The Mission is Remission

Hope for Controlling HIV Replication Without ART in Early-treated Perinatally HIV-infected Children

Paolo Palma, MD, PhD, Nicola Cotugno, MD,*†‡ Paolo Rossi, MD, PhD,†‡ and Carlo Giaquinto, MD, PhD§¶*

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An estimated 2.5 million children are now living with human immunodeficiency virus (HIV) with 250,000 infants newly infected every year (www.UNAIDS). Comparing the present situation with the beginning of the epidemic, children who are born with HIV infection now more commonly have access to effective antiretroviral therapy (ART) combinations, so that an increasing number of children are surviving to adolescence and adulthood. Currently, all international guidelines recommend that perinatally HIV-infected infants start ART as soon as the diagnosis is confirmed and remain on therapy for their whole life with a cumulative risk of toxicity and ART resistance. Long-term viral load suppression is essential for preventing HIV-related complications. However, maintaining life-long ART adherence is difficult, particularly among children and adolescents. Moreover, the risk of ART resistance and yet unknown long-term toxicity represent major limitations for this therapeutic strategy. The rate of virologic failure because of poor adherence increases over time in perinatally HIV-infected children and adolescents on ART as reported in African and other settings.[1] These findings highlight the urgent need to define novel treatment strategies to provide long-term viral suppression in the pediatric population by allowing safe treatment interruption without viral rebound.[2]

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From the *Research Unit in Congenital and Perinatal Infection, Immune and Infectious Diseases Division, Academic Department of Pediatrics, and †Academic Department of Pediatrics (DPUO), Bambino Gesù Children's Hospital, Rome, Italy; ‡University of Rome Tor Vergata, Rome, Italy; §Pediatric Infectious Diseases Division, Department for Woman and Child Health, University of Padua, Padua, Italy; and ¶Paediatric European Network for the Treatment of AIDS (PENTA), Padova, Italy.
The authors have no conflicts of interest to disclose.
Address for correspondence: Paolo Rossi, MD, PhD, Academic Department of Pediatrics (DPUO), Bambino Gesù Children's Hospital, Rome, Italy. E-mail: paolo.rossi@opbg.net or Carlo Giaquinto, MD, PhD, Pediatric Infectious Diseases Division, Department for Woman and Child Health, University of Padua, Padua, Italy. E-mail: carlo.giaquinto@unipd.it.

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EARLY ART PROVIDES THE FIRST STEP IN REACHING PROLONGED REMISSION, BUT IS NOT ENOUGH

Control of viral replication without reliance on long-term ART represents a major goal for scientists and clinicians in the field of pediatric HIV infection. To address this challenge, the EPIICAL (Early-treated Perinatally HIV-infected Individuals: Improving Children's Actual Life, www.epiical.org) Consortium has been formed to focus on research to find novel immunotherapeutics that could result in HIV remission in early-treated perinatally infected children. EPIICAL believes that these patients represent the optimal population as they have a unique combination of a very small pool of integrated viruses, a high proportion of relatively HIV-resistant naive T cells and an unparalleled capacity to regenerate an immune repertoire.[2–4] In recent years, advances in ART both in terms of availability of new and more efficacious drugs and the implementation of more effective early diagnostic strategies have encouraged the optimistic idea that a remission of HIV infection (ie, maintenance of undetectable viral load in the absence of ART) may be possible. It is thought that remission could be achieved through early ART that reduces the HIV reservoir to a low enough level, which is then maintained after ART interruption, a possible explanation for the 27 months of remission in the Mississippi Child.[5] There are also other cases of HIV remission reported in children treated during the first months of life.[6] The last case of sustained virologic remission for more than 8 years was reported in the Children with HIV Early Antiretroviral Therapy cohort.[7] However, remission is rare, and early ART alone is ineffective to help the majority of HIV-positive patients reach this goal. Indeed the attempts to replicate the pediatric cases of remission have proven that only a minority of very early-treated children can achieve prolonged viral control after ART

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interruption. When ART is interrupted, there is generally a rapid recrudescence of HIV to high levels.[8] The latent reservoir size is small in early-treated perinatally HIV-infected children,[9] but its maintenance plays a crucial role in viral rebound following treatment interruption. HIV provirus persists for years in resting CD4+ memory T cells and particularly in the peripheral follicular PD1+T helper cell subsets[10] in a latent state until they become activated and release replication-competent virus. It is still unknown whether routine vaccinations of childhood, which increases the T-cell memory compartment can also enlarge the HIV viral reservoir size (R01AI127347). Ridding the body of latently infected cells is thus a critical barrier in the effort to achieve viral remission (Fig. 1). The phenotypic profile of latently infected CD4+ memory T cells in perinatally HIV-infected children is not well characterized, and more studies are needed to inform innovative approaches that target persistent reservoirs. In fact, Descours et al[11] recently revealed that the low-affinity receptor for the immunoglobulin G Fc fragment, CD32a, may be a possible, albeit incomplete, cell surface signature of CD4+ T cells preferentially harboring latent HIV genomes. This finding is controversial in adults with HIV and has not been confirmed in perinatally HIV-infected children.[12]

The mechanisms for the post-treatment controller phenotype are unknown. Identification of specific markers associated with HIV remission represents an area of particular interest. In the past few years, it has been shown that the few children experiencing sustained viral remission after treatment interruption presented with undetectable HIV antibodies, which in turn are associated with lower HIV reservoir.

Approximately 50% of children who initiated ART within the first 6–8 weeks of life are seronegative on ART.[13–15] The HIV-specific memory profile of seronegative children and its relation to HIV remission still need to be elucidated. We have recently demonstrated that HIV-specific B cells are generated in children treated from infancy and that they persist after years of ART, with most being IgM+ memory B cells.[16]

This response, only partially explored in HIV, is known to be functional in other infectious disease models.[17]

Finally, a limited viral diversity from early ART (eART) theoretically may have aided the host immunity control of HIV in children who achieved sustained virologic remission without ART.[18,19] This virologic feature described in the majority of early-treated children[11] may facilitate the design of future immunotherapeutic interventions toward HIV remission.

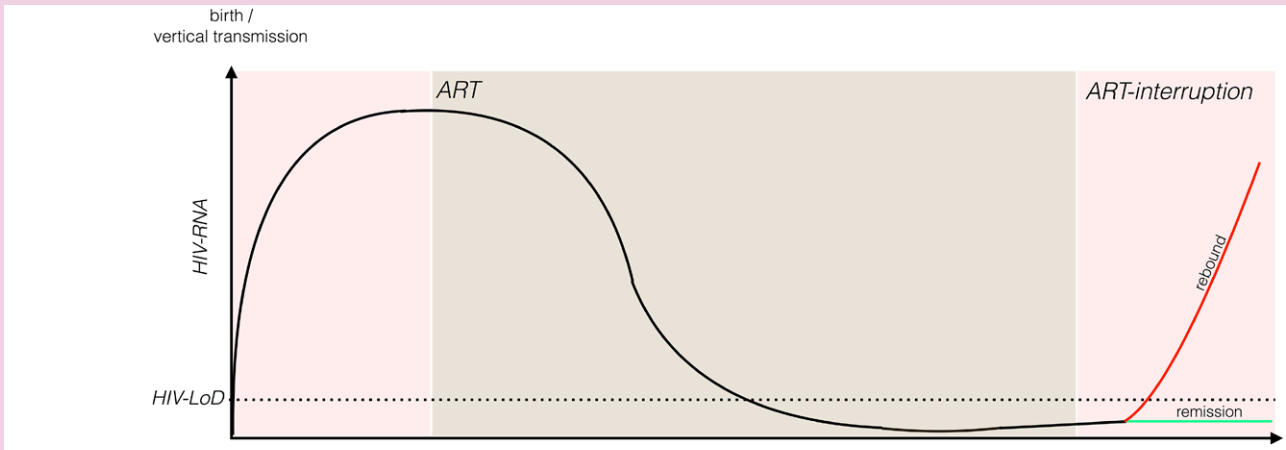
CURE REMISSION STRATEGIES IN eART: WHERE DO WE STAND?

The lower size of the HIV reservoir, better immune reconstitution and limited HIV genetic diversity in children with early ART forms a favorable framework to test novel immunotherapeutic interventions aiming at HIV remission. Although the HIV remission research field is one of the highest priorities in terms of funding policies, only recently clinical HIV remission studies specifically targeting e-ART children have moved forward.

Several attempts targeting different immunologic pathways have been evaluated in the past few years in adults with HIV: (1) HIV therapeutic vaccination strategies have shown to be safe and induce HIV-specific T cell–mediated immune responses[20–22]; (2) reversing immune exhaustion has been targeted by specific immune checkpoint blockers (anti-PD1, anti-CTLA4; reviewed in ref. 23) to preserve HIV-specific T cells and (3) passive immune responses, provided by broadly neutralizing antibodies (bNAbs) have shown to be safe and to delay viral rebound after ART discontinuation.[24]

To date, however, studies of such strategies in adults with HIV have been limited by the single interventions given in nonhomogeneous cohorts, and none have achieved effective and long-lasting HIV remission. We believe that proof of concept studies in patients with homogenous favorable characteristics such as early-treated pediatric populations could circumvent some of the limitations and enhance the chances for success. The lessons learned from such studies could be informative for the HIV cure field overall.

Very early ART intensive treatment (2 Nucleoside Reverse Transcription Inhibitors (NRTI) plus lopinavir/ritonavir (LPV/r)/RTV or plus an integrase inhibitor such as raltegravir) initiation, as a single strategy to achieve viral remission is under evaluation in a Phase



Timing of intervention trials in eART children	Acute phase in combination with eART	Long-term suppressive ART	Planned Treatment Interruption
Ongoing trials	NCT02256631	U01AI135941	IMPACT 2008. IMPAACT P1115.
Completed trials	-	PEDVAC study (2 out of 10 pts are e-ART)	

FIGURE 1. Remission trials in early-treated perinatally HIV-infected children according to timing of intervention. early ART indicates early initiation of antiretroviral therapy; LoD, limit of detection. full color online

I/II Proof of Concept Study (IMPAACT 1115) in perinatally HIV-infected children treated within 48 hours from delivery and under continuous viral control for 2 years (NCT02140255). Additionally, the IMPAACT 2008 study is testing the combination of early ART (within 12 weeks) with VRC01 bNAbs (NCT03208231). Primary outcomes include both safety and pharmacokinetics of VRC01 (NCT03208231). In addition, the reduction in viral reservoir measures after ART will be investigated.

However, analogous to current regimens of high combination of ART that targets multiple HIV gene products, recent data suggest that for this strategy to be effective, it will likely require multiple bNAbs that target different sites on the HIV envelope glycoprotein.

Along this line, promising data have been produced on the monoclonal antibody (Vedolizumab) targeting alpha4beta7, an integrin highly expressed on CD4+ T cells permissive to HIV during acute infection and representing one of the main pathways for HIV to disseminate to the gut tissue.[25] A sustained virologic control was reported after ART interruption in monkeys treated with a combination of anti alpha4beta7 and ART in the acute phase of the infection.[25] Vedolizumab, already approved for pediatric use in Crohn's disease treatment and largely shown to be safe, may facilitate exploratory trials in HIV-infected children. The combination of monoclonal antibodies and/or bNAbs could be particularly promising in perinatally infected children where the time of infection is known.

Therapeutic vaccines in children with early ART are an important strategy to augment virus-specific immune responses that could accelerate the decay of the reservoir during ART and/or improve control of viral rebound after ART interruption. First-generation therapeutic vaccines mainly failed because they typically expanded preexisting dysfunctional T-cell clones with limited CD8+ recognition because of virus escape mutation. In the past 2 decades, however, advances in adjuvants and vector design of HIV DNA vaccines together with specific boosting regimens such as Modified Vaccinia Ankara (MVA) have produced encouraging results of HIV immunogenicity. Functional CD8+ T cells specific to novel HIV-1 epitopes and broad (cross-clade) cell-mediated and antibody responses were shown in healthy adults.[21,26] In addition, a multiclade multigene DNA vaccine, the HIVIS DNA, was shown to be safe and well tolerated in perinatally HIV-infected children.[22] Recent studies support the use of therapeutic vaccines to reduce the reservoirs or to control viremia post-ART interruption, either when used alone or with agents that have adjuvanted or latency reversal properties, for example, Ad26/MVA ± TLR7 agonist in nonhuman primates, and MVA plus romidepsin or p24 conserved peptides vaccine plus romidepsin in humans.[27] The EPIICAL consortium will be conducting a proof-of-concept study funded by the US National Institute of Allergy and Infectious Diseases (U01AI135941: Principle investigator: Palma and Ananworanich) to evaluate the efficacy of a multiclade multigene DNA prime with or without a TLR4 adjuvant and MVA boost to reduce the size of viral reservoirs in early-treated children and adolescents.

CONCLUSIONS

Combined clinical interventions aiming at reducing HIV reservoirs and increasing specific HIV immunity may lead to viral remission if tested in perinatally infected children treated early in life. As the interest from research funding bodies to pursue HIV remission research grows, it is time to expand research networks and expert consortia that specifically aim at building cohorts of well-characterized early-treated children. The combination of the optimal model population, novel available methodologies and the establishment of dedicated research platforms will aid to accomplishing the goal of improving the quality of life of children who live with HIV.

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