Early antiretroviral therapy in children perinatally infected with HIV: a unique opportunity to implement immunotherapeutic approaches to prolong viral remission

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From the use of antiretroviral therapy to prevent mother-to-child transmission to the possibility of HIV cure hinted at by the Mississippi baby experience, paediatric HIV infection has been pivotal to our understanding of HIV pathogenesis and management. Daily medication and indefinite antiretroviral therapy is recommended for children infected with HIV. Maintenance of life-long adherence is difficult and the incidence of triple-class virological failure after initiation of antiretroviral therapy increases with time. This challenge shows the urgent need to define novel strategies to provide long-term viral suppression that will allow safe interruption of antiretroviral therapy without viral rebound and any associated complications. HIV-infected babies treated within a few days of birth have a unique combination of a very small pool of integrated viruses, a very high proportion of relatively HIV resistant naive T cells, and an unparalleled capacity to regenerate an immune repertoire. These features make this group the optimum model population to investigate the potential efficacy of immune-based therapies. If successful, these investigations could change the way we manage HIV infection.

Introduction

Study of the pathogenesis and management of HIV in paediatric populations has contributed pivotally to the collective understanding of the pathogen, from use of antiretroviral therapy to prevent mother-to-child transmission[1] to the possibility of cure suggested by the circumstances surrounding the Mississippi baby.[2] Babies infected vertically with HIV and treated within a few days after birth represent a unique opportunity to study novel approaches to HIV management and particularly therapeutic vaccines. These babies have a very small viral reservoir, rarely exhibit HIV-specific immunity, but still seem to maintain normal immune development.[3,4] The unique combination of a very small pool of integrated viruses,[5] a very high proportion of relatively HIV resistant naive T cells,[6] and an unparalleled capacity to regenerate an immune repertoire[7,8] makes this group the optimum model population to investigate the potential efficacy of immune-based therapies.

Infants born with HIV infection have access to potent combinations of antiretroviral therapy, so that increasing numbers of children are surviving to adolescence and older. Despite this optimistic outlook, several questions still need to be addressed (panel 1). An estimated 3–4 million children are living with HIV, more than 90% of whom are in sub-Saharan Africa, and almost all of these infections were acquired through mother-to-child transmission. As a result of widespread use of preventive interventions such as the administration of antiretroviral drugs to mothers and their babies, elective caesarean section, and bottle feeding, vertical HIV transmission has diminished to less than 2% from mother to baby in resource-rich countries. Similar results have been achieved in resource-poor settings, in which these strategies have also been implemented. Although new HIV infections in children declined by 53% from 2001 to 2012 because of the effective implementation of techniques to prevent mother-to-child transmission, about 250 000 HIV-infected infants are still newly infected every year.[9] Antiretroviral therapy has very effectively prevented mortality when initiated in infancy[10] and international guidelines now recommend initiation of antiretroviral therapy in all infants younger than 12 months infected with HIV, irrespective of clinical and immunological variables.[11] Thus, research can now focus on the effect of viral reservoirs in different antiretroviral therapy regimens started in early life. In terms of long-term viral control, evidence is growing to suggest that regimens containing lopinavir, if tolerated, started within the first year of life might be better than nevirapine regimens.[12] Moreover, a potential role for the use of integrase inhibitors during infancy has been suggested.[13] How the use of different or novel combinations of antiretroviral drugs will affect viral reservoirs is still unclear.

What did we learn from the Mississippi baby?

The Mississippi baby led scientists to think that very early and aggressive antiretroviral therapy in vertically infected infants could be sufficient to ensure HIV remission, defined as a prolonged period of undetectable plasma viraemia without antiretroviral therapy. The attempt to replicate this case with very early antiretroviral therapy (started within 48 h after birth) represents the objective of the IMPAACT1115 trial[14] announced by the National Institute of Health. The Mississippi baby initiated antiretroviral therapy at 30 h after birth during the acute phase of the infection. The child had a spontaneous antiretroviral therapy interruption at age 18 months followed by a period of 27 months with undetectable

plasma HIV RNA and no replication competent virus in CD4 T cells with only traces of HIV DNA in peripheral blood. These data led scientists to believe that a functional cure, or at least sustained control of HIV in the absence of antiretroviral therapy, could be achieved with very early treatment—namely, within a few hours after birth. However, at age 4 years, the child had a rebound of HIV RNA to nearly 20 000 copies per mL and antiretroviral therapy was resumed.[1,15]

This case shows that acute HIV infection targets could lead to a significant reduction in HIV reservoirs.[3,16] However, the reasons for the long duration of viral suppression without antiretroviral therapy for 27 months in this child still need to be elucidated (panel 1) and thus far, these factors are difficult to reproduce with antiretroviral therapy alone. In most early treated cases that interrupt antiretroviral therapy, plasma viral rebound is recorded in less than 2–4 weeks after interruption.[17,18] This outcome suggests that early antiretroviral therapy alone might not be sufficient for HIV remission. Furthermore, the instruments used to detect low numbers of HIV-infected cells[19] and undetectable HIV DNA, such as those used with the Mississippi baby, might not show whether all infected cells are cleared. Moreover, HIV RNA and DNA in the peripheral blood are insufficient biomarkers for viral clearance in these children as the virus could persist in different anatomical compartments and cell types. As shown in the adult population, the gut-associated lymphoid tissue[20,21] and the CNS[22] play a crucial part in contributing to the viral reservoir[23] and serving as a possible source of viral rebound after treatment interruption.[24] The ethics of tissue biopsy collection and of lumbar punctures for research in children who are not able to provide consent are challenging, and thus far, have restricted the ability of researchers to examine these reservoir compartments (panel 1).[25] However, use of these medical procedures in a subset of patients, such as in early treated, long-term virally suppressed adolescents,[26] could guide therapeutic strategies for cure.

Panel 1: Essential research questions to be solved to develop an effective immunotherapeutic strategy for use in children infected with HIV

- What are the mechanisms that drive the long-term viral remission reported in the so-called Mississippi baby?
- How frequently can prolonged HIV viral remission be established in neonates infected with HIV who have antiretroviral therapy initiated within 48 h of birth?
- What sampling should be done to adequately assess the HIV reservoir in children?
- What are the best methods to evaluate the HIV latent reservoir?
- What biomarkers could be used to guide drug interruption in seronegative children infected vertically with HIV?
- Which immunological responses should be elicited in a therapeutic vaccine study to achieve HIV viraemic control?
- Is it ethical to interrupt antiretroviral therapy supported by an immunotherapeutic approach?
- What affects the decisions of parents to allow their infant to participate in a therapeutic vaccine trial?
- What enrolment criteria and endpoints should be considered in a therapeutic vaccine trial that targets paediatric patients with HIV?

Virological and immunological benefits of early antiretroviral therapy in children

Emerging evidence suggests that the use of early antiretroviral therapy not only reduces HIV-1 related mortality but also preserves immune function and long-term control of viral production. Early antiretroviral therapy restricts the number of long-lived CD4 T cells that harbour HIV-1 DNA and viruses that are competent of replication.[4,26] Importantly, early treatment also preserves the predominant naive CD4 cell populations and restricts the generation of memory cells. Data in early treated children suggest that within the small population of memory cells that do exist, the contribution of the proviral reservoir is greater in the short lived transitional memory than the long lived central memory CD4 T cells or naive CD4 cells pool,[26] a profile reported in the post-treatment controllers from the VISCONTI cohort.[27] Furthermore, early antiretroviral therapy is advantageous to restrict viral diversity and reduce escape mutations, both secondary to the absence of viral evolution over time. Immunologically, early control of viral replication through antiretroviral therapy preserves the normal development of the memory B-cell and T-cell compartments as shown in several cohort studies.[28–30] Additionally, Schuetz and colleagues[20] reported that early antiretroviral therapy initiation prevents the functional and quantitative loss of mucosal Th17 cells in addition to the induction of a normalisation of local and systemic T-cell activation.

Well established evidence suggests that most children who achieve sustained viral suppression since the first days of life show undetectable HIV antibodies and little, if any, cellular HIV-specific responses attributed to the absence of antigen stimulation.[3,4,16,24,31–33] The few studies that investigated the relationship between serostatus and viral reservoir show a direct association between the concentration of HIV-specific antibodies and the size of the viral reservoir.[3,34]

One implication of the use of early antiretroviral therapy worldwide is the increased number of HIV-infected children in therapy for many years who remain seronegative, leading to a growing demand by parents and patients to interrupt therapy. Whether a safe way can be achieved to interrupt treatment has become a pertinent and urgent question in the paediatric community. Paradoxically, although children who are seronegative are most likely to achieve a period of drug-free viral

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