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Markers of Immune Activation in HIV-Exposed Infants

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Abstract

HIV-exposed infants represent a vulnerable population characterized by early exposure to HIV antigens, which profoundly influences immune development and function. This review explores key immune activation markers in HIV-exposed infants, focusing on their role in innate and adaptive immune responses, clinical implications, and therapeutic interventions. Innate immune activation markers, including soluble CD14 (sCD14) and pro-inflammatory cytokines such as IL-6 and TNF-α, reflect heightened monocyte/macrophage activation and systemic inflammation in HIV-exposed infants. Elevated sCD14 levels correlate with microbial translocation and are associated with increased disease severity and immune dysfunction. Dysregulated cytokine profiles contribute to chronic immune activation, impairing immune responses and potentially predisposing infants to opportunistic infections. Adaptive immune activation markers, notably CD38 expression on T cells, serve as sensitive indicators of T cell activation and disease progression in HIV-exposed infants. Increased CD38 expression on CD8+ T cells is associated with heightened viral replication and decreased CD4+ T cell counts, underscoring its role in predicting clinical outcomes and guiding antiretroviral therapy (ART) initiation. Monitoring CD38 expression facilitates early diagnosis of HIV infection, assesses treatment responses, and helps tailor ART regimens to optimize viral suppression and immune reconstitution.

Keywords: *HIV, immune activation markers, CD38, sCD14, cytokines*

Introduction

HIV infection continues to be a significant global health challenge, particularly affecting vulnerable populations such as infants exposed to the virus through vertical transmission. Perinatal transmission remains a predominant mode of HIV acquisition in infants, occurring during pregnancy, childbirth, or breastfeeding. While effective prevention strategies, including maternal antiretroviral therapy (ART) and avoidance of breastfeeding in resource-rich settings, have reduced transmission rates, a substantial number of infants worldwide continue to be exposed to HIV antigens early in life.[1-2] Early exposure to HIV antigens profoundly influences immune development in infants, shaping innate and adaptive immune responses from the outset. The

developing immune system faces a unique challenge in infants exposed to HIV, balancing the need to mount effective immune responses against viral antigens while avoiding immune hyperactivation that could lead to chronic inflammation and immune dysfunction. Immune activation markers play a pivotal role in this context, serving as sensitive indicators of immune system activation and inflammation levels.[3] Innate immune activation in HIV-exposed infants involves a cascade of events triggered by viral antigens interacting with innate immune cells such as monocytes, macrophages, and dendritic cells. These cells respond to viral stimuli by releasing pro-inflammatory cytokines and chemokines, contributing to systemic inflammation and immune activation. Elevated levels of soluble markers like sCD14, indicative of monocyte/macrophage activation and microbial translocation, underscore the extent of immune dysregulation and its potential impact on disease progression. Dysregulated innate immune responses may compromise the infant's ability to mount effective early defenses against HIV and other pathogens, highlighting the need for detailed exploration of these markers in clinical settings.[4-5]

Adaptive immune activation markers, particularly CD38 expression on T cells, provide further insights into immune dysregulation and disease progression in HIV-exposed infants. CD38, a surface marker associated with T cell activation, is upregulated in response to HIV antigens and correlates with viral replication and CD4+ T cell depletion. Monitoring CD38 expression helps predict disease severity, guide ART initiation, and assess treatment responses in infected infants.[6] Markers of immune activation not only serve as diagnostic and prognostic tools but also offer potential targets for therapeutic interventions in HIV-exposed infants. Strategies aimed at modulating immune activation pathways, such as immune modulatory therapies and anti-inflammatory agents, complement ART by reducing chronic inflammation and preserving immune function. The clinical implications of immune activation markers extend beyond immediate treatment decisions to include long-term health outcomes and the prevention of immune-mediated morbidities in exposed infants. This comprehensive approach underscores the importance of integrating immune activation markers into routine clinical care to optimize pediatric HIV management strategies.[7-8] Maternal factors, including maternal HIV viral load, ART use during pregnancy, and breastfeeding practices, significantly influence immune activation markers in HIV-exposed infants. Maternal viral load directly impacts the level of viral exposure and subsequent immune activation in the infant. ART administered during pregnancy reduces maternal viral load and decreases transmission risk but may also influence fetal immune development and alter immune activation profiles. Breastfeeding, while beneficial for infant nutrition and immune development, introduces additional complexities regarding viral exposure and immune activation, necessitating careful consideration in clinical management strategies.[9-10]

Innate Immune Activation Markers

Innate immune activation markers in HIV-exposed infants provide critical insights into the initial response to viral exposure and subsequent immune dysregulation. This aspect of immune activation encompasses various cellular and soluble markers that reflect the activation status of innate immune cells, including monocytes, macrophages, dendritic cells, and natural killer (NK) cells. [11] One prominent marker of innate immune activation in HIV-exposed infants is soluble CD14 (sCD14), a glycoprotein released by activated monocytes and macrophages. Elevated levels

of sCD14 in plasma serve as a biomarker of monocyte/macrophage activation and microbial translocation, reflecting systemic immune activation and inflammation (Marchetti et al., 2011). In HIV-infected adults and children, increased sCD14 levels are associated with disease progression, immune dysfunction, and heightened risk of non-AIDS-related morbidities. In infants exposed to HIV, elevated sCD14 levels may indicate early immune dysregulation and could potentially predict the risk of subsequent complications if left unmanaged.[12-13] Pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β), also serve as key innate immune activation markers in HIV-exposed infants. These cytokines are produced by innate immune cells in response to viral antigens and play critical roles in initiating and amplifying immune responses. Elevated levels of these cytokines contribute to chronic immune activation, systemic inflammation, and tissue damage, which are characteristic features of HIV pathogenesis. Dysregulated cytokine production in exposed infants may impair immune responses, exacerbate viral replication, and contribute to immune-mediated pathologies.[14-15]

Furthermore, the activation status of dendritic cells (DCs), crucial antigen-presenting cells that bridge innate and adaptive immunity, is a significant marker of immune activation in HIV-exposed infants. DCs capture and process viral antigens, presenting them to T cells to initiate adaptive immune responses. In HIV infection, DCs undergo phenotypic changes and functional alterations that impact their ability to stimulate effective T cell responses. Dysfunctional DCs in exposed infants may impair the generation of protective immune responses against HIV and other pathogens, highlighting the importance of assessing DC activation markers in understanding immune competence and vulnerability in this population.[16-17] Innate immune activation markers not only provide insights into the early immune response to HIV but also offer opportunities for therapeutic intervention. Strategies aimed at modulating innate immune activation pathways, such as targeting cytokine signaling or enhancing DC function, hold promise for mitigating immune dysregulation, reducing viral reservoirs, and improving immune responses in HIV-exposed infants. Integrating these markers into clinical practice allows for early identification of immune dysfunction and facilitates personalized management approaches aimed at optimizing immune health and long-term outcomes in this vulnerable population.[18-19]

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Clinical Implications

The clinical implications of immune activation markers in HIV-exposed infants are multifaceted, encompassing diagnostic, prognostic, and therapeutic considerations that shape management strategies and improve patient outcomes. These markers serve as pivotal tools for clinicians to assess immune status, monitor disease progression, guide treatment decisions, and optimize care in this vulnerable population.[31] Firstly, immune activation markers, such as CD38 expression on T cells and levels of soluble immune factors like sCD14, play a crucial role in early diagnosis of HIV infection in exposed infants. Elevated CD38 expression on CD8+ T cells is indicative of ongoing viral replication and immune activation, providing a sensitive marker for identifying infants who may benefit from early initiation of antiretroviral therapy (ART) to suppress viral replication and preserve immune function. Similarly, elevated sCD14 levels reflect monocyte/macrophage activation and are associated with microbial translocation, systemic inflammation, and disease progression in HIV-infected individuals. Monitoring these markers facilitates timely diagnosis of HIV infection in exposed infants, enabling prompt initiation of ART and potentially reducing the risk of long-term complications.[32-35]

Secondly, immune activation markers serve as prognostic indicators of disease progression and predictors of clinical outcomes in HIV-exposed infants. Elevated CD38 expression on T cells correlates with faster disease progression, decreased CD4+ T cell counts, and increased

susceptibility to opportunistic infections. Monitoring changes in CD38 expression over time helps assess treatment responses and predict the likelihood of achieving viral suppression and immune recovery with ART. Similarly, levels of pro-inflammatory cytokines such as TNF-α and IL-6 provide insights into the extent of immune activation and inflammation, which are linked to disease severity and non-AIDS-related morbidities. Identifying infants at higher risk of immune dysfunction based on these markers allows clinicians to tailor monitoring strategies and therapeutic interventions to optimize outcomes and reduce morbidity.[36-39] Furthermore, immune activation markers guide therapeutic decisions and strategies aimed at mitigating immune dysregulation and improving long-term health outcomes in HIV-exposed infants. Early initiation of ART based on immune activation markers helps suppress viral replication, preserve immune function, and prevent immune-mediated complications such as HIV-associated neurocognitive disorders and cardiovascular disease. Targeting immune activation pathways with adjunctive therapies, such as anti-inflammatory agents or immunomodulatory treatments, complements ART by reducing chronic inflammation and restoring immune homeostasis. Comprehensive management strategies that integrate immune activation markers into clinical practice facilitate personalized care approaches tailored to individual patient needs, optimizing therapeutic outcomes and improving quality of life for HIV-exposed infants.[40-44]

Impact of Maternal Factors

The impact of maternal factors on immune activation in HIV-exposed infants is substantial and multifaceted, influencing both the initial immune response to HIV exposure and long-term outcomes in these vulnerable individuals. Maternal factors encompass a range of variables, including maternal HIV viral load, maternal immune status, antiretroviral therapy (ART) use during pregnancy, mode of delivery, and breastfeeding practices, all of which significantly shape the infant's immune environment and susceptibility to HIV infection.[45] Maternal HIV viral load is a critical determinant of vertical transmission risk and directly influences the level of fetal and neonatal exposure to HIV antigens. Higher maternal viral loads increase the likelihood of intrauterine and intrapartum transmission, leading to higher levels of HIV exposure in the infant's blood and tissues. Increased viral exposure initiates a cascade of immune responses in the developing fetus or neonate, triggering innate and adaptive immune activation pathways that may impact immune maturation and predispose the infant to immune dysfunction later in life.[46-47] Maternal immune status, particularly the presence of HIV-specific antibodies and cellular immune responses, also influences immune activation in HIV-exposed infants. Maternal antibodies, transferred across the placenta or through breast milk, provide passive immunity against HIV and other pathogens, potentially modulating initial viral replication and immune activation in the infant. Conversely, maternal immune dysfunction, characterized by impaired T cell responses or defective antibody production, may compromise maternal-fetal immune interactions and increase the risk of vertical transmission and immune dysregulation in the infant.[48-49]

Antiretroviral therapy (ART) administered during pregnancy is a cornerstone of preventing mother-to-child transmission (PMTCT) of HIV and significantly impacts immune activation in exposed infants. Effective ART suppresses maternal viral load, reducing the level of viral exposure to the fetus and decreasing the likelihood of vertical transmission. By lowering viral replication

rates, ART minimizes the intensity of immune activation in infants exposed to HIV antigens, potentially mitigating early immune dysfunction and improving long-term immune outcomes. However, the effects of in utero ART exposure on fetal immune development and subsequent immune activation profiles in exposed infants require further investigation to optimize PMTCT strategies and ensure optimal infant health.[50-51] The mode of delivery, whether vaginal delivery or cesarean section, also influences immune activation in HIV-exposed infants. Vaginal delivery exposes the infant to maternal vaginal and cervical fluids potentially containing HIV, whereas elective cesarean section reduces exposure during childbirth, lowering the risk of vertical transmission. Differences in microbial colonization and immune priming at birth may impact the infant's initial immune responses and subsequent immune activation patterns. Understanding the immunological consequences of delivery mode is crucial for optimizing PMTCT strategies and minimizing the risk of early immune dysregulation in HIV-exposed infants.[52-53] Breastfeeding practices represent another critical maternal factor influencing immune activation in HIV-exposed infants. Breast milk provides essential nutrients, growth factors, and passive immunity through maternal antibodies and cytokines, contributing to infant immune development and protection against infections. However, breastfeeding also poses a risk of postnatal HIV transmission if maternal viral load is not effectively suppressed or if antiretroviral prophylaxis is not administered to the infant. Balancing the benefits of breastfeeding with the risk of HIV transmission requires individualized counseling and support to promote safe breastfeeding practices while minimizing viral exposure and immune activation in HIV-exposed infants.[54-55]

Therapeutic Strategies

Therapeutic strategies aimed at mitigating immune activation in HIV-exposed infants are critical for optimizing health outcomes and reducing the long-term burden of HIV-associated morbidities. These strategies encompass a range of approaches targeting both innate and adaptive immune activation pathways, with the goal of preserving immune function, reducing viral reservoirs, and improving overall quality of life in this vulnerable population.[56]

Antiretroviral Therapy (ART): Early initiation of ART is the cornerstone of therapeutic management in HIV-exposed infants. ART suppresses viral replication, reduces HIV-associated immune activation, and preserves immune function by maintaining adequate CD4+ T cell counts and suppressing viral load. Initiating ART soon after birth or as soon as HIV infection is confirmed optimizes treatment outcomes, prevents disease progression, and minimizes the risk of opportunistic infections and immune-mediated complications. Continuous adherence to ART is crucial to achieving sustained viral suppression and improving long-term health outcomes in exposed infants.[57]

Immune Modulatory Therapies: Adjunctive therapies targeting immune activation pathways represent promising approaches to complement ART in HIV-exposed infants. Strategies aimed at modulating innate immune responses, such as inhibitors of pro-inflammatory cytokines (e.g., TNF-α blockers) or agents targeting monocyte/macrophage activation (e.g., anti-CD14 antibodies), aim

to reduce chronic inflammation and mitigate immune dysfunction. Similarly, interventions enhancing regulatory T cell function or promoting immune tolerance may help restore immune balance and prevent immune-mediated pathologies in exposed infants.[58]

Anti-inflammatory Agents: Given the role of inflammation in driving immune activation and disease progression in HIV-exposed infants, anti-inflammatory agents have been explored as potential therapeutic options. Agents targeting inflammatory cytokines or pathways, such as IL-6 or NF-κB inhibitors, aim to dampen excessive immune responses and reduce tissue damage associated with chronic inflammation. These agents may offer adjunctive benefits when used in combination with ART, particularly in infants with persistent immune activation or inflammatory conditions.[59]

Nutritional and Supportive Interventions: Optimal nutrition and supportive care play integral roles in enhancing immune function and overall health outcomes in HIV-exposed infants. Adequate nutrition supports immune development and function, reduces susceptibility to infections, and promotes growth and development. Nutritional supplementation with essential vitamins, minerals, and micronutrients may help mitigate the impact of HIV on immune responses and improve treatment outcomes. Comprehensive supportive care, including psychosocial support for caregivers and early childhood development interventions, also contributes to overall well-being and resilience in exposed infants.[60]

Vaccination Strategies: Vaccination remains a critical component of pediatric HIV care, aiming to protect against vaccine-preventable infections and enhance immune responses in HIV-exposed infants. Early administration of routine childhood vaccines and timely catch-up immunizations, guided by immune activation markers and ART status, helps build protective immunity and reduce the risk of infectious complications. Strategies to optimize vaccine responses in HIV-exposed infants, such as vaccine adjuvants or booster doses, are areas of ongoing research to improve vaccine efficacy and durability.[61]

Behavioral and Psychosocial Support: Addressing psychosocial factors and promoting adherence to therapeutic regimens are essential for optimizing treatment outcomes in HIV-exposed infants. Comprehensive care models that integrate behavioral interventions, caregiver education, and peer support programs enhance treatment adherence, reduce stigma, and promote holistic well-being in affected families. Supporting caregivers in navigating complex treatment regimens and promoting positive health behaviors contributes to sustained viral suppression and improved quality of life for exposed infants.[61]

Future Directions

Future directions in the management of immune activation in HIV-exposed infants focus on advancing our understanding of immune pathogenesis, optimizing therapeutic strategies, and improving long-term health outcomes. Key areas of research and innovation include:

1. Novel Biomarkers and Diagnostic Tools: Developing sensitive and specific biomarkers of immune activation in HIV-exposed infants is essential for early diagnosis, monitoring disease progression, and assessing treatment responses. Advances in omics technologies, including genomics, proteomics, and metabolomics, hold promise for identifying novel biomarkers that reflect immune activation pathways and predict clinical outcomes. Integration of these biomarkers into clinical practice may enhance diagnostic accuracy, guide personalized treatment approaches, and improve long-term prognosis.[57]

2. Immune Modulation and Therapeutic Targets: Investigating novel therapeutic targets and immune modulation strategies is crucial for optimizing treatment outcomes in HIV-exposed infants. Targeting specific immune activation pathways, such as inflammasome activation or gut microbiota modulation, may offer new avenues to reduce chronic inflammation, preserve immune function, and enhance viral suppression. Advances in immunotherapy, including immune checkpoint inhibitors and engineered T cell therapies, hold potential for restoring immune homeostasis and achieving functional HIV cure in exposed infants.[58]

3. Personalized Medicine Approaches: Implementing personalized medicine approaches tailored to individual immune profiles and genetic susceptibilities is a priority for improving treatment outcomes in HIV-exposed infants. Integrating genetic screening, pharmacogenomics, and immune profiling into clinical decision-making may optimize ART selection, predict treatment responses, and minimize adverse drug reactions. Personalized medicine approaches also encompass individualized vaccination strategies and nutritional interventions aimed at enhancing immune responses and reducing the risk of infections in exposed infants.[59]

4. Early Intervention and Prevention Strategies: Emphasizing early intervention and prevention strategies is essential for reducing the global burden of pediatric HIV/AIDS. Enhancing prenatal and neonatal screening programs, expanding access to ART and PMTCT services, and promoting universal testing and treatment approaches are critical steps toward achieving virtual elimination of mother-to-child transmission. Implementing innovative strategies, such as long-acting antiretroviral formulations or microbicides, may further enhance prevention efforts and reduce HIV transmission rates in high-risk populations.[60]

5. Long-Term Immune Monitoring and Outcomes Research: Longitudinal studies and cohort analyses are needed to elucidate the long-term immune consequences of HIV exposure and ART in exposed infants. Long-term immune monitoring, including immune activation markers, T cell responses, and viral reservoir dynamics, will provide insights into immune recovery, durability of viral suppression, and susceptibility to opportunistic infections. Comprehensive outcomes research, spanning infancy through adolescence and into adulthood, will inform guidelines for lifelong HIV management and optimize health outcomes for exposed infants as they transition into adulthood.[61]

6. Global Health Equity and Access: Addressing disparities in HIV care and ensuring equitable access to diagnostic, therapeutic, and supportive services are essential for improving outcomes in HIV-exposed infants worldwide. Strengthening healthcare infrastructure, expanding access to

affordable medications, and implementing culturally sensitive care models are critical steps toward achieving health equity and reducing disparities in pediatric HIV/AIDS outcomes. Collaborative efforts between policymakers, healthcare providers, researchers, and community stakeholders are essential for advancing global health equity and achieving sustainable progress in pediatric HIV/AIDS care.[61]

Conclusion

In conclusion, the management of immune activation in HIV-exposed infants represents a dynamic and evolving field with significant implications for early diagnosis, treatment strategies, and long-term health outcomes. Immune activation markers, ranging from innate to adaptive immune responses, play crucial roles in assessing disease progression, guiding therapeutic decisions, and predicting clinical outcomes in this vulnerable population. Strategies such as early initiation of antiretroviral therapy (ART), immune modulation therapies, and personalized medicine approaches are pivotal in mitigating immune dysregulation, preserving immune function, and improving overall quality of life for HIV-exposed infants.

Collaborative efforts among researchers, healthcare providers, policymakers, and community stakeholders are essential for translating scientific advancements into effective clinical practices and improving outcomes for HIV-exposed infants. By fostering innovation, promoting health equity, and advocating for comprehensive care approaches, we can strive towards achieving the goal of ending pediatric HIV/AIDS and ensuring a healthier future for all children worldwide. Continued commitment to research, education, and advocacy will be pivotal in realizing this vision and achieving sustainable progress in pediatric HIV/AIDS management.

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