Accelerated aging in perinatally HIV-infected children: clinical manifestations and pathogenetic mechanisms

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ABSTRACT

Background: Premature aging and related diseases have been documented in HIV-infected adults. Data are now emerging also regarding accelerated aging process in HIV-infected children.
Methods: A narrative review was performed searching studies on PubMed published in English language in 2004-2017, using appropriate key words, including "aging", "children", "HIV", "AIDS", "immunosenescence", "pathogenesis", "clinical conditions".
Results: Premature immunosenescence phenotype of B and T cells in HIV-infected children is mediated through immune system activation and chronic inflammation. Ongoing inflammation processes have been documented by increased levels of pathogen-associated molecular patterns (PAMPS), increased mitochondrial damage, higher levels of pro-inflammatory cytokines, and a positive correlation between sCD14 levels and percentages of activated CD8$^+$ cells. Other reported features of premature aging include cellular replicative senescence, linked to an accelerated telomeres shortening. Finally, acceleration of age-associated methylation pattern and other epigenetic modifications have been described in HIV-infected children. All these features may favor the clinical manifestations related to premature aging. Lipid and bone metabolism, cancers, cardiovascular, renal, and neurological systems should be carefully monitored, particularly in children with detectable viremia and/or with CD4/CD8 ratio inversion.
Conclusion: Aging processes in children with HIV infection impact their quality and length of life. Further studies regarding the mechanisms involved in premature aging are needed to search for potential targets of treatment.

INTRODUCTION

Subsequently to the introduction of the combined highly active antiretroviral therapy (ART), life expectancy of HIV-infected adults has increased dramatically, but it is currently not yet comparable to that of healthy indivi-duals [1]. Indeed, despite ART, the lifespan of HIV-infected individuals in Western countries is shortened by an average of 10 years [2], and accelerate aging processes and occurrence of precocious diseases have been reported in comparison to age-matched HIV-uninfected controls [3]. Aging is defined as a prog-

ressive loss of physiological integrity, with heterogeneous organ decline, naturally ending by death [4]. This process is associated with decreased ability to face stress, increased frailty, and increased prevalence of age-related comorbidities [4,5]. Accumulating data suggest that aging process does not spare HIV-infected children, as well as adults. It is important to underline that by the end of 2013, 3.3 million children under 15 years old were living with HIV infection worldwide, and 630,000 of them had access to ART [6]. These children receive antiretroviral drugs for all their lifetime and, having a longer life expectancy than in the past, must face a chronic condition. Pathogenic mechanisms of premature aging, that are well documented in HIV-infected adults, are now emerging also in HIV-infected children, with an impact on their quality and length of life [7-11]. Clearly, HIV infection has different characteristics in adults than in children. Perinatally infected children have higher HIV plasma viremia and faster disease progression compared to adults [12,13]. This slower control of viral replication may depend from the fact that the immune system is still maturing. Exposure to HIV or to ART since, or before, birth may affect premature aging and immune senescence in children, even more than in adults. This narrative review describes the pathogenic mechanisms of premature aging in children, possibly underlying the main related clinical features.

RESULTS

Clinical conditions related to premature aging in HIV-infected children

The introduction of ART has changed the natural history of pediatric HIV infection and mortality in children has decreased by over 80-90% in Europe [14, 15]. Similar data has been reported in the United States where mortality rate in HIV-infected children declined from 7.2 per 100 child/year in 1994 to 0.6 per 100 child/year in 2006 [16]. Thus, HIV infection is now considered a chronic disease which persists for many decades. However, it has been estimated that HIV-infected children display mortality rates 30 times higher than uninfected children due to chronic diseases, such as metabolic, cardiovascular, kidney and neurological disorders, and cancers [7-11]. These "non-AIDS related pathologies" represent a group of conditions possibly associated with HIV-mediated aging; the ongoing inflammatory immune process, that may persist despite ART, may also drive the premature cellular aging. The whole picture is complex and probably due to the interaction of multiple biologic and pharmacologic mechanisms (Table 1).

Renal function

Renal function of HIV-infected children may be impaired not only due to the classic HIV-associated nephropathy (HIVAN), commonly reported in the pre-ART era, but also for the development of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, acute kidney injury, renal nephrotoxicity syndromes associated with some specific antiretroviral drugs (i.e. tenofovir), and for the ongoing inflammatory process. Overall, these conditions lead to a premature loss of renal function [17-19].

Compared to HIV-uninfected controls, the prevalence of albuminuria has been reported to be 2-5-fold higher in HIV-infected children [20]. Main risk factors are family history of renal disease, genetic predisposition (such as Apoliprotein (APOL)-1 renal risk variants), immune suppression, history of proteinuria, diabetes, hepatitis C virus co-infection, and treatment with certain antiretroviral drugs [20, 21]. ART has dramatically reduced the incidence of HIVAN, but a clear benefit in non-HIVAN kidney disease has not been demonstrated [22]. APOL-1 renal risk variants are strongly associated with chronic kidney disease and especially with HIVAN in individuals with sub-Saharan African ancestry; about 18% of children with perinatal HIV infection and high risk APOL-1 genotype develops chronic kidney diseases, but biological reasons for this phenomenon are still unknown [23]. It has been demonstrated that synergy between Vascular Endothelial Cell Growth Factor (VEGF)-A, Fibroblast Growth Factor (FGF)-2 and the HIV Tat protein can affect *in vitro* cytoskeletal structure and permeability of cultured renal endothelial cells (REC) and podocytes, which compound the glomerular filtration barrier. Urine samples from HIV-infected children with renal diseases showed high levels of VEGF-A and FGF-2, and induced similar changes in cultured REC and podocytes [24]. In addition, a recent study has demonstrated that transmembrane TNF-α facilitates HIV infection *in vitro* of podocytes and REC of children with HIVAN [25]. These mechanisms may lead to a precocious renal disease in HIV-infected children.

Neuropsychological conditions

Before the introduction of ART, HIV-infected children were often affected by HIV encephalopathy characterized by impaired brain growth, motor deficits and developmental delay [26]. After the introduction of ART, HIV encephalopathy has declined from 30%-50% to <2%, but other neuropsychological disorders have been reported at higher rates than in HIV-uninfected sex and age matched-controls with same ethnicity and socioeconomic status [27]. In addition, lower total

intelligence quotient, language impairment, poorer working memory, gross and fine motor functioning and visual-motor impairment have been extensively report-ed in ART-treated HIV-infected children, more frequently than in healthy controls [27-30]. On the other hand, memory and executive functioning domains seem

Table 1. Clinical conditions related to premature aging in HIV-infected children.

Features	Characteristics/mechanisms	References	
Renal function	Synergy between VEGF-A, FGF-2 and the HIV Tat protein affect the structure of renal endothelial cells and podocytes, leading to a precocious renal disease.		
	Transmembrane TNF-α facilitates HIV infection of podocytes and renal endothelial cells	Das Jr et al, 2016	[24]
		Li J et al, 2017	[25]
	In children with HIV-related nephropathy, podocytes express TNF-α mRNA and protein, as described in other renal inflammatory diseases		
Neuropsycological conditions	Neuropsycological disorders despite effective ART are reported in HIV infected children (CNS is a reservoir for HIV replication, some drugs have poor CNS penetration, persistent immune activation is ongoing)	Cohen S et al, 2015	[29]
		Vreeman RC et al, 2015	[30]
		Wilmshurst JM et al, 2018	[31]
		Van Arnhem LA et al, 2013	[32]
	White matter signal abnormalities has been described in HIV-infected children on early ART	Ackermann et al, 2014	[33]
	Cerebrovascular disease has been reported in HIV infected children in the HAART era possibly due to inflammatory or autoimmune response against vascular wall	Connor MD et al, 2009	[34]
		Hammond CK et al, 2016	[35]
Bone metabolism alterations	Senescent phenotype of osteoblasts have been described in HIV-infected children	Warriner AH et al, 2014	[38]
	Precocious bone abnormalities may be related to HIV-driven chronic inflammation: IL-1, IL-6, IL-17, TNF-α boost osteoclast, suppress osteoblast activity and cause apoptosis	Masky KC et al, 2010	[39]
		Puthanakit T et al, 2013	[40]
		Gibellini D et al, 2008	[42]
	HIV Tat and Nef directly alter osteoblastic differentiation;	Gibellini D et al, 2008	[42]
	HIV gp 120 promotes apoptosis of osteoblasts by upregulating TNF-α	Beaupere C et al, 2015	[43]
	HIV induces increased RANKL expression, stimulating osteoclastogenesis, and bone reabsorption	Natsag J et al, 2016	[41]
	High percentages of activated and senescent CD4^{+} and CD8^{+} T cells correlate with low bone mineral density	Manavalan JS et al, 2016	[44]
Cardiovascular disease	Coronary plaque is associated with markers of T-cell activation and E-selectine / endothelial inflammation / in HIV infected children	Mattingly AS et al , 2017	[51]
	Subclinical atherosclerosis is related with low CD8^{+} count	Sainz T et al, 2014	[50]
	Carotid intima-media thickness is related to high sensitivity C reactive protein levels	Ross AC et al, 2010	[52]
	ART-related lipodystrophy, dyslipidemiaand, and glucose intolerance predispose HIV-infected children to early cardiovascular disease	Loomba-Albrecht LA et al, 2014	[53]
Endocrine alterations	HIV-driven chronic inflammation can cause hypothalamic-pituitary-adrenal axis alterations and increasing glucorticoid production	Loomba-Albrecht LA et al, 2014	[53]
	Lypodystrophy and dysplidemia have been found in HIV-infected children not receiving ART		
Cancer risk	Increased incidence of non-AIDS related malignances has been found HIV infected children, despite ART	Chiappini E et al et al, 2007	[54]
		Alvaro-Meca A et al, 2011	[55]
		Davidson A et al, 2011	[56]
		Franceschi S et al, 2010	[58]
	Chronic activation, increased cell turnover and accelerated immune senescence is involved in cancer development	Simard EP et al 2012	[57]
		Chiappini E et al, 2014	[10]

to be only slightly affected in HIV-infected children, while they are frequently compromised in HIV-infected adults [29, 30]. This discrepancy in neurological impairment between children and adults may be due to the fact that in adults HIV neuro invasion occurs long after neuronal development has ended, while in children the viral spread is parallel to the neurological development [31]. Magnetic resonance imaging studies demonstrated that the neurological abnormalities observed in children are associated with ventricular and/or sulcal enlargement and white matter lesions. These findings are reported both in HIV-infected ART-treated and non-treated children, suggesting that the starting phase of active viral replication in central nervous system (CNS), occurring prenatally and prior to treatment, is crucial for the development of neuro-imaging abnormalities [32, 33]. One study demonstrated white matter abnormalities in children under 3 years of age that had started ART before 3 months of age, indicating that infiltration and damage of the CNS by HIV occurs at an early stage of infection [33]. In addition, CNS is a reservoir for HIV replication that causes itself immune activation and precocious neurological damage, despite ART [32]. The role of long-term ART is also unclear: despite good immunologic and systemic viral control, cognitive impairment may persist, probably due to the poor drug CNS penetration, or persistent immune activation despite ART. On the other hand, molecules with high CNS penetration may also display neurotoxic effect [30]. Another typical neurological finding in HIV-infected children is the HIV-associated cerebral vasculopathy, defined as an arteriopathy of medium-sized cerebral vessels with radiological evidence of vessel stenosis, occlusion or aneurysmal dilatation; it can be asymptomatic, or cause stroke, encephalopathy, or cognitive impairment and its prevalence does not decline after ART introduction [34,35]. The pathogenesis of such a cerebrovascular disease is still unclear, but it may be due to the inflammatory or autoimmune response against vascular wall [35].

Bone metabolism alterations

Children with HIV infection can develop precocious bone abnormalities with an increased risk of osteoporosis and fractures [36]. The risk of bone disorder is greater in children than in adults, because bone mass increases during childhood, accelerating during adolescence [37, 38]. The cause is multifactorial and not fully clear, but many demographic, genetic, hormonal, nutritional factors, HIV levels and drugs are involved. Long-term ART, especially including tenofovir, disoproxil, and fumarate, is associated with greater bone loss [36, 37]. Furthermore, precocious bone abnormalities are probably correlated with HIV-

related chronic inflammation: pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-17, and TNF-α can boost osteoclast and suppress osteoblast activity or cause their apoptosis [39-41]. HIV infection also induces an increased expression of receptor activator of nuclear factor (NF)-kB ligand (RANKL), stimulating osteoclastogenesis, and subsequent bone remodeling and reabsorption [41]. In addition, lower bone mineral density is correlated with a senescent phenotype of the osteoblast [38]. Several studies have demonstrated that HIV gp120 glycoprotein promotes apoptosis of osteoblasts through an up-regulation of TNF-α, and HIV proteins Tat and Nef induce precocious aging in bone marrow mesenchymal stem cells by increasing inflammation and autophagy processes [42, 43]. Manavalan et al. demonstrated that higher percentages of activated and senescent CD4+ and CD8+ T cells correlated with lower numbers of circulating osteoblastic precursor and lower bone mineral density (BMD) in perinatally HIV-infected children and adolescents [44]. However, Jimenez et al. showed that the low nadir CD4+ T cell, but not markers of T-cell activation or senescence, was an independent predictor for low BMD [45]. Thus, further and larger studies investigating the correlation between immunoactivation, immunosenescence and bone mass in HIV-infected children are needed.

Cardiovascular disease

After the introduction of ART, cardiovascular risk and incidence of related cardiovascular complications (i.e. cardiomyopathy) decreased significantly. However, asymptomatic structural abnormalities in HIV-infected children persist during ART and they may be related to subsequent clinically evident diseases in adult life [46]. In HIV-infected adults, many factors may contribute to vascular diseases, including classical risk factors (i.e., obesity, diabetes, hypertension, sedentary life, smoke), the side effects of long-term ART, and HIV-related inflammation and immune activation on heart and vessels [47-49]. The carotid intima-media thickness is considered as a reliable marker of subclinical atherosclerosis and consequently of cardiovascular disease) [49, 50]. Sainz et al. demonstrated that HIV infection in children is associated with thicker carotid intima media, and that a low CD4+ T-cell nadir is related to an increased carotid intima thickness; however, no relation was found between increased carotid intima thickness and inflammation, immune activation, or senescence [50]. On the other hand, a recent study in HIV-infected children has shown that coronary plaque was positively associated with activated CD8+ cells and levels of E-selectin, a marker of endothelial inflammation; these data support that immune activation and endothelial inflammation may accelerate the early stages of

atherosclerosis [51]. In a small study, higher levels of high sensitivity C-reactive protein was found in HIV-infected children compared to healthy controls, which support a role for inflammation in cardiovascular risk in this population [52].

Endocrine alterations

Chronic HIV infection drives the release of proinflammatory cytokines, such as IL-1, IL-6, TNF-α, and interferon (IFN) type 1, that can cause hypo-thalamic-pituitary-adrenal axis alteration, increasing glucocorticoid production [53]. In addition, HIV infected children may show changes in lipid and glucose metabolism including lipodystrophy, dys-lipidemia, and glucose intolerance that predispose to early cardiovascular disease. The main cause of these alterations seems to be the antiretroviral therapy, but a role of HIV infection itself cannot be excluded because lipodystrophy and dyslipidemia has been described in HIV-infected children ART-naïve [53].

Cancer risk

HIV-infected children display an increased cancer risk. Since ART introduction decreased rates of the three AIDS defining malignancies (ADM), i.e. Kaposi sarcoma, non-Hodgkin lymphoma (NHL) and cervical cancer, have been reported in children [54]. However, the incidence of several other "non-ADM" is increasing [10]. One study highlighted that, comparing the periods 1997-1999 and 2003-2008, ADM diagnoses rate fell from 9.1 to 1.0 cancers per 1000 children/year, but in the same periods non-ADM diagnoses rate rose from 0.6 to 8.7 cancers per 1000 children/year [55]. Typical non-ADM are anal cancer, Hodgkin's disease, leiomyo-sarcoma, squamous conjunctival carcinoma and hepato-carcinoma [10]. In addition, non-ADM present atypical histological subtypes and unusual sites compared to those occurring in immunocompetent children [56]. ADM are mainly caused by immunosuppression and co-infection with oncogenic viruses, such as HHV8, EBV, HPV [10]. The pathogenesis of non-ADM involves chronic immune activation, increased cell turnover and accelerated immune senescence (see below), and their incidence is rising [57, 58].

Pathogenetic mechanisms of premature aging in HIV-infected children

The effects of HIV-infection in children and adolescents, especially those who were perinatally infected, and thus are dealing with the virus from birth, are complex. HIV plasma viremia is higher in children than in adults, and the disease progresses faster [13] due to the incomplete maturation of their immune system.

Indeed, infants' immune systems are more plastic and dynamic than adults, and deserve particular attention. The reasons for the differences between children and adults are yet to be fully cleared, but one contributing factor may be the much higher thymic output of T-cells in children than in adults [59]. The mechanisms of premature aging and related disease in HIV-infected children compared to HIV-infected adults is therefore affected by the age-related changes, and most likely result from both lifelong exposure to pathogens and antigens, as well as intrinsic changes in immune cells [60].

The pathogenic mechanisms of aging, and in particular the accelerated immunosenescence, have been partly described in adults, whereas few studies are available in children.

Immunosenescence profile and aging

Results from several studies suggest that peripheral blood lymphocytes of perinatally HIV-infected children have typical features of an aging immune system. The following features have been considered as hallmarks of the aging process: i) high percentage of activated CD45RO$^+$CD95$^+$ T cells, which lack the costimulatory CD28 molecule and are prone to undergo apoptosis, ii) increased levels of Natural Killer (NK) cells, iii) decrease of CD19$^+$ B lymphocytes and iv) mito-chondrial damage (Table 2). Although the CD4$^+$ T cell is the target of HIV infection, also CD8$^+$ T cell compartment was found to be largely impaired in HIV-infected children, as well as in adults. Mansoor et al. studied T cell subsets over the first year of life of HIV-infected ART-untreated children, HIV-exposed uninfected children (i.e. born to HIV-infected mothers) and HIV-unexposed children; they found that in HIV-infected children the naïve CD8$^+$CD45RA$^+$CCR7$^+$ T cells were significantly decreased, while the percentage of CD8$^+$CD45RA$^-$CCR7$^-$ effector memory cells and terminally differentiated CD8$^+$CD45RA$^+$CCR7$^-$ cells were increased compared to the control cohorts: this profile may reflect the immune activation that drives cells into the state of terminal differentiation [61]. Notably, HIV-infected children over one year of age had also a significant higher percentage of CD8$^+$ cells expressing the CD57$^+$ molecule, a marker of replicative senescence [62, 63], than controls [61]. Similar data were observed by Diaz et al., that studied the immuno-senescence of CD8$^+$ T-cell subsets in perinatally HIV-infected children, and found that these children had a higher percentage of senescent CD8$^+$CD57$^+$ cells than age-matched healthy children, but, differently from the previous study, only HIV-infected children with detectable viral load showed increased frequencies of effector memory and terminally differentiated T cells

[64]. Notably, the alteration of memory and senescent T cells in infants may also have implications on the efficacy of childhood vaccination [61] and on cancers development; the progressive increase of senescent T cells with a senescent-associated secretory phenotype (SASP) can hamper immune surveillance during antigenic presentation facilitating the development of tumors [65, 66]. Another study suggested a correlation

between the persistence of inverted CD4/CD8 ratio during ART and the premature immunosenescence in HIV-infected children [67]. Notably, inversion of the CD4/CD8 ratio (<1) is a hallmark of untreated HIV infection, but in some cases this alteration persists despite effective ART and viral suppression, and is associated with increased levels of activated and senescent T cells, and a skewed T-cell phenotype from

Table 2. Pathogenetic mechanisms of premature aging in HIV-infected children.

Features	Characteristics/mechanisms	References	
T cell profile	Increased activated CD45RO$^+$CD95$^+$ T cells	Sainz T et al, 2013	[67]
	Decreased naïve CD8$^+$CD45RA$^+$CCR7$^+$ cells	Mansoor N et al, 2009	[61]
	Increased CD8$^+$CD45RA$^-$CCR7$^-$ effector memory	Sainz T et al, 2013	[67]
	Increased CD8$^+$CD45RA$^+$CCR7$^-$ terminally differentiated cells	Mansoor N et al, 2009	[61]
	Increased of CD8$^+$CD28$^-$CD57$^+$ senescent cells	Mansoor N et al, 2009 Diaz L et al, 2012 Gianesin K et al, 2016	[61] [64] [86]
	Increased CD8$^+$CD38$^+$HLA-DR$^+$ activated cells	Sainz T et al, 2013 Gianesin K et al, 2016	[67] [86]
	Increased PD-1$^+$ exhausted cells	Gianesin K et al, 2016	[86]
	Inverted CD4/CD8 ratio	Sainz T et al, 2013	[67]
B cell profile	Impaired immune response to vaccines	Hart M et al, 2007 Moir S et al, 2008 Cagigi A et al, 2014 Siberry GK et al, 2015	[69] [72] [71] [70]
	Increased levels of immature transitional B cells	Moir S et al, 2009	[73]
	Increased levels of activated memory B cells	Moir S et al, 2009 Cagigi A et al, 2014	[73] [71]
	Increased levels of double negative B cells [CD27$^-$IgD$^-$)	Moir S et al, 2009 Cagigi A et al, 2014 Rinaldi et al, 2017	[73] [71] [74]
NK cell profile	Increased levels of NK cells	Viganò A et al, 2001	[68]
Inflammation	Increased levels of PAMPs [sCD14 and LPS) and pro-inflammatory cytokines	Marks M et al , 2013 Gianesin et al, 2016	[94] [86]
	Correlation between sCD14 and percentages of activated CD8$^+$ cells	Gianesin et al, 2016	[86]
	Increased mitochondrial damage	Viganò A et al, 2001	[68]
Replicative cell senescence	Telomere shortening	Côté HC et al, 2012 Gianesin K et al, 2016	[85] [86]
	NRTIs inhibition of TERT, leading to premature telomeres shortening	Liu X et al, 2007 Tressler R et al, 2012 Hukezalie KR et al, 2012	[83] [82] [84]
	Downmodulation of telomerase expression and activity by HIV Tat protein	Ballon G et al, 2001 Reynoso R et al, 2006 Franzese O et al, 2007	[89] [90] [91]
Epigenetic changes	CpG DNA methylation	Gross AM et al, 2016	[99]
	Acceleration of age-associated methylation pattern	Rickabaugh TM et al, 2015	[100]

naïve toward effector memory [67]. Increased levels of T cells prone to apoptosis along with increased levels of NK cells and mitochondrial damage has been also reported in one study [68].

Several studies suggested that HIV infection can also affect B cell function in both adults and children; these alterations can, at least in part, persist during ART and can impair immune response to vaccines and increase susceptibility to vaccine-preventable diseases [69-72]. The main B cells alterations observed in HIV-infected subjects include increased levels of immature transitional B cells, activated memory double negative B cells (CD27-IgD-), and decreased resting memory B cells subset [73]. Cagigi et al. demonstrated that HIV-infected children with undetectable viral load showed B cell alterations typical of elderly people, such as an increased number of mature-activated and double negative B cells, and these findings have been associated with a poor humoral response versus seasonal influenza vaccination [71]. Rinaldi et al. investigated antibody responses versus flu vaccination in different groups of subjects on the basis of their HIV status and age: young people with HIV infection on ART showed increased frequencies of double negative B cells and decreased plasmablasts similar to older healthy controls, supporting that despite ART, HIV infection drives precocious immunosenescence of B cells [74].

Cellular replicative senescence and aging

An important mechanism of aging and immuno-senescence involves telomeres. Telomeres are repetitive DNA sequences at the end of chromosomes and are essential for protecting chromosome integrity [75]. Telomeres are progressively shortened during each cell division due to end-replication problems of DNA polymerase; when a critical length is reached the cell undergoes cycle arrest and replicative senescence. Senescent cells have a SASP phenotype and secrete factors that can influence age-associated diseases [76]. During life, telomeres get shorter with increasing age, infections, oxidative damage and other factors [77]. Premature telomere shortening leads to premature aging, and this shortening has been correlated with the development of particular pathologies, such as cardiovascular disease and cancer [78, 79]. The pathogenic mechanism(s) underlying the accelerated telomere shortening in HIV-infected children is still poorly understood. Telomerase, a ribonucleoprotein complex containing an internal RNA component (TR or TERC) and a catalytic protein (TERT, Telomerase Reverse Transcriptase), enables telomere elongation; it is active in cancer cells and, transiently, in tissue in rapid proliferation [75]. HIV reverse transcriptase shares

homology with TERT [80,81]; thus NRTIs, such as zidovudine and abacavir, may inhibit TERT and consequently telomerase activity, leading to premature telomeres shortening [82-84]. This inhibition has been shown in *in vitro* systems [83, 84] but the role of NRTIs in telomerase activity and subsequent telomere length in HIV-infected patients is an update question. Cotè et al. investigated whether in utero or childhood exposure to NRTIs affects leukocyte telomere length (LTL) [85]. They studied LTL in 94 HIV-infected (HIV+) children, 177 HIV-exposed uninfected (HEU; born to HIV-infected mothers) children who were exposed to ART perinatally and 104 HIV-unexposed uninfected (HIV-) control children. It was observed that there was no difference in LTL between the HIV+, HEU and HIV-groups, so there were no associations between children's LTL and their perinatal ART exposure or HIV infection; however, among HIV+ children an association was found between HIV load and LTL shortening [85]. In multivariate models older age (as expected) and male gender were the only factors associated with shorter LTL [85]. There is only one study in which both the immunosenescence profile and the leukocyte telomere length were analyzed in 0-5 years old age-matched groups of HIV+, HEU and HIV-children [86]. The percentages of senescent (CD28-CD57+), activated (CD38+HLADR-), and exhausted (PD1+) CD8 cells were significantly higher in HIV+ than in HEU and HIV- children, and LTL was significantly shorter in HIV+ than in HEU and HIV-groups, and, within the HIV+ group, in children without therapy. The different results of the two studies concerning the LTL marker may be caused by the different age of children enrolled in the two studies (0-5 vs 0-19 years old) [86]. Indeed, the telomere shortening is more rapid during the first years of life [87]. Thus, the difference between HIV-infected children and controls may emerge more clearly in a cohort of younger children. Finding that HIV-infected children accumulate CD8+CD38+ and CD8+PD1+ cells together with a higher percentage of senescent CD8+ cells is compatible with a scenario in which viremia leads to high turnover with continual loss and output of naive cells, which rapidly differentiate and exhaust their effector function, resulting in an accumulation of senescent cells with short telomeres. Furthermore, the finding that activated and exhausted CD8+ cells are inversely correlated with telomere length supports the idea that persistent immune activation and cellular exhaustion are closely linked to accelerated biological aging and immune senescence [86]. Chronic immune activation because of persistence of circulating virions may play a role in the senescence pathway; activated cells undergo clonal expansion in response to viral persistence, resulting in differentiation and accumulation of non functional senescent cells [88].

Moreover, it has been demonstrated that HIV infection *itself* and HIV Tat protein downmodulate telomerase expression and activity in lymphoblastoid cells and in peripheral blood cells lymphocytes [89-91]. Further studies are needed to clarify the link between HIV viremia and LTL and to determine whether short-term or long-term uncontrolled HIV viremia is involved and to define whether telomeres shortening is transient or permanent.

Inflammation and aging

An important feature of aging and most of age-related diseases is chronic inflammation. There is a over-whelming evidence that a state of mild inflammation, revealed by increased levels of pro-inflammatory cytokines, such as IL-6, IL-10, is associated to and predictive of many aging phenotypes, including immunosenescence. An important source of chronic inflammation in HIV-infected individuals is provided by microbial translocation due to damage to intestinal mucosa caused by massive HIV-induced T-cell depletion in the gut [92]. Translocation of intestinal bacteria and bacterial products into the bloodstream can activate the immune system by binding to receptors involved in the host inflammatory response, such as Toll-like receptors (TLRs). TLRs are pattern recog-nition receptors which recognize structural components belonging to bacteria, fungi and viruses, known as "pathogen-associated molecular patterns" (PAMPs), and activate the innate immune response [93]. PAMPs include bacterial lipopolysaccharide (LPS), 16S ribo-somal DNA (16S rDNA), and CpG DNA. A recent study demonstrated that high levels of PAMPs, generated by microbial translocation (sCD14 and LPS) are associated with the risk of NHL [94].

The loss of mucosal surface integrity in the gut, due to the massive depletion of $CD4^+$ T cells, involves not only increased mucosal permeability and consequent microbial translocation, but also an increase in "damage-associated molecular patterns" (DAMPs), endogenous molecules released after cell death, such as mitochondrial DNA (mtDNA) [95], high mobility group 1 protein (HMGB1) [96] and defensins [97]. The binding of PAMP and DAMP ligands to the extra- or intra-cellular domain of TLRs initiates a complex-signal transduction cascade which, *via* the NF-κB pathway, ultimately leads to increased transcription of pro-inflammatory cytokines, such as IL-6 and TNF-α [98]. The findings that in HIV-infected children levels of sCD14 were correlated with percentages of activated $CD8^+$ cells, and that HIV-infected children had higher levels of IL-6 and TNF-α than HEU and HIV- children, additionally support the concept that premature immunesenescence in HIV-infected children is mediated through immune system activation and chronic inflammation [86].

Epigenetic mechanisms and aging

A recent study found a correlation between CpG DNA methylation signature in blood cells of HIV- infected patients and premature immunosenescence [99]. DNA methylation status studied in peripheral blood cells from 137 HIV-infected individuals under ART was compared with that observed in peripheral blood cells from 44 healthy controls. By analyzing a set of 26,927 age-associated methylation sites, the authors found increased methylation changes in HIV-infected patients beyond their chronological age, that suggested about a 5 years increase in aging compared to healthy controls; moreover, the premature immunosenescence equally occurred in HIV-infected patients ART-treated for less than 5 years and in those treated for more than 12 years, suggesting that the infection *per se,* rather than therapies, accelerates the aging process [99]. These data partly differ from those of a similar study conducted in HIV-infected adults that reported an acceleration of age-associated methylation pattern of about 14 years [100]; this difference may be probably due to different cohorts. However, not all cells have displayed the same premature aging, and this is one of the major limitations of these studies. Further studies are needed to determine if the methylation status of DNA can affect the immune response to HIV infection *or viceversa.*

CONCLUSIONS

After the introduction of ART, HIV infection became a chronic disease, but HIV-infected children have not yet the same life expectancy of healthy children. The infection behaves differently in children and adults, with important clinical and immunological differences. ART and HIV infection coexist in children from birth, moving up immunosenescence and aging processes; these are more pronounced in children with detectable viremia, focusing attention on the need for early and long-standing control of HIV replication. The patho-genic mechanisms of immunosenescence are various, not completely identified and partly different from those described in adults. Senescent phenotype of T cells makes children more susceptible to infections and less responsive to vaccination. HIV-infected children and adolescents should be carefully monitored for the prompt detection and early treatment of noninfectious disorders related to premature aging. Notably, lipid and bone metabolism, cancers, cardiovascular, renal, and neurological systems must be carefully monitored adopting screening programs and preventive measures in high risk populations, such as children with detec-table viremia or with CD4/CD8 ratio inversion, mainly

due to increased levels of senescent and/or activated CD8$^+$ lymphocytes. The datum that no premature aging effect has been described regarding several organ systems may depend on the fact that no investigation has been executed to date and further studies are needed before excluding premature senescence of these organs. Finally, further studies regarding the mechanisms involved in premature aging are needed to search for potential targets of treatment.

METHODS

In order to perform a narrative review of the available literature, we searched PubMed, Medline, EMBASE and Cochrane databases from January 2004 through December 2017, using the following key words including: "aging", "children", "HIV", "AIDS", "immunosenescence", "pathogenesis", "clinical conditions". Articles were limited to English language and full text availability, and they were excluded if they were redundant or not pertinent. References of all relevant articles were also evaluated and studies published previously than 2004 or in adults were cited if considered relevant (Appendix). Results were critically summarized in the two paragraphs considering: 1) clinical conditions related to premature aging in HIV-infected children, and 2) pathogenetic mechanisms of premature aging in HIV-infected children.

CONFLICTS OF INTEREST

The authors declare conflicts of interest.

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SUPPLEMENTARY MATERIAL

APPENDIX

1) Search strategy for pathogenetic mechanisms in Medline/PubMed: "(Children[Title/Abstract] AND (HIV[Title/Abstract] OR (immunodeficiency[Title/Abstract] AND virus[Title/Abstract]) OR (antiretroviral [Title/Abstract] AND therapy[Title/Abstract]) OR ART[Title/Abstract] OR haart[Title/Abstract]) AND (pathogenesis[Title/Abstract] OR aging[Title/Abstract] OR senescence[Title/Abstract] OR senescent[Title/Abstract] OR apoptosis[Title/Abstract] OR (chronic[Title/Abstract] AND inflammation[Title/Abstract]) OR telomeres[Title/Abstract] OR epigenetic[Title/Abstract] OR (immune[Title/Abstract] AND activation[Title/Abstract]) OR exhaustion[Title/Abstract]) AND (("2004/01/01" [PDAT] : "2017/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Results: 365 articles were initially retrieved and additional 35 studies where recovered from references of selected studies; 360 articles were excluded because not pertinent or related to adults; finally 40 articles where selected for the present narrative review.

2) Search strategy for clinical conditions related to premature aging in Medline/PubMed:" Children[Title/Abstract] AND (HIV[Title/Abstract] OR (immunodeficiency[Title/Abstract] AND virus[Title/Abstract]) OR (antiretroviral [Title/Abstract] AND therapy[Title/Abstract]) OR ART[Title/Abstract] OR haart[Title/Abstract]) AND (pathogenesis[Title/Abstract] OR aging[Title/Abstract] OR senescence[Title/Abstract] OR senescent[Title/Abstract] OR apoptosis[Title/Abstract]) AND (cardiovascular[Title/Abstract] OR (intima[Title/Abstract] AND thickness [Title/Abstract]) OR pressure[Title/Abstract] OR heart[Title/Abstract] OR vasculitis[Title/Abstract] OR (organ [Title/Abstract] AND failure[Title/Abstract]) OR (organ[Title/Abstract] AND damage[Title/Abstract]) OR kidney[Title/Abstract] OR liver[Title/Abstract] OR renal[Title/Abstract] OR nephropathy[Title/Abstract] OR nephro-logic[Title/Abstract] OR cardiologic[Title/Abstract] OR neurological[Title/Abstract] OR psycological[Title/Abstract] OR bone[Title/Abstract] OR hormone[Title/Abstract] OR endocrinological[Title/Abstract] OR glucose[Title/Abstract] OR lipid[Title/Abstract] OR lypodystrophy[Title/Abstract] OR cancer[Title/Abstract] OR lymphoma[Title/Abstract] OR skin[Title/Abstract] OR cutaneous[Title/Abstract] OR muscle[Title/Abstract] OR lung[Title/Abstract] OR pneumologic[Title/Abstract] OR genital[Title/Abstract] OR fertility[Title/Abstract] OR encephalopathy[Title/Abstract] OR incidence[Title/Abstract] OR (adverse[Title/Abstract] AND event[Title/Abstract])) AND (("2004/01/01"[PDAT] : "2017/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang]) AND (("2004/01/01"[PDAT] : "2017/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Results: 91 articles were initially retrieved and additional 12 studies where recovered from references; 66 articles were excluded because not pertinent or related to adults; finally 37 where selected for the present narrative review.