REVIEW

Very early combination antiretroviral therapy in infants: prospects for cure

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Purpose of review
A single case of sustained HIV control in the absence of antiretroviral therapy or HIV-specific immune responses ensued following 18 months of combination antiretroviral therapy initiated at 30 h of age in a perinatally HIV-infected child (the Mississippi child). This case provides proof-of-concept that delay in HIV viremic rebound may ensue following very early treatment (VET) in perinatal infection, likely through marked reduction of latent replication-competent HIV reservoirs.

Recent findings
The latent HIV reservoir remains the critical barrier to remission. Several studies indicate that the earlier effective combination antiretroviral therapy is initiated, the smaller the size of the HIV reservoir. The unique ability of perinatally infected neonates to initiate VET at the time of birth maximizes the potential benefits of limiting latent reservoir size and permitting reservoir decay, likely lengthening the duration of remission and limiting the capacity for re-establishment of viremia.

Summary
This article covers the rationale and feasibility of VET to achieve sustained virologic remission in perinatal infection. Recent studies highlighting the effects of VET on biomarkers of HIV persistence in perinatal HIV infection are reviewed as well as implications and challenges for cure research in pediatric populations.

Keywords
HIV cure, HIV remission, latent reservoir, perinatal HIV

INTRODUCTION

The road to HIV cure has consisted of promising discoveries and disappointing developments. Despite significant progress in prevention of mother-to-child HIV transmission, about 240 000 incident HIV infections occur in infants each year [1]. Early combination antiretroviral therapy (cART) reduces mortality but lifelong therapy is needed because of early establishment of latent HIV reservoirs. Reduction in the size of latent HIV reservoirs is one step in the pathway toward HIV cure and characteristics of the infant immune system may contribute to this process. Optimism toward HIV remission and cure highlight the need for consideration of how we define cure, and how the timing and duration of cART affect the latent reservoir in perinatal HIV infection.

CASES OF VIROLOGIC REMISSION

Three adults and one child with HIV remission, defined as sustained virologic control without cART, have been reported (Table 1) [2▪▪,3,4,5▪▪]; however, only one adult is considered potentially cured with low levels of HIV RNA detected in a large volume of blood. After more than 7 years without cART, the Berlin patient lives without detectable replication-competent HIV and with diminishing levels of HIV-specific immune responses following allogeneic, myeloablative hematopoietic stem cell transplant (HSCT) from a delta32-CCR5 donor [5▪▪,6]. The Boston patients also underwent HSCT but with wild-type CCR5 donors [7] and remission after cART interruption was followed by virologic rebound 84 and 225 days later [4]. The Mississippi child, who received cART between 30 h of life and 18 months of

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KEY POINTS

- The first case of long-term remission in a perinatally HIV-1-infected child is described in the context of biomarkers of long-term remission and cure in adult HIV infection.
- Converging evidence suggests very early combination antiretroviral therapy is associated with very small proviral reservoirs and restricted HIV-specific immune responses in perinatal infection.
- Unique immunological aspects of perinatal HIV infection indicate that HIV remission in pediatric populations be defined as sustained virologic control to clinically undetectable levels in the absence of cART with maintenance of normal levels of $CD4^+$ T cells and the capacity to maintain immune responses to routine immunizations.
- Very early therapy, novel immunotherapeutics, and strategies that target latent HIV reservoirs in gut-associated lymphoid tissue and the central nervous system will advance the potential for pediatric HIV cure.

age [2▪▪], remained free of replicating HIV without cART for 27 months before virologic rebound [8]. Although the virologic rebounds of the Boston patients and the Mississippi child were disappointing, they nonetheless demonstrate the capacity for long-term HIV remission. Moreover, these cases have facilitated the adoption of the term 'remission' (sustained virologic control without cART) rather than 'cure' (lifelong virologic control without cART) and an increasing recognition of a latent HIV reservoir capable of re-establishing viremia after long periods of undetectable HIV viremia without cART.

EARLY cART RESTRICTS LATENT RESERVOIR ESTABLISHMENT

HIV reservoirs remain the critical barrier to remission. One major reservoir forms following infection of activated $CD4^+$ T cells and subsequent differentiation into stable, quiescent memory cells that are unaffected by cART and unrecognized by immune surveillance. Perinatal HIV infection has additional implications for HIV reservoir development, however. Although the low abundance of circulating memory $CD4^+$ T cells in neonates [9–11] suggests fewer activated $CD4^+$ T cells are available for HIV infection, high levels of $CD4^+$ $CCR5^+$ T cells in the gut mucosa provide ample targets for productive virus replication and spread through an infant's gastrointestinal tract [12]. With in-utero transmission, the more tolerogenic fetal immune system may create an environment that promotes HIV reservoir establishment [13]. The identification of a memory-like T cell phenotype in cord blood indicates susceptible neonatal target cells may be more prevalent than previously thought [14▪▪].

Standard clinical approaches to perinatal infection are to begin cART in all HIV-infected infants irrespective of $CD4^+$ T cell levels [15], as early cART is life-saving for HIV-infected children [16]. This typically occurs around 2 or 3 months of age in settings with access to early infant diagnosis and treatment. By this time, HIV reservoirs are fully established. Very early treatment (VET), or the ability to initiate cART at the time of birth or within a few days thereafter, is unique to perinatal infection and may avert or attenuate HIV reservoirs (Fig. 1). Studies of youth who began effective cART within months of birth also suggest the size and composition of the latent HIV reservoir in perinatal infection is related to the duration between HIV infection and virologic suppression. Long-term follow-up of children who suppressed HIV replication for over 14 years following cART initiation prior to 3 months of age demonstrated extremely low levels of circulating provirus [17▪▪]. Of 144 perinatally infected adolescents on long-term effective cART, virologic control before 1 year of age was significantly associated with smaller proviral burdens than virologic control between 1 and 5 years or after 5 years of age [18▪]. Furthermore, 46% of 13 adolescents with virologic control before 1 year of age had proviral DNA concentrations below the limit of detection of four copies/10^6 peripheral blood mononuclear cells (PBMC) compared with only 11% of 101 adolescents with virologic control at older ages [18▪]. This effect is also noted in infection with nonsubtype B HIV infections [19▪▪]. Among 15 HIV-infected Thai children who were virologically suppressed before 6 months of age, a median of seven copies of integrated HIV DNA/10^6 $CD4^+$ T cells was identified on long-term cART [19▪▪]. The relationship between early effective cART and smaller reservoir size is also noted in HIV-infected adults treated during acute infection, although this is approximately 10-fold higher (47 copies/10^6 PBMC) than that of early treated, perinatally infected youth [20▪▪]. By early arrest of HIV replication, expansion of latent HIV reservoirs is restricted and fewer cells harboring infectious viral genomes are capable of reactivating productive infection (Fig. 1). Indeed, we have previously reported marked restriction in replication-competent reservoirs following early cART [21].

EARLY cART DECREASES LATENT RESERVOIR SIZE

Effective early cART in perinatal HIV infection also appears to modify long-term decay of circulating

Table 1. Biomarker profiles in the Mississippi child, Boston patients, and Berlin patient during HIV remission

	Mississippi child [2▪▪,3]	Boston patients [4]		Berlin patient [5▪▪]
		Patient A	Patient B	
Plasma HIV RNA	<2 copies/ml	<20 copies/ml	<0.4 copies/ml	Intermittent detection[a]
Replication-competent HIV	<0.05 IU/10^6 cells	<0.007 IU/ 10^6 cells	<0.006 IU/ 10^6 cells	<1 IU/10^{7-9} cells
Peripheral blood cells				
PBMC	4.2 c/10^6 cells	<0.12 c/ 10^6 cells	<0.13 c/ 10^6 cells	Undetectable HIV RNA and DNA
Total $CD4^+$ T cells	NA	NA	NA	Undetectable HIV RNA and DNA
Resting $CD4^+$ T cells	<2.5 c/10^6 cells	NA	NA	NA
Activated $CD4^+$ T cells	<2.6 c/10^6 cells	NA	NA	NA
Myeloid-derived cells	<11.5 c/10^6 cells	NA	NA	NA
HIV-specific T cell responses	Undetectable HIV-specific CD4+ and CD8+ T cell responses to gag and nef peptides	No PBMC activation to nef or gag peptides	No PBMC activation to nef or gag peptides	Low levels to gag peptides
HIV-specific antibodies	Undetectable	Decreased to low concentration	Decreased to low concentration	Low concentration and declining
Cerebrospinal fluid	NA	(<20 copies HIV RNA/ml)	NA	<0.1 copy HIV DNA/ml
Lymph node biopsy	NA	NA	NA	Undetectable HIV RNA and DNA
Rectal biopsy	NA	NA	<2.4 c/10^6 cells	Intermittent detection with <1 c/10^6 cells overall
Ileal biopsy	NA	NA	NA	<1 c/ 10^6 cells
Duration of remission	27 months	84 days	225 days	Undefined

Values represent most recent published data in the potential cure case of the Berlin patient and prior to virologic rebound for the Mississippi child and Boston patients.
c/10^6, copies HIV DNA per million cells; c/ml, copies HIV DNA per milliliter of blood; IU/10^6, infectious units per million cells; NA, sample not collected.
[a]The intermittent detection of low level viremia in the Berlin patient was in a large volume of blood (17–24 ml) and detected in 1/24 replicates (70 copies/ml) and 2/6 replicates (4 to 5 copies/ml).

proviral reservoirs. Early hope for HIV cure was created by initial estimates suggesting 7–10 years of continuous suppressive cART would permit adequate natural turnover of latently infected cells to eradicate the reservoir [22]. Unfortunately, additional studies dampened this enthusiasm by demonstrating a slow and negligible decay of latently infected resting $CD4^+$ T cells, necessitating life-long cART [23–25]. In a study of five perinatally infected adolescents who initiated cART at about 2.5 months of age [17▪▪], the median proviral burden was seven copies/10^6 PBMC, considerably smaller than the 182 copies/10^6 PBMC in four adolescents who achieved virologic control at a median of 12.9 years of age. Long-term maintenance of small reservoir size reinforced the notion that early virologic control prevented ongoing seeding of HIV reservoirs. Additionally, longitudinal measures of proviral burdens from four of these adolescents showed decreased concentrations of circulating proviral reservoirs and undetectable proviral burdens after 14–25 years of effective cART, indicating a lifetime of cART may not be necessary for extensive reservoir reduction.

The time frame for reservoir attenuation with VET that creates a state of permanent remission in which cART can be stopped without viremic rebound is unclear (Fig. 2). Although minimizing reservoir size may lengthen the duration of virologic remission [26▪▪,27▪▪], the question remains: how early is early enough to achieve permanent HIV remission and cure? The Mississippi child provides proof-of-concept that VET may influence HIV reservoir size and sustain long-term virologic remission. After receiving cART 30 h after birth and for approximately 18 months, virologic rebound did not occur for 27 months [2▪▪]. In a second neonate from Long Beach, California, USA, who initiated cART 4 h after birth, standard diagnostic tests for HIV nucleic acid became negative after 6 days and coculture assays of $CD4^+$ T cells failed to show replication-competent reservoirs through 9 months

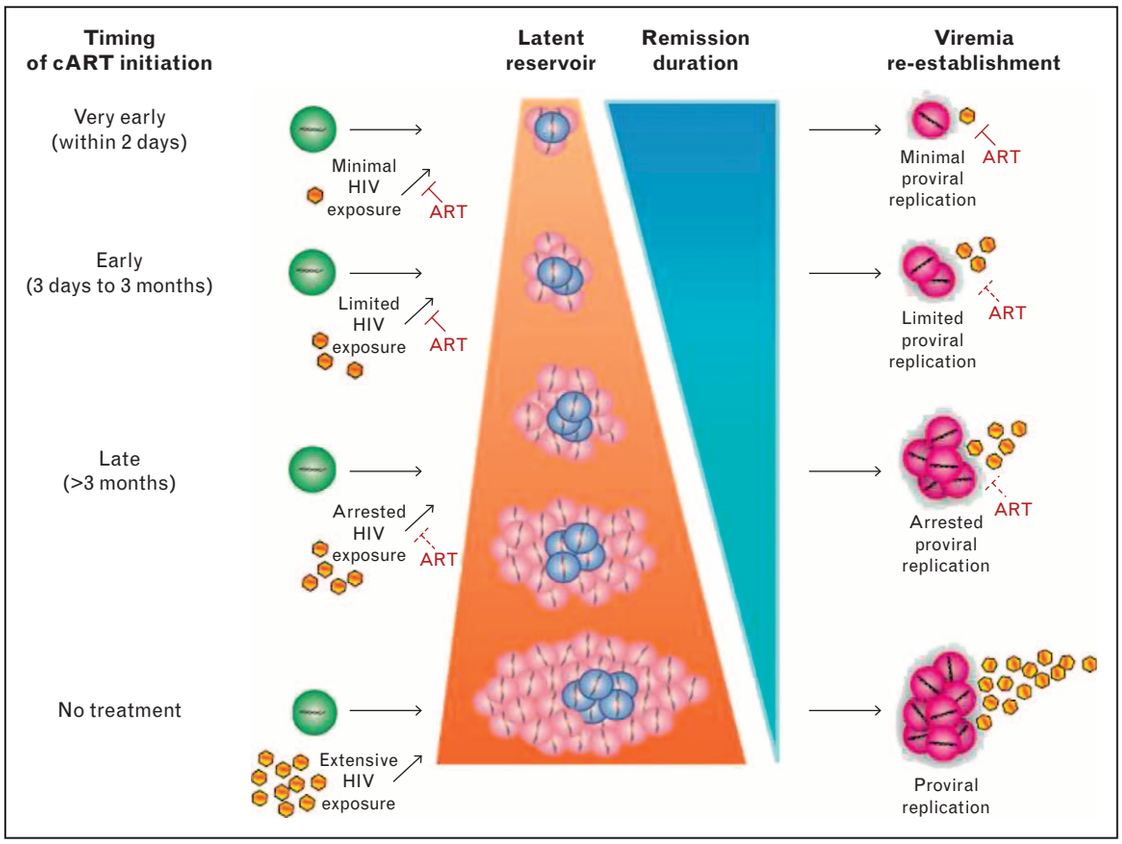

FIGURE 1. Reservoir size and duration of HIV remission is directly affected by the time from HIV infection to initiation of cART. Susceptible $CD4^+$ T cells (green) become infected with HIV (yellow) and transition to either productively infected $CD4^+$ T cells (pink) or latently infected $CD4^+$ T cells (blue). Reactivated $CD4^+$ T cells (purple) from latency re-establish viremia. ART, antiretroviral therapy; cART, combination antiretroviral therapy.

of age [3]. A recent report of four Canadian children who initiated cART within 24 h of birth indicates replication-competent HIV and HIV DNA remained undetectable after 2.5–7 years on cART [28▪▪,29]. Therefore, understanding why the Mississippi child achieved virologic remission with VET is critical. The VET cases described above acquired HIV *in utero* and therefore were infected for an unknown duration before cART initiation. The potential to achieve long-term HIV remission and cure through VET of neonates may be more likely in infants with more recently acquired infection through peripartum or breast-milk transmission routes. Regardless of transmission route, however, minimizing the size of the reservoir will inform new strategies aimed at achieving virologic remission, such as latency reversing agents, broadly neutralizing antibodies, or therapeutic vaccines.

ABSENT HIV-SPECIFIC IMMUNE RESPONSES

Perinatal HIV infection results in decreased immune responses to not only HIV but also routine childhood immunizations. Many studies have documented HIV-infected children with waning immunity to vaccinations received prior to cART initiation or with poor cART adherence [30,31], suggesting revaccination may be necessary. Limited or absent HIV-specific immune responses are a hallmark of restricted HIV replication following VET in infants (Fig. 2) [2▪▪,3,17▪▪,18▪,19▪▪,28▪▪,32▪▪] and were associated with low proviral reservoir size in early treated, perinatally infected youth [17▪▪,18▪]. Of those in whom T cell responses to HIV peptides have been measured, HIV-specific cellular responses are also absent [28▪▪,32▪▪]. Thus, restricted reservoir size occurs in the setting of absent or restricted HIV-specific immunity. Factors contributing to this may include low levels of HIV antigen exposure, decreased efficiency of HIV-specific memory response formation in neonates and cytopathic effects of HIV on $CD4^+$ T cells with consequent loss of $CD4^+$ T cell help [33]. Importantly, the absence of HIV-specific immune responses does not signify lack of replication-competent latent reservoirs or cure as the Mississippi child and one

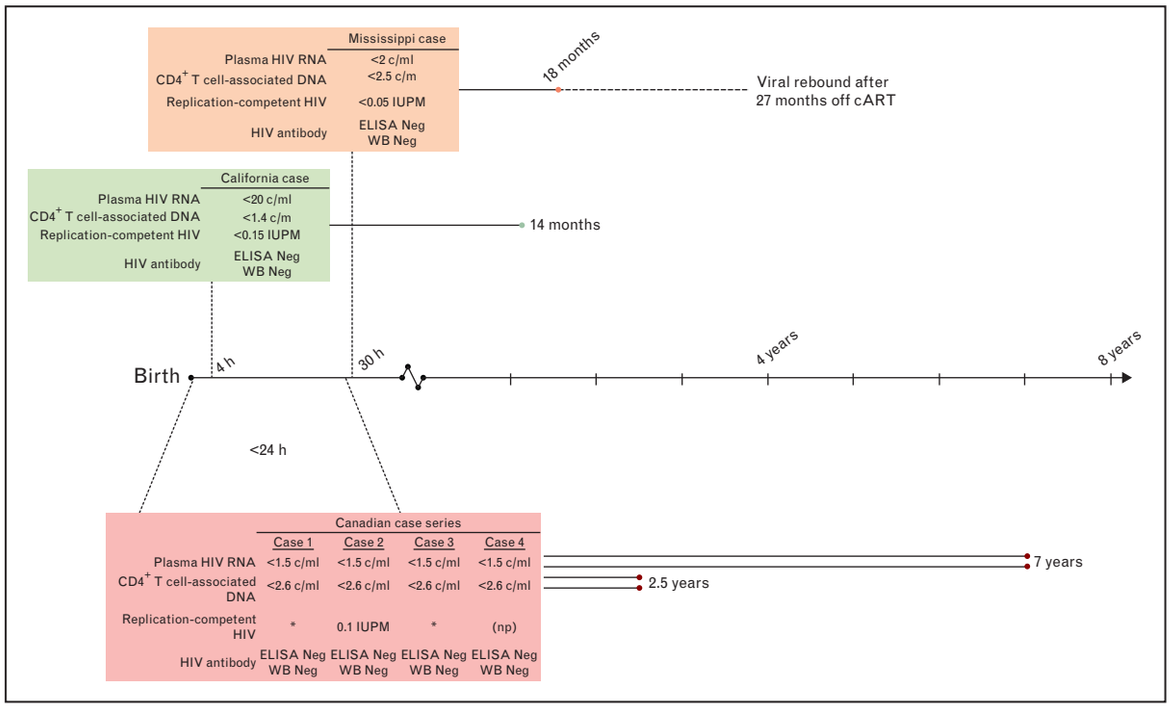

FIGURE 2. Summary of potential HIV remission biomarkers in perinatally infected children who initiated very early cART. Solid lines represent time since cART initiation with duration in text. Dotted line connected to time line indicates age at cART initiation. Dashed line for Mississippi case indicates period off combination antiretroviral therapy. * No replication-competent HIV detected. c/m, copies per million cells; c/ml, copies per milliliter blood; cART, combination antiretroviral therapy; ELISA, enzyme immunoassay; IUPM, infectious units per million resting CD4$^+$ T cells; Neg, negative; np, assay not performed; Undet, undetectable; WB, western blot.

Canadian child lacked both humoral and cellular immune responses yet developed rebound viremia [8,29].

DEFINING HIV CURE AND BIOMARKERS

Definitions for HIV cure continually evolve with increased understanding of the latent reservoir and HIV persistence. The broadest definition of cure is the permanent remission of disease following cessation of therapy [8]. Although this definition is an overarching, long-term goal for the HIV field, it lacks specific benchmarks from which we can evaluate whether an individual would be capable of long-term remission. As a field, we have yet to define what these benchmarks should be, however. Replication-competent HIV, as measured through the activation of latent CD4$^+$ T cells and the resulting viral outgrowth, has long served as the standard for estimating latent reservoir size and the capacity for re-establishment of viral replication. Comparisons of potential biomarkers for remission between the Mississippi child, the Berlin patient, and the Boston patients demonstrate that the inability to detect replication-competent HIV in peripheral blood and circulating cells is insufficient to predict HIV remission (Table 1). Thus, the quantitative coculture assay lacks sensitivity for the purposes of deeming an infected individual as 'cured' [2▪▪,7,34]. Molecular approaches lack specificity as the detection of HIV DNA may simply represent defective viral genomes incapable of re-establishing productive infection. In a recent summary of the Berlin patient's clinical follow-up [5▪▪], the authors suggest the lack of HIV-specific immune responses as a biomarker for cure. However, both Boston patients and the Mississippi child lacked HIV-specific immune responses during treatment cessation and later experienced virologic rebound, suggesting an absence of HIV-specific immune responses may be necessary but insufficient to define cure. Cell-associated RNA has yet to be vetted as a potential biomarker. Although it was the only HIV-associated biomarker detected in the four Canadian children treated within 24 h of birth who remain on cART [28▪▪] and was undetectable in the Berlin patient [5▪▪], it was not measured in the Boston patients or the Mississippi child.

Bifurcation into functional and sterilizing cure definitions essentially represents the presence and

Table 2. Proposed definitions of HIV remission and cure

	Definition	Implications for clinical biomarkers
Comprehensive [8]	Permanent remission of disease following cessation of therapy	
Adults		
Functional cure [35]	Host-mediated control of HIV replication in the absence of cART and:	Detectable replication-competent HIV by viral outgrowth assay
	Normalized, effective immune function	Normalization of inflammatory biomarkers
	Decreased HIV-related inflammation	
	Reduced risk of HIV transmission	
Sterilizing cure [35]	Complete elimination of replication-competent HIV	Undetectable replication-competent HIV
Children		
Pediatric remission	Sustained virologic control in the absence of cART that includes:	Undetectable replication-competent HIV
	Normal $CD4^+$ T cell levels	Normalization of $CD4^+$ T cell percentages and absolute numbers
	Preservation of immune responses to routine immunization[a]	Maintenance of vaccine-specific antibodies and CMI

cART, combination antiretroviral therapy; CMI, cell-mediated immunity.
[a]Proposed by the IMPAACT Cure Committee.

absence of replication-competent HIV capable of reigniting viremia (Table 2) [35]. Functional cure describes a state in which HIV replication is controlled through host-mediated immune mechanisms in the absence of cART and encompasses the long-term nonprogressor status, whereas sterilizing cure requires eradication of replication-competent HIV from the host. These definitions can be broadly applied to both adult and pediatric HIV, but the differing pathogenesis in perinatal infection may necessitate a more specific pediatric definition that accounts for the developing immune system throughout childhood. Given the unpredictability of virologic rebound following cART cessation [26▪▪], the most appropriate terminology for the majority of HIV-infected individuals is not 'cure' but 'remission'. In the context of perinatal infection, we propose HIV remission be defined as sustained virologic control to clinically undetectable levels in the absence of cART with maintenance of normal levels of $CD4^+$ T cells and the capacity to maintain immune responses to routine immunizations. This definition provides specific benchmarks for measuring remission for perinatally infected individuals (Table 2).

CHALLENGES

Implementation of VET to achieve viral remission in perinatal infection is a challenge. First, current diagnostic tests have limitations. Diagnosing infection in HIV-exposed infants requires nucleic acid testing, for which there are no widely available rapid diagnostic tests. Low HIV DNA concentration at birth leads to delay in diagnosis [36▪] and these infants are the most apt to benefit from VET. Also, long turn-around times for test results and the patient's need to return for clinical follow-up can result in several months of delay before cART can be started in perinatally infected infants [37], at which point the latent viral reservoir is established [38]. Second, VET restricts viral spread and prevents immune responses. This can result in conflicting diagnostic test results. Confirming infection with the current state-of-the-art HIV DNA and RNA assays require a high concentration of HIV DNA to detect infection, which is limited in low blood volume samples. Third, exceedingly large blood volumes are required to comprehensively assess patients approaching near-negligible reservoir size for HIV cure research despite the high sensitivity of current methods, emphasizing the need for improved assays to detect persistent replication-competent HIV.

The presence of latent reservoirs in sites beyond the lymphocytic compartment of peripheral blood remains a fundamental challenge in moving patients to a state of HIV remission. Detection of replication-competent HIV in gut-associated lymphoid tissue or the central nervous system is likely important for assessing a child's propensity for viremic rebound upon cART cessation [39,40]. Using simian immunodeficiency virus, intrarectally infected rhesus monkeys initiating cART 3 days postinfection harbored infectious SIV in lymph nodes and the gastrointestinal tract [41▪▪], highlighting the rapidity with which the reservoir

develops following infection. How to measure gut-associated lymphoid tissue and central nervous system reservoirs in a pediatric population is a challenge as rectal biopsy and lumbar puncture procedures are invasive. Moreover, whether a small sampling of gut cells or a few milliliters of spinal fluid are the relevant sample types for accurately assessing replication-competent HIV capable of re-establishing productive infection in children are unknown but important for moving the field forward.

Controversy ensues over the ethical implications surrounding treatment cessation to assess virologic remission in the absence of clear biomarkers heralding long-term HIV remission for cure research. The planned P1115 clinical trial by the IMPAACT Network aims to conduct closely monitored treatment cessation among HIV-infected infants who initiated cART within 48 h of age [42] Frequent, careful evaluation for potential virologic rebound and detailed safety monitoring are of the utmost importance to maintain the principle of beneficence [43▪▪]. Moreover, understanding risk factors from participants who experience virologic rebound will aid in future cure research efforts.

CONCLUSION

HIV-infected children face a lifetime of treatment because of the persistent nature of HIV. VET alone or in combination with immunotherapeutic approaches provides the first glimmer of hope toward virologic remission for perinatally infected children. The unique aspects of perinatal infection with respect to knowledge of timing of infection and a developing immune system set the pediatric cure agenda apart from that of adults. Global efforts to enhance earlier diagnosis and implement VET will greatly facilitate the overall goal of pediatric HIV cure. Other novel strategies that target gut-associated lymphoid tissue and central nervous system reservoirs or augment the immune system's response may be necessary to achieve this goal. Even if not curative, VET yields substantially reduced reservoir size, which will place children in a better place for treatment with new approaches expected to emerge from this endeavor.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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