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REVIEW

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A gut check: understanding the interplay of the gastrointestinal microbiome and the developing immune system towards the goal of pediatric HIV remission

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Abstract

Despite the efficacy of antiretroviral therapy (ART) in reducing the global incidence of vertical HIV transmissions, more than 120,000 children are still infected with the virus each year. Since ART cannot clear the HIV reservoir that is established soon after infection, children living with HIV (CLWH) are forced to rely on therapy for their lives and suffer from long-term drug-related complications. Pediatric HIV infection, like adult infection, is associated with gut microbial dysbiosis, loss of gut epithelial integrity, bacterial translocation, CD4 + T cell depletion, systemic immune activation, and viral reservoir establishment. However, unlike in adults, HIV that is vertically acquired by infants interacts with a gut microbiome that is continuously evolving while concomitantly shaping the infant's immune ontogeny. Therefore, to determine whether there may be interventions that target the HIV reservoir through microbiome-directed approaches, understanding the complex tripartite interactions between the transmitted HIV, the maturing gut microbiome, and the developing immune system during early life is crucial. Importantly, early life is the time when the gut microbiome of an individual is highly dynamic, and this temporal development of the gut microbiome plays a crucial role in educating the maturing immune system of a child. Therefore, manipulation of the gut microbiome of CLWH to a phenotype that can reduce HIV persistence by fostering an antiviral immune system might be an opportune strategy to achieve ART-free viral suppression in CLWH. This review summarizes the current state of knowledge on the vertical transmission of HIV, the developing gut microbiome of CLWH, and the immune landscape of pediatric elite controllers, and explores the prospect of employing microbial modulation as a potential therapeutic approach to achieve ART-free viral suppression in the pediatric population.

Keywords Children living with HIV, Gastrointestinal microbiome, Immune ontogeny, ART-free HIV remission, Microbiome modulation

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Background

Despite the widespread availability and efficacy of antiretroviral therapy (ART) in reducing vertical HIV transmissions [1], pediatric HIV continues to be a major global health concern, with nearly 120,000 children infected with the virus annually [2]. As a result, approximately 1.4 million children worldwide were living with the virus, in 2023 [2]. While ART is efficacious in suppressing productive HIV replication and controlling HIV-associated disease progression, it cannot eliminate the viral reservoir that is established soon after infection. Consequently, to keep the productively replicating virus suppressed, children living with HIV (CLWH) are forced to adhere to ART for their entire lives. Life-long ART is associated with huge financial burden [3], social stigma [4] and complications such as the development of drug-resistant viral variants [5], and long-term metabolic and neurologic diseases [6]. These limitations highlight the necessity for the development of safe and cost-effective novel approaches to achieve drug-free viral suppression in the pediatric population.

Colonization of the gastrointestinal (GI) tract by microbes begins at parturition and/or immediately after birth (though some have proposed potential colonization even in utero [7–9]) and continues to evolve during the first three years of life. The evolution of early life microbiome is dependent on multiple factors such as birth mode, gender, maternal microbial composition, diet (breast milk or formula), antibiotic exposure, geographical locations, and environmental factors [10]. The maturing microbiome plays a crucial role in shaping a child's immune development [11] and has been increasingly recognized as a contributor to human disease [12] including infectious diseases [13]. Notably, the first 2 years of life is also the time when children are exposed to HIV both perinatally (in utero and during delivery) and postnatally (during breastfeeding). Pediatric HIV infection is associated with alterations in the gut microbial composition [14, 15], massive depletion of CD4 + T cells in the GI tract [16], inflammation and immune activation [17], and establishment of viral reservoirs [18]. Therefore, to identify strategies that can reduce viral reservoir size and achieve viral remission in the absence of ART, delineating the interactions of gut resident microbes with the maturing immune system of a child living with HIV will be key. This review will summarize our current knowledge of the trans-kingdom interactions between the vertically-transmitted HIV and gut microbiome with the maturing immune system of CLWH. Additionally, we will focus on interventions targeting the microbiome with implications for drug-free HIV remission in the pediatric population.

Main text

HIV persistence in the pediatric population

The majority of children who are infected perinatally or postnatally through breastfeeding, if left untreated, succumb to AIDS within two to three years of age [19]. Initiation of ART in children results in suppression of plasma viral loads, with almost equal potency as that of adults [20, 21]. Early initiation and adherence to ART significantly impede disease progression and result in a relatively smaller HIV reservoir size [22–24], but do not eliminate the reservoir. This is evident from the case of "Mississippi baby" who was born with HIV and was put on ART within 30 h of birth [25]. After 18 months of ART, treatment was discontinued. Although this child remained virally-suppressed without ART for 27 months, HIV eventually rebounded, indicating very early seeding and persistence of rebound-competent HIV in therapy-suppressed children. Similar rapid rebound in viremia within 7 to 35 days of analytical treatment interruption has been documented in experimentally Simian/Human immunodeficiency virus (SHIV)-infected infant rhesus macaques [26, 27]. In contrast to adults, the rate of decay in proviral DNA levels is considerably slower in children [28] which might indicate either inherent differences in the nature of latently infected cells in adults and children, or an inefficient elimination of infected cells by the relatively immature immune system of children. Furthermore, clonal expansion of latently infected cells is considered a major mechanism for the maintenance of HIV reservoirs over time [29, 30]. Latently infected, resting CD4 + T cells isolated from vertically-infected children can be activated to produce replication-competent virus, confirming their potential to contribute to the viral recrudescence upon therapy cessation [31].

HIV persistence on ART in children is not very well-characterized due to the challenges of inadequate volume of blood samples available for quantitative assessments [32]. Unlike adults, where memory CD4 + T cells are the main cellular source of harbored HIV during ART [33–35], in children, naïve CD4 + T cells are a major contributor to the total HIV reservoir [27, 36]. Additionally, using SHIV-infected infant rhesus macaques, the GI tract was demonstrated as a major anatomical site that harbors viral RNA/DNA-positive T cells after long term ART-suppression [26, 37]. In these infant macaques, upon treatment interruption, gut resident CD4 + T cells were the source of the quickest and strongest viral rebound. Therefore, HIV persistence within cellular reservoirs in children represents a challenge that needs to be overcome to achieve ART-free viral control in the pediatric population.

Gut microbiome in pediatric HIV infection

HIV exposure is associated with disruption of the gut epithelial barrier and translocation of GI microbes and microbial products to the lamina propria, and eventually to systemic circulation [38]. Microbial translocation is a key driver of immune activation and chronic inflammation that leads to HIV disease progression [38–40]. HIV exposure-induced gut mucosal damage provides favorable conditions for alterations in the composition of gut microbial communities, also known as microbial dysbiosis [41]. Multiple studies in adults have discussed microbial dysbiosis in the GI tract, including alterations in the diversity of bacteria [42], fungi [43, 44] and virome [45, 46]. To date, only a few studies have focused on microbial dysbiosis in children and have only studied the gut bacteriome [14, 15, 47–50].

Similar to adults [51], the gut microbiome of CLWH also demonstrates a lower bacterial richness and diversity with altered colonization of bacterial taxa compared to children without HIV [14, 49, 50]. While there are differences in specific taxa altered upon HIV infection among various studies, owing to alterations in geographical location, age, route of HIV exposure and potential differences in the microbial sequencing approach, most of the studies have demonstrated an increase in the relative abundance of bacteria associated with immune inflammation and activation and a decrease in bacteria associated with maintenance of gut permeability and integrity. For instance, using a cohort of perinatally infected CLWH from India, Kaur et al., demonstrated an elevated relative abundance of *Prevotella*, a bacterial taxon associated with upregulation of microbial translocation marker, soluble CD14 [52], and immune inflammation marker [53], interferon-gamma inducible protein 10 (IP-10) [49]. In the same cohort of children and additional cohorts from Zimbabwe, Spirochaetes and Corynebacterium, bacteria that promote immune inflammation [54, 55], were upregulated during chronic HIV infection [49, 50]. Finally, *Lachnospiraceae* [49, 50, 56] and *Clostridia* [14], bacterial taxa that can produce anti-inflammatory short chain fatty acids such as butyric acid [57] and can maintain gut barrier integrity [58] were found to be downregulated in CLWH on suppressive ART, compared to uninfected children. Whether this HIV-induced modulation of the gut microbiome creates an immune environment that provides a competitive advantage for establishment and maintenance of a stable reservoir needs further investigation. In fact, in a recent clinical trial in adults living with HIV, the Bacteroidales:Clostridiales ratio was inversely correlated with HIV reservoir size and viral control post-analytical ART interruption (ATI) [59], highlighting the potential contribution of the microbiome of an individual on their HIV persistence status. Furthermore, in an in vitro study, butyric acid producers that are downregulated in CLWH on ART were shown to induce viral reactivation from latency [60], further highlighting the complex interaction that exists between gut bacterial environment and the vertically transmitted virus in maintaining a stable viral reservoir. To date, the majority of pediatric studies to understand the impact of viral infection on the gut microbiome in CLWH have focused on cohorts from low- and middle-income countries (LMICs), where the prevalence of HIV is highest. Consequently, HIV-mediated gut microbial dysbiosis in US pediatric cohorts remains uncharacterized. A recent study comparing the fecal microbiome of adults from the US, Botswana, and Uganda has indicated that despite the occurrence of HIV-mediated gut microbial dysbiosis in individuals from each region, there was no similarity between altered bacterial taxa across geographical regions [61]. Since the phylogenetic composition of the gut microbiome of children from different geographical locations is distinct due to differences in diet, cultural and socioeconomic status [62], studies focused on profiling any potential effect of HIV-mediated gut microbial changes on established viral reservoirs in children from distinct geographical locations would be crucial to better understand the interactions of vertically acquired HIV with the gut microbiome.

Moreover, to date, studies in CLWH interrogating the interactions of the virus with the gut microbial taxa have not specifically categorized children into perinatally (in-utero or during delivery) or postnatally (breastfeeding) infected. Therefore, future studies to delineate the differences in microbial dysbiosis among perinatally and postnatally infected children should be performed.

While the interactions of the developing gut microbiome of CLWH with the establishing viral reservoir are investigated, the impact of small molecular antiretrovirals and common childhood antibiotics, that have the potency to alter the colonization of gut microbiome needs to be considered. Based on the recommendations from The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, currently, ART is initiated on every child diagnosed with HIV [63]. Studies in CLWH have demonstrated that despite the administration of effective ART, alterations in gut microbiota composition persist and long-term ART only partially resolves gut microbial dysbiosis [14, 50]. However, ART can also potentially contribute to an altered microbiome [14, 49]. Moreover, exposure to multiple types of ART regimens such as Ritonavir-boosted protease inhibitor or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens resulted in differential microbial colonization [14]. Specifically, children on protease inhibitor-based regimens had lower bacterial diversity

compared to those on NNRTI-based regimens. It is hypothesized that this protease inhibitor-mediated alteration of the gut microbial colonization is due to altered microbial metabolism, that inactivates cytochrome P450 [14]. Similar to ART, the effect of cotrimoxazole, a broad-spectrum antibiotic commonly prescribed in children of developing countries [64], has also been investigated in the setting of HIV infection [15, 50]. Antibiotic treatment resulted in the alteration of the gut microbiome of CLWH to a dampened inflammatory phenotype [65]. Furthermore, differential gut bacterial taxa were reported in CLWH treated with ART and cotrimoxazole compared to antibiotic-naive ART-treated children [15], implying interactions of antibiotics and antiretrovirals. Additionally, HIV-induced microbial dysbiosis in children might also lead to differential metabolism of antiretrovirals and antibiotics leading to reduced bioavailability of the drugs [66], although this hypothesis needs to be investigated in the setting of pediatric HIV infection.

Impact of gut microbiome on the developing immune system in pediatric HIV infection

The immune system of pediatric elite controllers (PECs), an extremely rare group of children who can control HIV without ART [67, 68], provides a model to guide the development of therapeutic strategies to achieve drug-free long-term HIV suppression. An altered immune profile in PECs compared to pediatric progressors (PPs), a population that progresses to disease, in the absence of therapy, has been documented [68]. Since the gut microbiome in a child plays a crucial role in educating and shaping the immune system [69], we hypothesize that modulating this microbiome-driven early-life immune ontogeny to a landscape that mimics that of PECs might be a potential way to achieve ART-free viral suppression. To build an immune system that can control HIV replication without treatment, understanding the influence of specific gut microbial species on the immune response observed in PECs is key.

The acute phase of HIV infection is characterized by activation and dramatic depletion of CD4+T cells. After ART initiation, CD4+T cell levels are partially restored, active HIV replication is suppressed, and life-long viral latency is established in memory CD4+T cells [70–72]. Unlike PPs, PECs have higher proportions of naïve CD4+T cells and lower activated and exhausted memory CD4+T cells [68]. Since multiple studies demonstrated that in the pediatric population, naïve and not memory CD4+T cells are the major contributors to the total HIV reservoir [27, 36], understanding how gut commensal microbes interact with these two populations of CD4+T cells will be important to determine the influence of gut microbiome on HIV persistence. Gut commensal bacteria can drive the differentiation of intestinal naïve CD4+T cells to T cell effector subsets, including Th17 and regulatory T cells (Tregs). Importantly, *Faecalibacterium* was correlated with a higher abundance of naïve CD4+T cells [73]. A proper balance of functional Th17 and regulatory T cells (Tregs), involved in the maintenance of gut mucosal integrity and dampened immune activation, was indicated to be crucial for HIV suppression in the pediatric population [74–76]. Interestingly, gut bacterial species including, *C. coccoides*, *Staphylococcus*, *C. perfringens* and *Bacteroides fragilis* predicted the levels of Tregs and Th17 cells in pediatric cohorts living with the virus [15]. On the other hand, gut bacterial commensals can interact with intestinal memory CD4+T cells and drive their activation and release of epithelial barrier-protective cytokines [77]. While the association of CD4+T cell activation status with HIV reservoir is lacking in PECs, in adult elite controllers, this T cell phenotype was associated with a reduced HIV reservoir size [78, 79]. Therefore, gut microbial components that can induce a CD4+T cell phenotype as observed in PECs might lead to reduced viral persistence. Using multiple cohorts of vertically-infected CLWH, a higher relative abundance of gut bacterial taxa *Clostridium coccoides*, *Staphylococcus*, *Clostridium perfringens*, *Succinivibrionaceae,* and *Lachnospira* were associated with elevated counts of systemic CD4+T cells [15, 50, 73].

While the influence of the gut microbiome on CD8+T cell functionality in CLWH has not been characterized yet, taxa such as *Lachnospira* have been associated with an elevated frequency of CD8+memory T cells [73]. Humoral immunity, especially B cell functionality and non-neutralizing antibody functions has been associated with improved HIV control in the pediatric population [80, 81]. However, the relationship between gut microbiome and HIV-specific humoral immune responses has not been characterized in CLWH. Owing to the relatively immature adaptive immune response in children, innate immune cell functionality is crucial for achieving HIV control. While studies characterizing innate immune cell functionality in PECs are currently lacking, these cells were shown to be influenced by gut microbial species. For instance, in a cohort of CLWH, *Ruminococcus* was negatively associated with the NK cell population [73]. Additionally, gut bacterial taxa such as *Lachnospira* and *Ruminococcus* dampened overall immune inflammation in CLWH [49, 73]. To determine whether these associations are indicative of any causal relationships, further intervention studies delineating the role of these commensal bacteria on the HIV reservoir in the pediatric population will be needed. Profiling the gut microbiome of PECs might also be crucial to understanding the role of commensals on HIV persistence. However, one should

be cautious in interpreting the data, as viral control due to the pre-existent immune and genetic features in PECs [67, 68] might contribute to an altered gut microbial profile in this population. In this scenario, non-human primate models of viral infection where the temporal nature of gut microbial evolution and establishment of HIV reservoir can be studied in parallel could be instrumental.

Microbial modulation as a potential therapy to achieve pediatric HIV remission

The intestinal microbiome of children is most plastic during the first 2–3 years of life, when it can be shaped by external factors such as diet and environmental exposure. It is believed that the mother's womb is mostly sterile and the first microbial seeding of an infant starts during birth. However, several groups have documented the possibility of microbial colonization in utero by demonstrating the presence of microbial communities in the placenta, amniotic fluid, and meconium [8, 82, 83]. As the baby descends through the birth canal, bacterial taxa such as *Lactobacilli* and *Bifidobacteria*, commonly found in the mother's vaginal tract, colonize the baby's intestine by entering through their mouth [84, 85]. Therefore, the mode of delivery of the baby is a crucial predictor of their gut microbial profile. Babies delivered by Cesarean section exhibit an abundance of bacterial taxa obtained from their mother's skin and the environment, including *Clostridiodes difficile*, *Staphylococcus*, *Corynebacterium* and *Propionibacterium* [86, 87]. After parturition, an infant's gut microbial community drastically develops and is influenced by factors such as skin-to-skin contact and breastfeeding vs. formula feeding. Compared to formula-fed, breastfed infants exhibit an abundance of *Lactobacillus* and *Bifidobacterium* species [88], which evolve to a *Bacteroides*- and *Firmicute*-rich phenotype upon introduction of solid food [89]. Upon weaning, a child's gut microbiome rapidly undergoes maturation for the first 2–3 years of life, leading to a more stable adult-like microbiome [90]. Therefore, the period when the microbiome of a child is most dynamic might be the window of opportunity when microbiota-targeted interventions can modulate the child's intestinal microbiome composition and build a metabolic and inflammatory condition that could potentially reduce HIV replication and persistence. Similar to adults living with HIV [91, 92], several gut microbiome-targeted approaches have been investigated in CLWH, with an aim to alter their gut microbiome and associated immune phenotypes. In a pilot placebo-controlled double-blinded study in CLWH [56], nutritional supplementation with PMT25341, a mixture of probiotics (*Saccharomyces boulardii*), prebiotics (long chain fructo-oligosaccharides, galacto-oligosaccharides) and supplements such as essential amino acids (arginine and glutamine), long chain fatty acids (eicopentaenoic and docosahexanoic acid), vitamin D and AM3, a glycopeptide produced by *Ricinus communis* was shown to restore the gut microbial imbalance caused by HIV infection, suggesting the feasibility of modulating the microbial composition in a pediatric population. The impact of this nutritional supplement on alterations of gut microbiome composition has also been shown in adults living with HIV [91], where the PMT25341 intervention group demonstrated enrichment of anti-inflammatory bacterial taxa that are depleted among CLWH [57]. However, this nutritional supplementation did not result in immune modulation among children [73]. In contrast, short-term oral probiotic therapy with milk containing bacterial species including *Bifidobacterium bifidum*, *Streptococcus thermophilus*, *Lactobacillus casei* Shirota (LcS), *Lactobacillus sporogens* and *Lactobacillus plantarum IS-10506* resulted in modulation of the maturing immune system of CWLH, including an increase in the frequency of peripheral CD4 + T, Th17 and Th2 cells, decrease in activated CD8 + T cells [93–95], and reductions of bacterial translocation marker, blood lipopolysaccharide (LPS) [96], and HIV plasma viral load [93]. Probiotics are clinically safe for most individuals [97], result in improved nutrition and growth in CLWH [93] and lead to persistent intestinal bacterial colonization with the administered organism [98]. In a pilot double-blind placebo-controlled study, oral capsular fecal microbial transplantation (FMT) of adults living with HIV demonstrated changes in the intestinal microbial composition to a phenotype observed in people without HIV and alterations in markers of intestinal injury [99, 100]. While FMT studies have not yet been conducted in CLWH, this gut modulation approach has been successfully applied for the treatment of several gastrointestinal diseases in children such as *Clostridiodes difficile* infection (CDI), ulcerative colitis and Crohn's disease, where stool from healthy donor children of the same age and unrelated to the patient was used [101, 102]. This approach has been found to be safe in children [102]. In a retrospective study using 372 patients aged 11 months to 23 years, FMT to treat CDI was shown to be comparably safe and efficacious among children and young adults [103]. Taken together, these studies highlight the feasibility of modulating the gut microbiome of CLWH immediately after HIV diagnosis to a phenotype that might reduce HIV disease progression and interfere with HIV persistence by generating an anti-HIV immune system (Fig. 1).

Conclusions

The gut microbiome of an individual evolves and matures for the first 3 years of life, before achieving a stable adult-like phenotype. As the microbiome develops in a child,

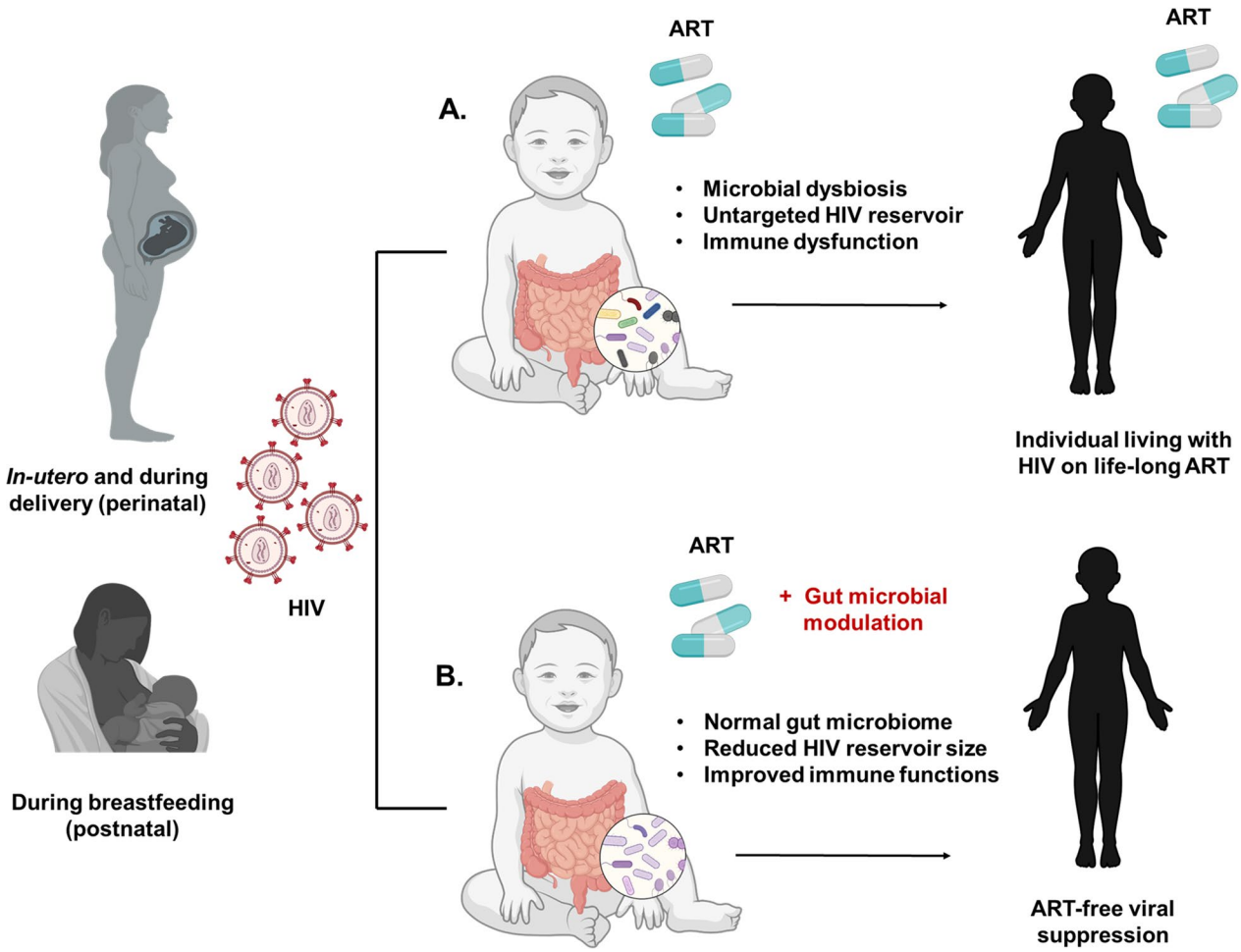

Fig. 1 Gut Microbial modulation as a potential strategy to achieve ART-free HIV remission. Modulation of the gut microbiome of children who acquired HIV perinatally (in utero or during delivery) or postnatally (via breastfeeding) to a phenotype that reduces HIV reservoir size and repairs HIV-mediated immune imbalances might potentially lead to ART-free viral suppression in the pediatric population

it also influences immune ontogeny. Therefore, understanding the interactions of the continuously evolving microbiome and maturing immunity in CLWH can be used to guide the development of strategies to achieve ART-free HIV control in the pediatric population. Here, we have reviewed the specific components of an early-life microbiome and immune responses in CLWH that might be exploited to reduce HIV persistence. Finally, we have discussed the currently used approaches of microbial modulation in this population that lead to altered immune phenotypes. Building a gut microbiome during early life that can reduce HIV persistence and improve anti-HIV immunity might be a promising approach to achieving ART-free long-term HIV control in the pediatric population.

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N.S, O. F, A. C, S.B, and R. G conceived and wrote the manuscript. N.S, O.F, S.B, and R. G prepared the figure. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

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The authors declare no competing interests.

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