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REVIEW ARTICLE

Influence of the antiretroviral therapy on the growth pattern of children and adolescents living with HIV/AIDS☆

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Abstract
Objective: Weight and height growth impairment is one of the most frequent manifestations in HIV-infected children and may be the first sign of disease, being considered a marker of disease progression and an independent risk factor for death. The aim of this review is to evaluate the influence of antiretroviral therapy on the growth pattern of children and adolescents living with HIV/AIDS.
Source of data: A non-systematic review was carried out in the PubMed database, with the terms ''HIV'', ''Weight and height growth'', ''ART'' and ''children''. The most relevant publications were selected.
Data Synthesis: Antiretroviral therapy has significantly reduced morbidity and mortality in HIV-infected children and is clearly associated with recovery of weight and height-for-age Z-scores, especially when started early, in the asymptomatic child still without weight–height impairment. Therapeutic strategies involving the GH/IGF-1 axis, especially for children with growth impairment, are still being studied.
Conclusions: HIV-infected children show early weight–height impairment; antiretroviral therapy improves the anthropometric profile of these children.

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PALAVRAS-CHAVE
HIV;
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Terapia antirretroviral

Influência da terapia antirretroviral no padrão de crescimento em crianças e adolescentes vivendo com HIV/Aids

Resumo
Objetivo: O acometimento do desenvolvimento pondero-estatural é uma das manifestações mais frequentes nas crianças infectadas pelo HIV e pode ser o primeiro sinal de doença, é considerado um marcador de progressão para doença e um fator de risco independente para morte. O objetivo desta revisão é avaliar a influência da terapia antirretroviral no padrão de crescimento em crianças e adolescentes vivendo com HIV/Aids.
Fonte dos dados: Foi feita uma revisão não sistemática na base de dados PubMed, com os termos ''HIV'', ''desenvolvimento pondero estatural'', ''TARV'' e ''crianças''. Foram selecionadas as publicações mais relevantes.
Síntese dos dados: A terapia antirretroviral reduziu substancialmente a morbimortalidade em crianças infectadas pelo HIV e está claramente associada à recuperação do escore-z de peso e de estatura para idade, principalmente quando iniciada precocemente, na criança assintomática e ainda sem comprometimento pondero-estatural. Estratégias terapêuticas que envolvem o eixo GH/IGF-1, principalmente para crianças com comprometimento do crescimento, ainda estão em estudo.
Conclusões: As crianças infectadas pelo HIV apresentam comprometimento pondero-estatural precoce e a terapia antirretroviral melhora o perfil antropométrico dessas crianças.

Introduction

Infection by the human immunodeficiency virus (HIV) represents a major pediatric disease worldwide, affecting an estimated 1.8 million children and adolescents under 15 years of age living with HIV. Despite the decrease in the number of new infections in children, the data are still alarming. According to the Joint United Nations Program on HIV/AIDS (UNAIDS), in 2017, 180,000 children acquired HIV infection, and 110,000 died from causes related to acquired immunodeficiency syndrome (AIDS).[1]

Mother-to-child transmission of HIV, also called vertical transmission (VT), is the most common cause of HIV infection in children and may occur during pregnancy, childbirth, or breastfeeding. The elimination of HIV VT worldwide, through the implementation of public health programs, is one of the priorities of UNAIDS and the World Health Organization (WHO).[1] Despite the incontestable progress achieved over the last few years, significant VT rates are unfortunately still observed in low-income countries.[1]

Globally, according to the UNAIDS 2017 newsletter, 36.9 million people are living with HIV worldwide, of whom 51% are women. Infections in young women aged 15–24 years were 44% more frequent than in men in the same age group, despite a 17% decrease when compared to 2010.[1]

In the Latin American scenario, the number of new infections in adults remained stable between 2010 and 2016. There were 96,000 new infections estimated for 2016, compared to approximately 94,000 new infections in 2010. Approximately 90% of these infections occurred in seven countries, with almost half of them (49%) occurring in Brazil. Approximately 1800 infections occurred in children in 2016, most of them in Venezuela, Guatemala, and Brazil.[1]

In Brazil, between 1980 up to mid-2016, 882,810 cases of AIDS were reported, representing a prevalence of 0.4% of the overall population, with 306,444 cases in women. During this period, the total number of children vertically infected by HIV was 14,749.

In the past 10 years, 592 new cases of HIV infection have been reported in children under 5 years of age. Despite an increase in the absolute number of new annual cases between 2007 ($n = 33$) and 2016 ($n = 87$), there was a decrease in the proportion of new cases in children under five, from 0.5% to 0.2%.[2]

The natural history of HIV infection in childhood is quite variable. Clinical manifestations of infection at birth are rarely observed, since transmission occurs predominantly during childbirth. It is estimated that 15–25% of HIV-infected children develop AIDS or die within the first year of life (rapid progressors). Half of the children show some sign or symptom between 5 and 10 years of age (normal progressors) and 15–25% achieve adolescence with no clinical signs or symptoms of the disease (slow progressors). One of the most frequent manifestations is weight and height growth (WHG) impairment, which can occur from the first months of life, with a higher incidence in rapid progressors.[3]

The introduction of the combination antiretroviral therapy (cART) with three drugs in the 1990s substantially reduced the morbidity and mortality of HIV-infected children, adolescents, and adults, causing the disease to be considered a chronic one. Global data for 2017 show that 80% of pregnant women, 59% of adults, and 52% of children and adolescents living with HIV had access to antiretroviral therapy (ART).[1]

Taking into account the strong evidence that shows the benefits of immediate ART, including mainly the reduction of mortality in children under 10 years, improvement of

weight–height growth and pubertal development, immunological improvement, and reduction of inflammation, the World Health Organization (WHO) and guidelines from several countries recommend the initiation of ART for all people living with HIV/AIDS regardless of the clinical, immunological, or virological picture.[4]

Despite the improvement in life expectancy with treatment, children may still have comorbidities related to the underlying disease or to treatment. Among these comorbidities are endocrine alterations, such as adrenal failure, thyroid alterations, lipodystrophy, dyslipidemia, insulin resistance, and alterations in the growth hormone (GH) axis.

Growth failure in children living with HIV occurs due to several factors: the infection itself, with lack of virological and immunological control, opportunistic diseases, and the abovementioned endocrine alterations.

In childhood, the decrease in growth velocity can be the first sign of disease in HIV-infected children, representing a marker of disease progression and an independent risk factor for death. Growth monitoring in children living with HIV is of the utmost importance and can be an indicator of the response to ART in places with limited availability of virological and immunological markers.[5] Therefore, the WHG of these children should be carefully evaluated in all consultations and the lack of improvement observed after the initiation of ART can be considered as a sign of poor prognosis.

Next, the authors describe the growth in HIV-infected children, according to age group.

Prenatal and infant growth

Usually, the weight and length of the newborn are adequate, since the infection transmission occurs at the time of delivery in 70–80% of cases. Infected newborns with birth weight <2400 g show, in general, earlier and more severe clinical manifestations.[6–9] The infected infants show a reduction in the weight and height gain velocity, present as early as 3 months of age, which worsens with time.[8,9] Infants with more severe disease usually have a reduction in weight and height gain before the immune dysfunction becomes evident. Exposed uninfected infants born to HIV-positive mothers also show lower growth rates when compared to non-exposed children. Some justifications for this fact would be multiple caregivers and intrauterine exposure to antiretrovirals.[10,11] A study carried out in Zimbabwe, Africa, also found higher incidence rates of microcephaly in HIV-infected children, when compared to uninfected children.[7]

Growth during childhood

The growth impairment in children living with HIV is multifactorial and includes: inadequate caloric intake, increased energy expenditure and catabolism, HIV enteropathy, gastrointestinal infestations, recurrent opportunistic infections, persistent chronic inflammation, and endocrinopathies (GH-axis alterations, hypothyroidism, and adrenal failure).

GH is a pituitary hormone secreted in pulses and especially at night. It acts on hepatic receptors, stimulating the production of insulin-like growth factor (IGF-1). IGF-1 is transported in the bloodstream by carrier proteins, and the main carrier protein is IGFBP-3.

Both GH and IGF-1 act on growth cartilage, promoting linear bone growth. In addition to the effects on growth, GH also acts on metabolism, such as the stimulation of protein synthesis, lipolysis, and gluconeogenesis.[12]

HIV-infected patients have hepatic resistance to GH (secondary to malnutrition and increased production of pro-inflammatory cytokines), with a reduction in the serum levels of IGF-1 and IGFBP-3. However, asymptomatic patients and those without weight loss have normal concentrations of GH and IGF-1.[13]

GH production in HIV-infected patients seems to be impaired, with approximately 30% of these patients suffering from GH deficiency. The reports of ART-related lipodystrophy led to a greater accuracy of the studies investigating the behavior of the GH-IGF-1 axis in these patients. The most plausible hypothesis is that the visceral fat distribution and the lipid alterations found in these patients would be secondary to GH deficiency.[14]

Infected children usually show a higher frequency of malnutrition and short stature than the non-infected. Additionally, severe malnutrition without edema is more frequent in HIV-infected children, requiring higher caloric supply in symptomatic cases, especially those with more severe clinical pictures.[15] Malnutrition has a multifactorial etiology, such as inappetence, infectious lesions of the digestive tract, malabsorption syndrome, and increased basal energy expenditure.[16]

The mean weight-for-age *Z*-score in infected children younger than 5 years prior to ART initiation is −1.2 to −2.2 and the height-for-age *Z*-score is −2.3 to −2.9.[17,18]

Growth in adolescence

Growth in adolescents before the start of ART is more impaired in low- and middle-income countries, probably due to a delayed diagnosis and start of treatment.[16] In high-income countries, despite height impairment, studies found normal body mass index in infected adolescents.[19] The infected adolescents may also have a later pubertal onset, and the delay magnitude is directly related to the severity of the infection clinical manifestations.[19]

Influence of the antiretroviral therapy on the growth pattern of children and adolescents living with HIV/AIDS

With the introduction of ART, there was a substantial morbidity and mortality reduction in HIV-infected children, with a large decrease in the number of hospitalizations[20] and a lower frequency of opportunistic infections.[21]

The main objective of ART is to suppress viral replication and recover/preserve the immune system.[15] Moreover, there is a decrease in proinflammatory cytokines, which also contributes to preserve the immune system, reducing opportunistic infections and, consequently, improving nutritional status.[22]

Several publications have shown that ART is clearly associated with growth recovery in children living with HIV, usually with faster weight than height gain, in both developed and developing countries.[23]

In the past, the use of ART as monotherapy or dual therapy was already associated with temporary improvement in growth velocity and weight gain. However, since the 1990s, combination antiretroviral therapy (cART) with three drugs has led to viral suppression and a more lasting increase in weight and height, although not enough to reach the means of the overall population.[24]

Data from developed countries show improvement in the weight and height-for-age *Z*-scores, ranging from 0.2 to 0.68 and 0.2 to 0.43, respectively, after 2 to 4 years of ART.[25–27]

In developing countries, weight and height recovery is more notable than in developed countries, with increases in *Z*-scores of 0.4–1.0 in height and 0.4–1.5 in weight after 2 years of ART.[26,28–30] An Asian cohort of adolescents showed improvement in height-for-age *Z*-scores from −2.3 to −1.6 after 5 years of ART.[29] Similar results were observed in African cohorts.[26,31,32]

The recovery of the anthropometric parameters depends on the age at the start of treatment, the nutritional status, and treatment adherence.[24–26] Much has been debated regarding whether there is an interference of the immune status, clinical stage, gender, type of ART scheme, and use of prophylaxis against opportunistic infections.[33]

A Brazilian study[34] carried out in the city of Belo Horizonte, state of Minas Gerais, evaluated 196 children living with HIV, showing an increase in weight-for-age *Z*-score from −1.62 to −1.14 and height-for-age *Z*-score from −1.88 to −1.66, after 24 weeks of ART.

The benefits of ART in the recovery/maintenance of WHG are more evident with an early treatment in younger children, as observed in several publications.[31,35–41] The CHER[42] (Children with HIV Early Antiretroviral Therapy) study compared the early ($n = 252$) *versus* the late ($n = 125$) start of ART in infants, concluding that the early treatment reduced mortality in this group by 76%. Moreover, growth failure was more frequent in the late treatment group. A study[36] carried out in South Africa evaluated the effect of the age at ART initiation on growth, concluding that the start of ART before 6 months of age was associated with a better weight, height, and BMI recovery. Despite the improvement, the height *Z*-score did not reach the normal population values.

The nutritional status in the beginning of ART is of the utmost importance. In countries with limited resources, more than 50% of the children already show a weight and height delay at the beginning of ART.[33] A recent study in Cameroon,[43] evaluating HIV-infected children under the age of 5 years not receiving ART, showed that 63.6% had height-for-age *Z*-score <−2, 37.8% had weight *Z*-scores <−2, and 18.4% had body mass index (BMI) *Z*-score <−2.

Height prior to treatment is an important predictor. Patients with significant height impairment cannot achieve full recovery after ART initiation.[19,29,31,44]

Children with severe malnutrition who start ART show higher morbidity, higher hospitalization rates, and higher risk of loss of follow-up and death. A deterioration of nutritional status may also occur in the first 3 months. During this period, the WHG should be strictly monitored.[41] Data from African countries show that this is the group of children that demonstrates greater weight and height recovery after starting the treatment, but without reaching normality.[38,39,45,46]

Some studies have shown better weight and height gain in HIV-infected children with a higher degree of immunosuppression and/or a more advanced clinical stage.[35,37,39]

However, other authors did not find this association.[16,26,28,31,32,40] Some studies suggest a stagnation of height gain after 1–2 years of ART, even in the presence of documented virological suppression.[18]

Few studies have evaluated whether there is a difference in nutritional recovery regarding gender, and the results are controversial.[30,31,38,47]

The initial ART type does not seem to have an impact on growth reconstitution. Regimens that include protease inhibitor (PI) are associated with better virological response and less acquisition of resistance mutations, but its effect on growth is still uncertain.[48] Data from North-American[49] and European[50] cohorts initially showed better weight and height recovery results with PI, but this effect was not observed in Asian and African cohorts.[48] A recent study also showed similar recovery of weight, height, and BMI in children using PI or non-nucleoside reverse transcriptase inhibitor (NNRTI), with viral suppression.[27] The same was observed in the study by Schomaker et al.[26] These studies emphasize the importance of viral suppression.

The prophylactic use of sulfamethoxazole-trimethoprim for pneumocystosis, together with ART, was beneficial for weight recovery in children with CD4 values <10%.[51] Nutritional supplementation is also associated with WHG improvement.[16]

In the beginning of the epidemics, in the 1980s, AIDS left many infected children orphaned, with a great social affective impact, which was associated with persistent growth deficiency.[29]

A meta-analysis that compared children from less developed regions with children from developed ones showed that children from underdeveloped regions had greater weight and height impairment at the start of ART, when compared to those living in more developed places. The results of this meta-analysis corroborate the aforementioned data. After the start of ART, both groups showed rapid weight (usually around 6 months after the start of ART) and height gain (slower and later improvement). Although children from the underdeveloped regions showed a higher weight and height gain after ART, they maintained weight and height values about 1 standard deviation lower than the children from the developed region group, 12–24 months after the start of treatment. When ART was introduced to younger children, especially before the age of 3 years, there was better height recovery in both groups. Regarding the influence of the ART regimen on growth reconstitution, the data are still inconclusive, with no evident difference between the regimen with PI *versus* NNRTI. The use of nutritional supplements was also associated with anthropometric parameter improvement.[25]

A recent systematic review[23] evaluated the effect of ART on the growth of children and adolescents living with HIV. Of the 44 studies included in the review, the authors retrieved 33 studies that showed an impact on WHG, ten on weight,

and one on height. Despite this impact, infected children were unable to reach normal height values.

Growth evaluation in HIV-infected children

The WHO recommends that weight be assessed at all consultations and height, every 3 months, throughout childhood. Head circumference should also be evaluated every 3 months during the first 2 years of life. Additionally, the BMI should be calculated. These data should be plotted on the WHO growth curve to identify any growth alterations before severe malnutrition occurs.[52]

Another good indicator of overall nutritional status is arm circumference. HIV-infected children with malnutrition lose more muscle than undernourished uninfected ones.[51]

Nutritional status is part of the WHO clinical staging of HIV infection.[53] For adults and adolescents aged ≥15 years, the following is used:

- Stage 2: moderate unexplained weight loss (<10% of body weight).
- Stage 3: unexplained severe weight loss (>10% of body weight).
- Stage 4: cachexia or emaciation syndrome.

For children and adolescents aged <15 years, the following:

- Stage 3: moderate malnutrition (for children under 5 years of age, it is defined as unexplained BMI *Z*-score <−2 or arm circumference between 115 mm and 125 mm) that does not respond adequately to standard therapy.
- Stage 4: unexplained emaciation or cachexia, severe malnutrition (for children under 5 years it is defined as a BMI *Z*-score <−3 or arm circumference <115 mm or presence of edema) that does not respond adequately to standard therapy.

If any growth alteration is identified, an assessment should be made of the child's feeding routine, screening for opportunistic infections, and adherence and response to ART.

GH treatment

The use of GH in HIV-infected patients was approved by the Food and Drug Administration (FDA) for the treatment of adults with cachexia secondary to HIV. Studies using high GH doses for a short period of time (12 weeks) showed an increase in body weight, with a lean mass increase and total fat reduction, but with an increase in fasting glycemia and glycated hemoglobin levels.[54]

Several therapeutic strategies involving the GH/IGF-1 axis have been tested to control the accumulation of fat in cases of lipodystrophy associated with HIV infection. Tesamorelin, an analog of GHRH, showed to be the most effective, but it requires continued administration to exert its positive effect on visceral fat control. Despite the positive results in the short term, it is important to emphasize that the benefits of this treatment remain uncertain in the long-term.[14]

There are still few studies in children and adolescents regarding GH secretion and the presence of GH deficiency. There has been no approval by regulatory agencies for infected children with a reduction in height *Z*-score.

Conflicts of interest

The authors declare no conflicts of interest.

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