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Advances and hope for perinatal HIV remission and cure in children and adolescents

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Abstract

Purpose of review—The known timing of HIV infection in perinatal transmission combined with the capacity for early antiretroviral therapy (ART) initiation and immune reconstitution can provide unique insights into HIV persistence. The scientific basis for a pediatric-specific research agenda aimed at HIV remission and cure is discussed.

Recent findings—Accumulating evidence supports a favorable biomarker profile for immunotherapeutic interventions in early treated, perinatally-infected individuals. HIV DNA concentrations in infected cells of early treated infants decrease over the first few years of life and, after >10 years of ART, the overwhelming majority of non-induced proviral genomes are replication-deficient. With early ART initiation, approximately half of perinatally-infected individuals become seronegative. Studies of untreated infants and vaccine trials indicate infected infants can generate HIV-specific humoral responses. Taken together, this evidence suggests early treatment results in low levels of replication-competent provirus, an absence of HIV-specific immunity, and the capacity to generate immune responses to potential immunotherapeutic interventions.

Summary—Perinatally HIV-infected individuals require lifelong ART due to the prompt establishment of viral latency in long-lived resting memory CD4⁺ T cells that rekindle viremia upon treatment cessation. However, intense research efforts are ongoing to perturb HIV latency towards reservoir clearance for virologic remission and cure in which perinatally-infected individuals can discontinue ART.

Keywords

Perinatal; HIV; reservoir; latency; immunotherapy; antiretroviral

INTRODUCTION

With the nearly 2.6 million children living with HIV and the 260,000 new cases in 2014, it is imperative to continuously align the pediatric treatment agenda with that in adults. As in

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CONFLICTS OF INTEREST

None

HIV-infected adults, antiretroviral therapy (ART) HIV-infected infants and children significantly improves morbidity and mortality, as demonstrated by 75% decreases in the risks of disease progression and death [1]. The almost immediate establishment of HIV latency in a small pool of resting memory CD4+ T cells, however, presents the major barrier to HIV clearance and cure [2]. This is due to the intrinsic, long-lived nature of the reservoir for HIV in resting memory CD4+ T cells, which self-renew, promote viral quiescence in their resting state, and preclude targeting by antiretroviral drugs and immune surveillance mechanisms. The hope for remission in perinatal infection stems from the capacity to treat infection soon after birth given that the timing of HIV exposure is known, resulting in a favorable state for immunotherapeutic interventions aimed at HIV remission.

LATENT RESERVOIR PREVENTS CURE

Reducing the size of the reservoir is the direction of novel HIV therapeutics. To this end, significant efforts are now underway to identify new classes of anti-HIV drugs that can reverse HIV latency (latency reversing agents or LRAs) to promote clearance of latent reservoirs towards HIV remission and cure, where HIV remission can be defined as a prolonged period of undetectable plasma viremia without ART [3]. A recent mathematical model showed that the size of the latent reservoir is important with respect to rebound times off cART based on the stochastic nature of re-activation [4]. It is estimated that reducing the size of the reservoir from $1/10^6$ to $1/10^{8-9}$ may afford one year of HIV remission in which patients can discontinue ART without experiencing viremic relapse within the typical 2–3 weeks of stopping treatment [5–8]. Several proof-of-concept studies have demonstrated that latent HIV in infected adults can indeed be induced to become transcriptionally active with LRAs [9–11], though this has not led to measureable reductions in latently-infected cells [9;10].

One approach to reduce HIV reservoirs in infected individuals is through early treatment [12–15] and becomes more tangible for adults with recent 2015 WHO guidelines to treat all HIV-infected persons [16]. This is particularly relevant to pediatric HIV infection as early treatment (within 2–3 months of age) is standard of care for its lifesaving effects [1]. In non-human primate studies, treatment initiated three days after infection decreased the amount of HIV infected cells in peripheral blood and lymph nodes of early-treated animals compared with treatment at seven or more days post-infection [17]. Lower concentrations of infected cells achieved with treatment at three days post-infection was also associated with a longer time to virologic rebound when ART was stopped. Similarly, delayed virologic rebound was observed in two adult patients with low reservoirs following bone marrow transplantation [18] and also from very early treatment within 48 hours of birth in the Mississippi Child [19]. Cases of virologic remission have also been reported in a group of post-treatment controllers (VISCONTI Cohort) who have relatively low reservoir size [20], which now includes in a perinatally-infected adolescent who has remained off ART for 11 years [21]. Together, these cases support the idea that the size of the HIV reservoir in peripheral blood may be an important indicator for time to virologic relapse, though more studies are needed to confirm this association.

BIOMARKERS OF HIV PERSISTENCE

Perinatal HIV infection may occur in utero during the last trimester, peripartum, or postnatally through breastfeeding, all of which are preventable with identification and treatment of pregnant women. Nevertheless, new infections in children provide an opportunity to systematically study the effects of very early and early treatment (defined as ART initiation within 2–3 days or 2–3 months of age, respectively) on reservoir reduction to enable virologic remission. In case of the Mississippi Child, virologic rebound occurred after an unprecedented period of 27 months of virologic remission [19;22]. The recurrence of viremia following a period of absent HIV specific immune responses and circulating infected cells highlights the unpredictable nature of viremic rebound, overt lack of biomarkers to detect persistent replication-competent HIV, and support the notion of HIV dormancy. While unfortunate for the individual child, rebound viremia provides hope that HIV can indeed be controlled for prolonged periods through latency.

Although very early treatment of perinatal infection is not standard of care, a clinical trial of this approach to perinatal infection is underway that should provide new knowledge on the effects of very early virologic control on early restriction of HIV reservoirs and HIV remission (NCT #02140255; also known as the International Maternal Pediatric Adolescent AIDS Clinical Trials Network's P1115 study). In a recent study [13], treatment of HIV infection within 2–3 months of age did not immediately restrict reservoirs from forming, emphasizing the need for very early interventions to immediately influence HIV reservoirs in perinatal infection. In this study, a high concentration of transcriptionally active HIV-infected cells was established in perinatally-infected infants by a median of two months of age. Although HIV-infected cells decreased significantly with two years of virologic suppression, proviral HIV DNA was detectable in 100% of 12 infants and HIV transcripts were detectable in 75% of eight infants. A significant correlation was observed between HIV DNA concentrations before and after ART, suggesting that the proviral DNA reservoir after two year of virologic suppression is determined by the size of the infected cell pool established before ART initiation. In another recent study of perinatally-infected children treated early with cART [23], time to virologic suppression and age at ART initiation was associated with size of the proviral DNA reservoir after at least seven years of virologic suppression. Infants who initiated ART by 12 weeks of age had six-fold lower proviral DNA concentrations than those who initiated ART by 12–54 weeks of age. This strongly suggests early treatment initiation results in small proviral reservoir size, possibly by skewing seeding of short-lived cells and permitting continual decay of HIV-infected cells [23]. Low proviral DNA concentrations do not ensure long-term remission, however, as perinatally-infected children experience plasma viral rebound within days of ART discontinuation irrespective of their proviral DNA load (reviewed in [24]). Therefore, small proviral reservoir size may not result in permanent virologic remission, but it may provide an optimal platform for studies aimed at purging the reservoir with other immunotherapeutic interventions.

The reservoir is established in the context of immunologic memory for which the developing infant immune system may be differentially affected than adults (Table). The nearly 15 years of experience with early treatment of perinatal infection has led to the identification of unique virologic and immunologic features with durable suppression. While smaller HIV

reservoir size is strongly associated with early ART initiation, the composition of the reservoir is also affected by early treatment. HIV persistence during early effective therapy is of limited genetic diversity [37]. Over time, however, HIV persistence may be driven by clonal expansion of infected cells. Studies of HIV-infected adults and children observed identical HIV sequences integrated in the same human genes across multiple cells [38;39], suggesting specific integration sites are associated with clonal expansion of HIV-infected cells. In early treated, long-term suppressed perinatally-infected children and adolescents, >99% of non-induced proviral genomes were replication-defective using molecular methods to probe cultured cells that did not yield replication-competent HIV via the traditional quantitative viral outgrowth assay [33]. Thus, the state of latent HIV genomes and their integration sites may serve as important considerations in HIV remission strategies.

Small proviral reservoir size in the circulation has been associated with negative HIV serostatus in perinatal infection [14;26]. Many studies have shown that the majority of early-treated infants and children lack HIV-specific immune responses [12;35;36] and this state is maintained through adolescence [14;26;33]. Two studies have reported that identifying HIV-specific antibodies is significantly more likely in late-treated compared to early treated infants, children and adolescents [14;35]. The combination of low infected cell concentrations [13–15], absent HIV-specific immune responses [12;14;26;33;36], and restricted HIV diversity [33;37] provides a favorable framework for remission strategies that rely on immunotherapeutic strategies.

IMMUNOTHERAPEUTIC INTERVENTIONS

The prevention of HIV-specific immune responses by early treatment initiation allows the development of uninhibited autologous immunity following HIV-specific vaccination that can be measured without interference by autologous immunity and the use of monoclonal antibodies without *de novo* antibody-mediated viral escape mutations. Several HIV vaccines tested in HIV-exposed infants were safe and immunogenic, as demonstrated by durable Env-specific IgG responses that remained detectable through two years of age in 56% of recipients [40]. Anti-V1V2 IgG, identified in the RV144 vaccine trial in adults as a correlate of protection from HIV infection [41], was also elicited in HIV-exposed infants receiving an ALVAC HIV vaccine series or the Novartis gp120 subunit protein vaccine, providing support for further trials of protein-only or single gene vaccines in perinatal infection [42]. Env-specific antibodies have potential to neutralize HIV, a feature that may be particularly relevant in children rendered antibody seronegative from early treatment, and these antibodies are undergoing studies of very early treatment to achieve virologic remission. Goo et al. identified cross-clade neutralizing antibodies in 71% of 28 HIV-infected Kenyan infants, indicating that infants are also capable of developing HIV-specific neutralizing antibody responses despite their perceived “immature” immune systems [43]. Infant-derived ADCC was recently reported to be associated with increased survival in Infants, suggesting infant, rather than maternal, antibody repertoires are the important measure of protection [44].

Broadly neutralizing antibodies (bNAbs) are rapidly emerging as HIV immunotherapeutics and are derived from naturally-occurring antibodies isolated from HIV-infected individuals

(reviewed in [45]). Typically, these antibodies develop several years after HIV infection and poorly neutralize the circulating virus of the individual from which the bNAb was isolated. bNAbs confer antiviral activity against HIV in murine [46;47] and non-human primate [48] models by targeting of the envelope protein and have exceptionally broad and potent neutralizing activity against a diverse panel of HIV variants [49], including almost all HIV subtypes [50]. A recent study in adults showed 44–72% of HIV latent reservoir clones were neutralized by the bNAbs VRC01 and PGT121 [41], which have entered into Phase 1 clinical trials in HIV-infected adults [51] (NCT #02411539, 02568215, 02471326 and 02463227) and infants (NCT #02256631). A recent study of untreated mother-infant pairs showed 50–78% neutralization of circulating HIV subtype B and G viruses with bNAbs, albeit in the setting of uncontrolled virus replication in the first year of life [52]. Whether bNAbs would prevent viremic relapse in early-treated perinatal infection will require study, but conceivably could serve to neutralize HIV emerging from latency. Additionally, the duration of bNAb efficacy after administration is currently unclear but will be particularly promising when long-acting preparations become available. There is extensive pediatric experience on the use of monoclonal antibodies to prevent or attenuate viral infections; most notably, Synagis is used for prevention of respiratory syncytial virus infection in high-risk infants [53;54]. Therefore, a monoclonal antibody approach will likely have acceptability in the HIV remission/cure space. Given that re-establishment of viremia with ART cessation is likely derived from re-activated HIV from latent reservoirs, knowledge of the inhibitory profiles of bNAbs against latent perinatal HIV reservoir viruses is an important first step for assessing this strategy.

CONCLUSION

The inclusion of HIV-infected women and their newborns in clinical trials investigating novel approaches to HIV prevention and treatment is not without precedent. Despite the vulnerable nature of involving pregnant women and their newborn infants in clinical trials, important lessons were learnt from the first studies of antiretroviral drugs to prevent HIV transmission. These studies led to marked reductions in the risk of mother-to-child HIV transmission from as high as 30–40% without interventions to < 2% [55;56], making perinatal HIV a largely preventable disease. The landmark Pediatric AIDS Clinical Trials Group 076 (PACTG076) clinical trial [55] highlights how knowledge of HIV exposure provided the optimal framework to study interventions towards shifting treatment paradigm for pregnant women and their infants and transforming an epidemic. The HIV Prevention Trials Network 040/PACTG 1043 trial demonstrated that combination ART initiated within 48 hours of birth decreased HIV transmission by 50% in non-breastfed infants born to mothers who did not receive antenatal ART [56], suggesting more potent ART regimens may be effective during the eclipse phase of early infection. Thus, the perinatal HIV remission agenda should be considered for the unique components from which insights into HIV persistence can be gained. Without remission, perinatally-infected individuals are destined to live with this infection for their entire lives. Issues such as ART adherence, toxicities, and drug resistance should further motivate this cause. Current efforts to scale up early infant diagnosis and treatment, including the development of rapid, point-of-care testing and immediate treatment of high-risk infants, should affect the significant morbidity

and mortality associated with untreated HIV infection in infancy, while at the same time providing a platform for studies of HIV remission and cure.

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KEY POINTS

1. The Mississippi Child, who maintained 27 months of virologic remission, and the French Adolescent, who has remained in remission for more than a decade, provide hope for HIV remission among perinatally HIV-infected infants, children, and adolescents.
2. The known timing of HIV infection in perinatal transmission combined with the capacity to treat early and to immune reconstitute distinguish perinatal infection from adult infection, thereby permitting evaluation of timing of interventions on changes in the size and composition of the latent HIV reservoir and the effects of interventions.
3. Early treatment remains the standard of care in perinatal HIV infection and generates a favorable viro-immunologic profile in which immunotherapeutic strategies can be evaluated.
4. Studies are under development to evaluate the effects of immunotherapeutics such as monoclonal broadly neutralizing antibodies in the context of early antiretroviral therapy initiation.

Table

Similarities and differences in biomarkers of HIV persistence between early treated perinatal and adult HIV infection stratified by short (<2 years), intermediate (2- <10 years) or long (10+ years) durations of virologic suppression.

	Infants, Children, Adolescents				Adults			
	Suppression Duration							
	Short	Intermediate	Long	Short	Intermediate	Long	Short	Long
Reservoir Size								
Replication-competent HIV (infectious units/ 10^6 resting CD4+ T cells [IUPMI])	0.32 [25]	<0.1-0.1 [7]	<0.1 [26]	<0.07-0.42 [27;28]	0.28 [29]	0.00064 $\ddagger$ [30]		
Cell-associated HIV DNA ($\log_{10}$ HIV DNA copies/ 10^6 PBMC)	1.0-2.1 [13;26]	1.7 [15]	0.6-0.7 [14;26]	2.9-3.0 $\ddagger$ [27;31]	1.7 [29]	2.15 [32]		
Cell-associated HIV DNA ($\log_{10}$ HIV DNA copies/ 10^6 CD4+ T cells)	nr	<0.4-2.1 [7;12]	<0.6-0.99 [26]	nr	2.3 [29]	nr		
Cell-associated HV usRNA ($\log_{10}$ HIV RNA copies/ 10^6 PBMC)	0.94* [13]	0.7 [15] 1.11-1.94* [7]	nr	0.4 [31]	nr	nr		
Reservoir Composition								
Replication-intact non-induced proviral genomes	<1% [33]	nr	nr	nr	11% [34]	nr		
HIV-Specific Immune Responses								
HIV-specific antibodies	46-94% seronegative [35;36]	47% seronegative [12]	36-100% seronegative [7;14;26]	nr	nr	nr		
HIV-specific T cell responses	0% undetectable [36]	50-100% undetectable [12;36]	100% undetectable [7;26]	nr	nr	nr		

usRNA: unspliced RNA, nr: not reported.

[‡] Single patient who initiated ART within 6 months of HIV infection measured after 10.5 years of ART.

[†] calculated DNA copies/ 10^6 PBMC assuming 6ug DNA/ 10^6 cells.

* usRNA reported as copies/ug cellular RNA.