mucosal sites dictates susceptibility to SIV transmission in the natural hosts, including transmission via breastfeeding [7, 10].

It thus appears necessary to strictly control the clinical circumstances of mucosal inflammation and the resulting increase in target cells at oral mucosal sites of infants breastfed by HIV-infected mothers. One of these circumstance is vaccination, which has been reported to increase HIV target cells at mucosal sites [11]. Vaccination is frequent in the first 6 months of life (when children are exclusively breastfed), a period during which, based on the WHO recommendations for routine immunizations, children are vaccinated against 9 different infections, receiving approximately 19 doses of vaccines at 4 different time points [12]. One of the earliest vaccines administered is the BCG vaccine, for the prevention of tuberculosis. BCG vaccination is recommended by the WHO and is included in most national immunization programs worldwide (at least 153 countries currently have a universal national BCG vaccination policy) [13]. BCG vaccine is particularly important in the context of HIV infection, as the areas with a high incidence of tuberculosis and HIV infection generally overlap. This is the case in sub-Saharan Africa, where nearly 80% of HIV and *Mycobacterium tuberculosis* coinfections occur [14]. In these areas,

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BCG vaccination is critical because, should children born to HIV-infected mothers become HIV infected, they are at a higher risk of acquiring mycobacterial infection and developing active, more severe tuberculosis as compared to HIV-uninfected children [14]. Furthermore, in HIV-infected children, tuberculosis may increase immune activation, accelerating HIV disease progression [15].

BCG vaccination results in a marked reduction in overall infant mortality rates [16], as well as a dramatic reduction of the risk for miliary tuberculosis and tuberculous meningitis [17]. In addition, BCG vaccination can also protect against leprosy and other nontuberculous mycobacterial pathogens [17]. Finally, by preventing tuberculosis and thus limiting the increases in immune activation that can be induced by tuberculosis, BCG vaccination may improve the clinical outcome of HIV infection [18].

The WHO recommends a universal single dose of BCG vaccine at birth in settings with a high tuberculosis and/or leprosy burden. Countries with low rates of tuberculosis and/or leprosy may choose selective vaccination in high-risk groups. For neonates born to mothers with an unknown HIV status and neonates with an unknown HIV status born to HIV-infected mothers (regardless of their ART status), the WHO recommends BCG vaccination, as the benefits outweigh the risks. For a neonate confirmed by virologic testing to be positive for HIV, it is recommended that BCG vaccination be delayed until ART has been started [12].

Whether BCG vaccination is safe in children who are born to HIV-infected mothers and exposed to HIV through breastfeeding is still the subject of intensive debate. Similar to tuberculosis, BCG vaccination results in increased immune activation and expression of inflammatory cytokines [15], which can amplify the risk of HIV infection and disease progression [19]; these are considered reasons in favor of changes in the current recommendations. Also supporting caution for BCG vaccination in children exposed to HIV through breastfeeding are the results of multiple in vitro and ex vivo studies in which BCG vaccination caused sustained elevation of HIV target cells in humans, which may increase the susceptibility to HIV infection in HIV-exposed infants [15, 20–22]. However, these ex vivo studies cannot provide evidence as to whether this increase in HIV target cells caused by BCG vaccination is sufficient to significantly increase the risk of HIV acquisition in exposed infants.

This very important question is elegantly addressed in a very exciting study by Wood et al in this issue of *The Journal of Infectious Diseases* [23]. To assess the impact of intradermal BCG vaccination on MTIT of HIV, Wood et al performed standard BCG vaccination of infant rhesus macaques, whose response to intradermal BCG vaccination is comparable to that of humans [24]; starting 3 weeks after vaccination, they administered multiple oral SIV challenges, thereby recapitulating infant exposure to HIV through breastfeeding [23]. When they compared the rates of oral transmission of SIV between BCG-vaccinated and unvaccinated rhesus infants, they did not observe any clear influence of BCG vaccination on SIV transmission [23]. As such, they concluded that BCG vaccination does not alter the rate of SIV transmission or disease progression [23], providing a definitive answer to a very important and clinically relevant question and supporting the administration of BCG vaccine to breastfed children born to HIV-infected mothers.

One of the alterations in the BCG vaccination strategy to further reduce its deleterious effects on the susceptibility to and outcome of HIV infection in children could involve delaying administration of the vaccine, to enable HIV testing and control in newborns and infants. This delay is supported by the results of a clinical trial by Tchakoute et al, showing that deferred BCG vaccination does not compromise its ability to induce BCG-specific T-cell responses [19]. With continued attempts to improve the efficacy of BCG vaccination [25], such studies should further optimize BCG vaccination in HIV-exposed infants. For children in whom HIV transmission has occurred, such a delay would permit not only confirmation of HIV infection status, but also initiation of ART before vaccination, thus avoiding the issues related to immune reconstitution inflammatory syndrome (IRIS), a paradoxical worsening of a previously treated infection or exacerbation of a subclinical infection following initiation of ART by HIV-infected patients [26]. Among HIV-infected infants in South Africa, IRIS induced by BCG vaccination is one of the most common forms of IRIS [26], causing considerable morbidity. ART initiation before BCG vaccination or clinical manifestations of HIV infection could dramatically reduce the risk of IRIS [27].

The study by Wood et al reaffirms the necessity of using nonhuman primate models to directly assess the impact of immune interventions on the outcome of a given infection in humans. This study points out that, while important as a first step in characterizing pathogen-host interactions, the surrogate in vitro or ex vivo models have limitations for the study of in vivo pathogenesis. Because experiments of virus transmission are prohibited in humans, animal studies in adequate models tailored for the questions addressed are unavoidable. As such, a parallel can be drawn between permitting breastfeeding by infants born to HIV-infected mothers and studying nonhuman primates to assess the impact of vaccines on HIV transmission: they are both imperfect solutions and heavily criticized and are not without ethical limitations. Yet in both cases, the benefits largely outweigh the drawbacks. And so, for pathogen transmission and vaccine studies, animal models are here to stay.

Note

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