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Mini-review

Pediatric Human Immunodeficiency Virus infection and cancer in the Highly Active Antiretroviral Treatment (HAART) era

Elena Chiappini [a], Elettra Berti [a], Ketty Gianesin [b], Maria Raffaella Petrara [b], Luisa Galli [a], Carlo Giaquinto [c], Maurizio de Martino [a], Anita De Rossi [b,d,*]

[a] Anna Meyer Children's University Hospital, Department of Health Sciences, Firenze, Italy
[b] Section of Oncology and Immunology, Department of Surgery, Oncology and Gastroenterology-DiSCOG, University of Padova, Padova, Italy
[c] Department of Pediatrics, University of Padova, Padova, Italy
[d] Istituto Oncologico Veneto (IOV)-IRCCS, Padova, Italy

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ABSTRACT

Highly active antiretroviral therapy (HAART) changed the natural history of pediatric HIV infection. This review focuses on trends of HIV-associated cancers in childhood in the HAART era and analyses potential pathogenetic mechanisms. HAART reduced AIDS-defined-malignancies (ADM), but incidence of several non-ADM is increasing. HIV-associated immune activation and inflammation, promoting tumorigenesis, can only partially be reduced by HAART. In addition, HIV-infected children may undergo accelerated immune senescence that favors cancer development. How HAART affects this condition is an open question. Lastly, there is no evidence that prenatal exposure to HAART increases the risk of cancer in childhood, but long-term studies are needed.

1. Introduction

At the end of 2012, Human Immunodeficiency Virus (HIV) infection was still the top leading cause of death from infectious disease in the world; 3.4 million children were estimated to be HIV-infected, 70% of whom live in sub-Saharan Africa [1]. Despite the global initiatives and efforts to eliminate mother-to-child transmission of HIV and to extend the use of antiretroviral therapy, 210,000 new pediatric HIV infections still occurred worldwide in 2012, and only one-third of eligible children were receiving treatment [1].

HIV-infected children present a higher risk of developing malignancy than the general population, essentially due to immune system impairment, as the result of the progressive depletion of $CD4^+$ lymphocytes and loss of immune functions, and complex interactions with other oncogenic viruses, such as Epstein-Barr Virus (EBV), Human Herpes Virus type 8 (HHV-8) and Human Papilloma Virus (HPV) [2–5] (Table 1).

Non-Hodgkin's lymphoma (NHL) is the most common type of cancer, followed by Kaposi's sarcoma (KS) and leiomyosarcoma [4,6–8]. The Centers for Disease Control and Prevention (CDC) added NHL and KS to the list of Category C disease for children (AIDS-defining malignancies, ADM), while leiomyosarcoma was included in the Category B list (non-AIDS-defining malignancies, non-ADM) (Table 1). The CDC also included invasive cervical cancer as a Category C disease for HIV-infected adolescents [9,10]. Many other neoplastic disorders, such as Hodgkin's Disease (HD), anal cancer, oral squamous carcinoma, hepatocarcinoma, and Merkel cell carcinoma have also been linked to HIV infection and included in the group of non-AIDS-defining illnesses [4,8,11–13]. Notably, besides immunosuppression and lack of immune surveillance against tumor viruses, chronic immune activation, a hallmark of HIV pathogenesis, may play a role in the onset of malignancies. Manifestations of chronic immune activation include increased levels of pro-inflammatory cytokines and chemokines, polyclonal B-cell activation, increased cell turnover and accelerated immune senescence, all features which may increase the risk of cancer [14–16].

Starting from 1996, the use of a combined therapy including antiretroviral drugs of different classes, named highly active antiretroviral therapy (HAART), has been widely adopted in Western countries. This strategy has been associated with a dramatic change in the natural history of HIV infection in developed countries, giving rise to substantial improvement in terms of survival

* Corresponding author at: Istituto Oncologico Veneto (IOV)-IRCCS, Via Gattamelata 64, 35128 Padova, Italy. Tel.: +39 049 8215894; fax: +39 049 8072854.
E-mail address: anita.derossi@unipd.it (A. De Rossi).

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Table 1
AIDS-defining malignancies and non-AIDS-defining malignancies and related oncogenic viruses.

	Virus
AIDS-defining malignancies	
Kaposi's sarcoma	HHV-8
Non-Hodgkin's lymphoma	EBV, HHV-8
Invasive cervical carcinoma	HPV
Non-AIDS-defining malignancies	
Anal cancer	HPV
Hodgkin's Disease	EBV
Leiomyosarcoma	EBV
Squamous conjunctival carcinoma	HPV
Hepatocarcinoma	HBV, HCV

and quality of life in HIV-infected children [17–21], and HIV infection is now considered a chronic disease [22]. As a consequence, most of the perinatally infected children are aging into adolescence and young adulthood, requiring HAART treatment for decades and close follow-up for occurrence of resistance to therapy as well as long-term toxicity and adverse events, including cancers. Recent findings suggest that the widespread use of HAART and the related increase in life expectancy are associated with changes not only in the incidence but also in the pattern of malignancies in HIV-infected children.

The aim of this review is to analyse epidemiological changes among HIV-associated malignancies in childhood over the HAART era and to evaluate their potential causes. This review also focuses on the relationship between prenatal exposure to antiretroviral drugs and malignancies in childhood.

2. Epidemiology of cancers in HIV-infected children in the HAART era

Malignancies are well-known to occur with higher frequency in HIV-infected children with respect to general population [2,4,6–8,11,23–26], as described for HIV-infected adults [3,27–30]. However, the impact of HAART on cancer incidence in childhood is still unclear, whereas it has been well described in adulthood [3,31–37].

During the pre-HAART and early-HAART eras (i.e. <year 2000) the incidence of malignancy in HIV-infected children varied among studies. In an Italian pediatric population of 1190 perinatally HIV-infected children increased survival and decreased class B/C clinical events were documented during the HAART era [21]. In the same population, significantly decreased cancer rates were observed from pre- to late-HAART periods, from 4.49 to 0.76 per 1000 person/year [8] (Table 2). Accordingly, in the study of Kest et al. [25], comprising 2969 children followed in the Pediatric AIDS Clinical Trials Group (PACTG) from 1993 to 2003, a significantly lower incidence of cancer was documented in HIV-infected children who received HAART for prolonged period (>2 years) than in those treated for less than two years (Table 2). Despite these findings, a case-control study of 1307 perinatally HIV-infected Spanish children showed that the overall rate of cancer did not change significantly from 1997 to 2008, remaining high even in the HAART era [11] (Table 2). Interestingly, the rate of ADM diagnoses fell dramatically from 9.1 (1997–1999) to 1.0 (2003–2008) cancers per 1000 children/year, but in the same period the rate of overall non-ADM diagnoses, in particular malignant neoplasms of bone and articular cartilage, liver, and HD, rose from 0.6 to 8.7 cancers per 1000 children/year [11] (Table 2). Recently, data from the U.S. HIV/AIDS Cancer Match Study were also analysed in order to investigate changes in cancer incidence between the pre-HAART (1980–1995) and HAART eras (1996–2007) in people diagnosed with AIDS during childhood (0–14 years) [23]. The results reflect the findings of the Spanish study. The incidence of ADM declined during the HAART era: the incidence of KS and NHL significantly decreased by 87% and 60%, respectively [23], but the incidence of non-ADM remained high during both time periods, especially for leiomyosarcoma [23]. Leiomyosarcoma is becoming a particularly complex issue and will deserve further research. Although it accounts for only 2–4% of childhood soft tissue sarcomas, it is now the second most frequent malignancy in children infected with HIV or other immunodeficiency diseases in the United States [38]. The prognosis is worst in HIV-infected children compared with non-infected patients, and there is currently a lack of uniform and effective therapies [38].

3. Potential mechanisms for the onset of malignancies in the HAART era

Overall, epidemiological data suggest that HAART is effective in reducing the incidence of ADM in childhood, as in adults, probably due to the improved immune surveillance induced by HAART [3,31–37,39–47]. It is well-known that $CD4^+$ T cell number is strongly associated with the risk of KS and NHL; however, the decline in NHL is less dramatic than that observed in KS [23,30]. Immune dysregulation, such as immune activation, has been described to persist in several children on HAART, even with a normal $CD4^+$ cell counts [42–47], and this may explain the relatively high risk of NHL even in the HAART era. In addition, the incidence of non-ADM is increasing. Etiological agents of non-ADM remain an important open question. Both leyomiosarcoma and HD are EBV-associated cancers [48]. The HIV-related impairment of the immune system represents a favorable setting for both primary EBV infection and subsequent proliferation and/or reactivation, allowing EBV-infected cells to escape from immune control. Immunosuppression may promote the emergence of virally transformed clones, because they are not properly recognized and eliminated by the immune system [49,50]. It has been reported that HIV infection may be associated with a selective loss of EBV-specific $CD4^+$ T cell responses, which may predispose to EBV-related lymphomas [51,52].

3.1. Chronic immune activation and EBV-associated tumors

The immunosuppression induced by HIV is not the only aspect of the complex interplay between HIV and EBV leading to cancer development. Interestingly, Biggar et al. [53] reported that HIV-related immunosuppression appears to have a non-linear effect on HD risk. In particular, the relation between HD risk and $CD4^+$ T cell count has an "inverted U" shape because the risk increases as $CD4^+$ lymphocytes declines, peaking at 225–249 cells/μL, and then falling to very low values. It is plausible that severe immunosuppression, causing considerable alteration of growth signals and cytokine responses, may constrain the development of cancer, whereas immune activation may play a further important role in the genesis of EBV-related tumors. Accordingly, hyperactivation of B cells, characterized by hypergammaglobulinemia, polyclonal B-cell activation, increased expression of activated markers, has been well described in HIV-positive individuals and may be central into the carcinogenic process [54,55]. HIV infection causes massive depletion of $CD4^+$ T cells in the gastrointestinal tract, where it leads to an early breach in the integrity of the mucosal surface, with subsequent translocation of microbial products [56]. Microbial products, such as bacterial lipopolysaccharide (LPS), 16S ribosomal DNA and CpG DNA, are known as pathogen-associated molecular patterns (PAMPs). Loss of mucosal surface integrity also leads to an increase in damage-associated molecular patterns (DAMPs),

Table 2
Epidemiologic data on cancer rate in HIV-infected children during pre-HAART and HAART era.

	Study		
	Kest et al. (2005) [25]	Chiappini et al. (2007) [8]	Alvaro-Meca et al. (2011) [11]
Study period	1993–2003	1985–2004	1997–2008
Study population	2969	1190	1307
Cases (ADM:non-ADM)	20 (3:17)	35 (23:12)	123 (50:73)
Pre-HAART era	1993–1997	1985–1995	
New cases (ADM:non-ADM)	7 (1:6)	22 (14:8)	
Cancer incidence	2.01	4.49	
ADM incidence		2.97	
Non-ADM incidence		1.69	
HAART era	1998–2003	1996–2004	1997–2008
New cases (ADM:non-ADM)	13 (2:11)	13 (9:4)	123 (50:73)
Cancer incidence	1.39		9.4
ADM incidence			3.8
Non-ADM incidence			5.6
Early HAART era		1996–1999	1997–1999
New cases (ADM:non-ADM)		11 (7:4)	33 (31:2)
Cancer incidence		4.09	9.7
ADM incidence		2.60	9.1
Non-ADM incidence		1.48	0.6
Mid HAART era			2000–2002
New cases (ADM:non-ADM)			31 (13:18)
Cancer incidence			8.7
ADM incidence			3.6
Non-ADM incidence			5
Late HAART era		2000–2004	1997–1999
New cases (ADM:non-ADM)		2 (2:0)	59 (6:53)
Cancer incidence		0.76	9.7
ADM incidence		0.76	1
Non-ADM incidence		0	8.7

Note: Incidence rates are per 1000 person/year.

endogenous molecules released after cell death, such as mitochondrial DNA [57]. All these factors released into circulation engage particular pattern recognition receptors, such as Toll-like receptors (TLRs) [58]. The binding of PAMPs and DAMPs to TLRs initiates a complex signal transduction cascade by activation of the NF-kB pathway, inducing increased transcription of pro-inflammatory cytokines, such as IL-6, IL-10, interferon-α, and tumor necrosis factor-α (TNF-α), which drive the B-cell hyperactivation. Chronic activation may favor a microenvironment which triggers tumor development, including expansion of EBV-infected cells. The serum levels of these B-cell stimulatory cytokines and other molecules, such as soluble CD27 and sCD30, generated from the corresponding B-cell receptors during the process of immune activation, are significantly high 1–5 years prior to diagnosis of systemic AIDS-NHL [15,59]. A recent study demonstrated that levels of PAMPs, generated by microbial translocation (sCD14 and LPS), are associated with the risk of NHL [60]. Because of the role played by chronic immune activation in the genesis of NHL, it may be argued that this mechanism partially persists even during HAART. A study of a cohort of HIV-infected patients under HAART found that the increase in $CD4^+$ T cells without suppression of HIV plasmaviremia was accompanied by an increase in EBV load, paralleled by an increase in immunoglobulin levels [61]. Matching this, the EBV-DNA load was higher in patients with detectable HIV plasmaviremia, despite good immunological status (>500 $CD4^+$ T cells/μl) than in patients with undetectable HIV plasmaviremia, regardless of immunological status [41]. It has also been demonstrated that patients with high EBV load have higher levels of pro-inflammatory cytokines (IL-6, IL-10, TNF-α) and PAMPs (LPS) than patients with low levels, and EBV load is strongly correlated with the percentage of activated B cells [41]. In addition, HAART only partially normalizes the serum cytokine levels; IL-6 remains high even 2-3 years after HAART initiation [62]. The association between markers of B-cell activation and the risk of NHL persists even after adjustment for $CD4^+$ T cell count and HIV load, thus supporting the independent role of these markers with NHL risk [60,63,64]. These findings additionally support the concept that B-cell activation, regardless of $CD4^+$ immune reconstitution, favors expansion of EBV-infected cells and the onset of EBV-related malignancies. This aspect may be of particular importance in children; a substantial proportion of children (about 20–30%) develop discordant responses to HAART, characterized by a significant increase in peripheral $CD4^+$ lymphocytes (immunological response), despite persistent detectable viremia (lack of virological response) [42–47]. The reasons for this dissociated response to HAART are not fully understood, but thymic output [42,43,65] and the impaired replicative capacity of drug-resistant viruses [46,66] may be involved. In children with such discordant responses, persistent detectable viremia, despite immune reconstitution, results in persistent immune activation [44]. The chronic state of immune activation/inflammation and expansion of EBV may contribute to explaining the incidence of EBV-related non-ADM in the HAART era.

3.2. HIV infection and immune senescence

Several pieces of evidence have suggested that HIV-infected individuals undergo immunological changes similar to those found in uninfected elderly subjects [16,67]. Compared with age-matched controls, HIV-infected patients have reduced thymic function, as determined by T cell receptor rearrangement excision circle (TREC) frequencies, loss of naïve cells, reduced telomere length of T cells, expansion of end-differentiated effector T cells, which have lost the expression of the CD28 molecule essential for effective T-cell activation, and a contracted T cell repertoire [68–70]. It is thought that early immune senescence in HIV disease is a consequence of immune activation and systemic low-grade inflammation due to persistent activation [16]. These changes, which are well documented in HIV-infected adults, are also

emerging in HIV-infected children. Mansoor et al. [71] have shown that, during the first year of life, in HIV-infected infants there is a greater frequency of $CD8^+$ T cells displaying a senescent phenotype ($CD8^+CD28^-$) than in age-matched HIV-uninfected children. These data were confirmed by Diaz et al. [72] and support the importance of maintaining undetectable viral load in HIV-infected children to avoid premature immune senescence and dysfunction of $CD8^+$ T cells. The effects of chronic immune activation and immune senescence are likely to be more deleterious in vertically HIV-infected children, since their immune system co-evolves from birth with the virus. Phenotypic and functional T cell alterations observed during advancing human age lead to poor responses to vaccines, and increased susceptibility to new infections and tumors in the elderly. With accelerated aging and T cell decline induced by HIV infection, a similar impact on T cell immunity may occur in perinatal HIV-infected children as they pass into adolescence. The progressive accumulation of senescent $CD8^+CD28^-$ T cells may indeed hamper immune surveillance during antigenic presentations or effector functions, facilitating the development of certain types of cancers [73]. Recent findings also indicate that senescent cells acquire a senescent-associated secretory phenotype involving secretion of several inflammatory cytokines, growth factors and proteases which render the tissue microenvironment favorable for tumor growth [74,75].

3.3. HAART and premature aging

Premature aging of HIV-infected patients may also be caused by the adverse effects of HAART. Nucleoside reverse transcriptase inhibitors (NRTIs) may inhibit human telomerase reverse transcriptase [76]. Since immune system functioning depends largely on its capacity for extensive cell division and clonal lymphocyte expansion, telomere length and its regulation by telomerase have attracted considerable attention, due to their potential roles in controlling cell replication [77]. The NRTIs zidovudine (AZT), didanosine (ddI) and abacavir (ABC) have been shown to inhibit telomerase activity in replicating cell lines *in vitro* leading to accelerated shortening of telomere length [78–80]. Recently, it has been demonstrated in adults that the duration of NRTI-containing HAART is inversely associated with telomere length, suggesting that NRTIs, by inhibiting telomerase activity, may be a potential factor contributing to HIV-associated accelerated aging [81]. To date, only one study has investigated the impact of HIV infection and HAART exposure on telomere length in pediatrics, and no association between children's telomere length and their HAART exposure was found [82]. However, a significant association between detectable HIV plasmaviremia and shorter telomere was observed, indicating that uncontrolled viremia may be associated with acceleration of telomere shortening [82]. Although the limitation of this study, due to the unequal age distribution between the groups of HIV-infected and uninfected children enrolled warrants further investigations, it should be emphasized that telomere erosion, due either to HIV and/or NRTIs, does play an important role in carcinogenesis, because it promotes genetic instability, a key event in the oncogenetic process [83,84].

Emerging data suggest that HIV protease inhibitors (PIs) may also trigger premature senescence. It is well-known that PIs have promising antitumor properties; they have several effects on some cellular pathways which are important for tumorigenesis, including reduction of angiogenesis and cell invasion, induction of autophagy, and promotion of apoptosis. In addition, some PIs, including nelfinavir, inhibit the replication of oncogenic viruses, such as HHV-8 [85]. Nonetheless, PIs also have the potential to induce oxidative stress in several cell types and trigger premature aging by a mechanism involving the accumulation of farnesylated prelamin A, that may perturb the DNA damage response and lead to genomic instability [86,87].

4. Cancer risk in children exposed to antiretroviral drugs *in utero*

The widespread use of HAART in pregnancy, *intrapartum* to the mother and *postpartum* to the infant, together with elective caesarean delivery and avoidance of breastfeeding, have significantly reduced the rate of vertical transmission of HIV [88–90]. In the first study, the PACTG076, the protocol was based on AZT monotherapy [91,92], but a combination of antiretroviral drugs is currently recommended in pregnancy to the mother and in some circumstances also to the infant [93–95]. The benefits of prenatal prophylaxis seem to far exceed the short-term adverse events, as reported by the Antiretroviral Pregnancy Registry [96], but the risk of long-term consequences, such as the development of malignancies, is still little known.

Evidence obtained from animal models, as well as from humans, has indicated the potential genotoxic and carcinogenic effects of transplacental exposure to NRTIs, particularly AZT which has been the most frequently studied drug. The other NRTIs, alone or in combination, have been poorly evaluated, but some of them, including lamivudine (3TC), have shown *in vitro* effects similar to those reported with AZT and also seem to strengthen AZT-induced

Table 3
Genotoxicity markers induced by perinatal exposure to antiretroviral therapy.

Mice models	Monkeys models	Humans cells
DNA incorporation of AZT [100]	DNA incorporation of AZT [100]	DNA incorporation of AZT [103,104] DNA incorporation of 3TC [104]
Micronucleated RBCs [106–108]	Micronuclei in mesenchymal cells [109]	Micronucleated reticulocytes [105] Altered heterochromatin organization [114]
	Centrosomal amplification [109]	Centrosomal amplification [102] Aneuplody [102,110] Alterations of gene expression profiling of CD34 + hematopoietic stem/progenitor cell compartment [110]
HPRT mutant frequencies in T-cells [108] *TK* mutant frequencies in T-cells [109] *K-RAS* gene mutations in lung tumors [113] *P*53 gene mutations in lung tumors [113] *H-RAS* gene mutations in skin tumors [119]		*GPA* variant frequencies in RBCs [111] *HPRT* mutant frequencies in T-cells [112]
mtDNA tRNA gene mutations [117]	mtDNA depletion [115,116]	mtDNA depletion [115] mtDNA tRNA gene mutations [118]
Mitochondrial toxicity; changes in oxidative phosphorylation enzymes [117]	Mitochondrial toxicity; changes in oxidative phosphorylation enzymes [116]	

genotoxicity when used in combination [97,98]. Several researches have demonstrated that AZT, being a nucleoside analog and presenting elevated affinity for DNA in mammals, is usually incorporated into eukaryotic nuclear and mitochondrial DNA in place of thymidine by the host polymerases [90,97–100]. This incorporation results in a complex network of events determining mutagenesis, clastogenesis and telomere attrition, leading to genomic instability [98–102]. During the last 15 years, a series of genotoxicity markers has been found and analysed in humans, monkeys, hamsters and mice to demonstrate nuclear and/or mitochondrial DNA damage induced by perinatal NRTIs exposure, as shown in Table 3 [100,102–119].

Transplacental studies in mice have also documented the potential carcinogenetic effects of AZT. The offspring of AZT-treated mice presented a significant and dose-dependent increase in the incidence of tumors involving lungs, liver, and reproductive tracts [100,120]. Transplacental administration of AZT to mice followed by postnatal topical application of 12-O-tetradecanoyl-phorbol-13-acetate (TPA) resulted in a higher incidence of skin tumors compared with mice given TPA alone [119]. Transplacental AZT administration caused hemangiosarcomas and hepatocellular carcinomas in B6C3F1 male mice and mononuclear cell leukemia in F344 female rats [121]. According to these findings, the International Agency for Research on Cancer (IARC) classified AZT as "possibly carcinogenic to humans (Group 2B)", although evidence of the carcinogenicity of AZT in humans is still inadequate [99].

Among clinical trials, Hanson et al. [122] performed a review evaluating the short-term risk for tumors in 727 children with known perinatal AZT exposure who were enrolled into the PACTG 076/219 and the Women and Infants Transmission Study (WITS) and followed from birth onward for a mean of 1.2 (PACTG 076/219) or 3.2 years (WITS). No malignancy of any type was recorded in the AZT-exposed infants. An update from the PACTG 219 and 219C [123], including 2077 HIV-uninfected children, reported that the rate of cancer was not increased in children exposed to NRTIs *in utero*. A study performed in 2612 children, uninfected or with indeterminate infection status, born to HIV-infected women from 2001 to 2004 in England and Wales, disclosed no cases of cancer by the end of 2005 [124]. Benhammou et al. [90] performed the largest and longest prospective cohort study to evaluate the incidence of cancer in HIV-uninfected children or with indeterminate infection status, exposed to NRTIs *in utero*. Between September 1984 and May 2007, 9127 children were enrolled and then followed from birth onward (median age 5.4 years). Ten cases of cancer were detected and the overall incidence did not differ from that expected in the general population (8.9 and 9.6 cases expected in 1990–1999 and 2000–2004, respectively). However, 5 central nervous system (CNS) tumors were observed when only 1.6 and 2.1 cases were expected ($P = 0.05$). Of the 5 CNS tumors, 4 cases of highly malignant primitive embryonal tumors (2 pineoblastomas and 2 retinoblastomas) were observed. This finding should not be underestimated, as these forms are extremely rare in the general population [90]. Although the combination of ddI and 3TC was given to fewer than 4% of the treated women, it was associated with one-third of the cancers and the children exposed to the ddI + 3TC combination presented a higher risk of cancer than those exposed to AZT alone (adjusted Hazard Ratio = 13.6; $P < 0.001$).

To date, there is no evidence of the carcinogenic effects of PI exposure *in utero*. Moreover, no increase in the risk of overall birth defects has been detected among infants prenatally exposed to Lopinavir/ritonavir, the preferred PI recommended for use in pregnancy [125,126], although an association between prematurity and PIs exposure in pregnancy has been described [127].

Overall, conclusive evidence of the carcinogenic effects of transplacental administration of NRTIs has not been documented. Exposure to a genotoxic agent during fetal and neonatal life may have important consequences in view of the intense DNA replication activity which characterizes these periods of life. Further experimental data concerning the genotoxicity of various NRTIs, alone and in combinations, are therefore needed. More larger and longer cohort studies are necessary to evaluate the long-term health consequences of prenatal exposure to antiretroviral agents.

5. Conclusions

The widespread use of HAART has been associated with decreased ADM incidence rates, but the incidence of some non-ADMs is increasing in Western countries. These trends have led to a shift in the spectrum of cancer among HIV-infected children. Available literature data indicate no increased cancer risk in children *in utero* exposed to antiretroviral drugs, but conclusive evidence requires long-term follow-up studies. Further research is needed to clarify how HAART can influence cancer development and the pathogenic mechanisms of ADM and non-ADM in children.

Conflict of Interest

The authors have no conflicts of interest.

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