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Nutritional status of pediatric patients living with human immunodeficiency virus in Bogotá, Colombia

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Abstract

Background: Undernutrition is frequent among children living with HIV in developing countries. An interaction between malnutrition and HIV pediatric infection remains incompletely characterized in Colombia.

Methodology: Retrospective longitudinal study, descriptive in nature, in 28 patients with a diagnosis of HIV infection, less than 18 years of age and receiving antiretroviral therapy. Variables were retrieved from clinical records at start of antiretroviral therapy and after 12 months. Statistical analysis was exploratory.

Results: 4 out of 28 patients were stunted (14,3%; 95%CI: 1,3 – 27,2), 2 out of 7 patients were wasted (28,6%; 95%CI: 0 – 62), 5 out of 17 patients were underweight (27,8%; 95%CI: 7,1 – 48,5) and 4 out of 28 patients had thinness (29,6%; 95%CI: 12,4 – 46,8). No clinically relevant anthropometric change was detected during follow-up. Anemia prevalence was 52% and 82% of patients had some degree of dyslipidemia. Both viral load (p=0,001) and CD4 count (p=0,01), significantly increased and the proportion of patients with therapeutic failure remained invariable during follow-up.

Conclusion: Malnutrition is frequent and its prevalence might have decreased. HIV program improved medical control of the disease, with stable therapeutic failure rates that were comparable with previous reports. Nonetheless, anemia and dyslipidemia remain to be a paramount therapeutic challenge.

Keywords: Human immunodeficiency virus, malnutrition, antiretroviral therapy, therapeutic failure, pediatrics.

Nutritional status in children with HIV

Resumen

Introducción: La desnutrición es frecuente en niños con VIH en países en desarrollo. En Colombia, la interacción entre la desnutrición y la infección pediátrica por VIH se encuentra insuficientemente caracterizada.

Metodología: Estudio longitudinal retrospectivo de carácter descriptivo, en 28 pacientes con diagnóstico de infección por VIH, edad menor a 18 años y con terapia antirretroviral en curso. Se extrajeron variables mediante revisión de historias clínicas en el momento de inicio de la terapia antirretroviral y 12 meses después. El análisis estadístico fue exploratorio.

Resultados: 4 de 28 pacientes sufrían retraso del crecimiento (14,3%; IC95%: 1,3 – 27,2), 2 de 7 pacientes sufrían emaciación (28,6%; IC95%: 0 – 62), 5 de 17 pacientes sufrían insuficiencia ponderal (27,8%; IC95%: 7,1 – 48,5) y 4 de 28 pacientes se encontraban en delgadez (29,6%; IC95%: 12,4 – 46,8). No hubo cambios antropométricos clínicamente relevantes con el seguimiento. La prevalencia de anemia fue del 52% y 82% de los pacientes tenían algún grado de dislipidemia. Tanto la carga viral (p=0,001) como el conteo de CD4 (p=0,01), mejoraron significativamente y la proporción de pacientes con fallo terapéutico no cambió durante el seguimiento.

Conclusión: La desnutrición es frecuente y su prevalencia podría haber disminuido. El programa de VIH mejoró el control médico de la enfermedad, con tasas de fallo terapéutico estables y comparables con reportes previos. No obstante, la anemia y la dislipidemia continúan siendo un gran reto terapéutico.

Palabras clave: Virus de inmunodeficiencia humana, desnutrición, tratamiento antirretroviral, fallo terapéutico, pediatría.

Introduction

More than a half of children who start antiretroviral therapy (ART) in developing countries are underweight and malnutrition has been associated to triplication of mortality during the first month of ART[1]. In Colombia, proportion of patients with undernutrition during course of pediatric HIV infection has not been recently determined. Latin American sources have reported a prevalence of malnutrition among children living with HIV that varies between 52,4% to 69,3% in countries such as Peru and Venezuela[2,3]. In Colombia, a hospital based study in Cali found that 72% of children infected with HIV by vertical transmission were underweight, 67% stunted and 35% wasted[4], which is consistent with a 70,4% of children with underweight that was found in a University Hospital in Medellin[5]. However, it has been more than a decade since the

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publication of those findings and Colombian nutritional panorama could have changed. The objective of this work is to describe nutritional status of pediatric patients infected with HIV in Bogota, and to explore a possible interaction between malnutrition and ART failure.

Patients and methods

Retrospective longitudinal descriptive study, in a simple of 28 patients belonging to HIV program of the outpatient clinic Asistencia Científica de Alta Complejidad SAS, in Bogota city. Variables were retrieved from clinical records between years 2012 and 2020. Given the exploratory nature of the study, sampling was made by convenience, gathering information of all pediatric patients who met two inclusion criteria: 1) A confirmed diagnosis of HIV, according to local guidelines[6] and 2) An age of less than 18 years. In order to calculate Z scores of Weight for height (WHZ), height for age (HAZ), weight for age (WAZ) and BMI for age (BAZ) in children under 5 years, the software WHO Anthro v3.2.2 (OMS 2011, Geneva, Switzerland) was used. To calculate HAZ, WAZ and BAZ in children from 5 to 19 years of age, the software WHO AnthroPlus v1.0.4 (OMS 2009, Geneva, Switzerland) was used.

For nutritional diagnosis the following definitions were adopted[7]:

- *Wasting or acute malnutrition:* WHZ < -2.
- *Stunting or chronic malnutrition:* HAZ < -2
- *Underweight or global malnutrition:* WAZ < -2.
- *Thinness:* BAZ < -2[8].

Different therapeutic failure definitions that were used can be consulted in supplementary material.

Variables were typed in the software Microsoft Excel 2016. Statistics were processed in the software STATA 13 MP-Parallel Edition for Windows. Differences among categorical variables were explored with Chi squared test or Fisher F test, and relative risks with 95% confidence intervals were estimated using a generalized lineal model. Shapiro-Wilk normality test was applied and then differences were explored with non-paired Student t test, assuming equal variances, or Wilcoxon signed rank test. In spite of the assumption of a one tailed p<0,05 as a limit to consider statistical significance, interpretation must be cautious, given the exploratory and hypothesis generating nature of this study, that was conceived from the moment of sampling calculation. In order to describe the longitudinal behavior of some variables, a comparison was made from the entry to the HIV program to 12 months later, with paired Student t test and McNemar marginal homogeneity test. Patients with missing data were excluded from respective analysis. Figures were generated using the software Prism 7 for Windows (GraphPad Software Inc, San Diego, CA, United States). As this research posed no risk for investigation subjects, no informed consent was obtained from recruited patients and data retrieved from clinical records were protected with confidentiality and privacy. An institutional Ethics Review Board superintended this process.

Results

36 clinical records met the inclusion criteria and 8 patients were excluded because of missing longitudinal anthropometric data in 5 of them, erroneous data in 1 patient and missing longitudinal immuno-virological data in another patient. One additional patient was excluded because of pregnancy. A total of 28 patients were included in this work.

In table 1, basal features at the moment of entry to the HIV program are shown. 21 out of 28 patients had vertical transmission of HIV (75%; 95%CI: 59 – 91), 9 (32,1%) had at least one non-HIV associated comorbidity, among which bronchiolitis, acute lymphoid leukemia and resolved B hepatitis were highlighted. On the other hand, 11 (39,3%) patients had opportunistic infections such as chronic diarrhea, recurrent pneumonia, oropharyngeal and esophageal candidiasis, herpes zoster and ganglionic tuberculosis. Only 7 (25%) patients were ART naive and time interval from HIV infection diagnosis to start of ART had a median of 22 days (intercuartil range: 4 – 74).

Table 1. Baseline features of recruited patients

Variable	Total (n=28)
Genre, n (%)	
Male	19 (67,8)
Female	9 (32,2)
Age §	8,76 (4,50)
Age category, n (%)*	
Less than 1 year	2 (7,14)
1 – 4,9 years	5 (17,86)
5 – 9,9 years	10 (35,71)
10 a 14,9 years	9 (32,14)
More than 15 years	2 (7,14)
Weight (Kg) §	26,8 (13,3)
Height (cm) §	122,6 (28,1)
BMI (Kg/m^2) §	16,6 (2,5)
Anthropometric indices §	
WHZ	-0,87 (1,51)
HAZ ¥	-1,12 (-1,63 - 0,52)
WAZ	-0,73 (1,95)
BAZ	-0,28 (1,37)
Immuno-virological control markers §	
CD4 count (cells/uL)	877 (682)
CD4 percentage	32,65 (19,82)
Viral load (copies/mL) ¥	10893 (40 - 104187)
Blood analytics §	
Hemoglobin (g/dL)	13,6 (1,6)
Total cholesterol (mg/dL)	150,9 (34,4)
HDL cholesterol (mg/dL)	41,9 (16,8)
LDL cholesterol (mg/dL)	81,4 (29,8)
Triglycerides (mg/dL)	136 (55)
Creatinine (mg/dL) ¥	0,42 (0,32 – 0,59)
Estimated glomerular filtration rate (mL/min)€	113,9 (29)

Anthropometric and paraclinical features of patients at the moment of entry to the HIV program are shown. n: number of subjects; BMI: Body mass index; WHZ: Weight for height Z score; HAZ: Height for age Z score; WAZ: Weight for age Z score; BAZ: BMI for age Z score; HDL: High density lipoprotein; LDL: Low density lipoprotein; §: Mean (SD). ¥: Median (ICR). * Frequency (%). €: Determined with Schwartz formula[9]

After a clinical follow-up interval elapsed, just 1 patient changed ART from zidovudine-lamivudine-efavirenz (AZT-3TC-EFV) to raltegravir-lamivudine-lopinavir/ritonavir (RAL-3TC-LPV/r) because of virological failure. 6 out of 28 patients suffered adverse events (AE) to ART (21,4%; 95%CI: 6,2 – 36,6%), such as LPV/r –associated vomiting in half of all cases and hypertriglyceridemia in the remaining half of affected patients. No AE led to treatment discontinuation. ART adherence was 82,1% (95%CI: 68 – 96,3). Percentage distribution of different ART is depicted in supplementary figure 1.

Most of patients were classified in clinical and immunological A1 category (supplementary table 1). Except for ART naïve patients, just 5 out of 21 (23,8%) participants had undetectable viral load at program entry. Proportion of patients with virological, immunological and clinical failure could be determined in all patients except for 7 of them who were ART naïve and 3 participants who had started ART less than 90 days before being recruited. After a mean clinical follow-up interval of 424 (SD: 82,5), virological, immunological and clinical failure outcomes were determined again, according to WHO[10], the Department of Health and Human Services of the United States[11] and the Expert Panel of Spanish Society of Pediatric Infectology - National AIDS program standards[12]; this time in all patients. The results are shown in supplementary figure 2; keeping in mind that there is neither a standardized definition of clinical failure in Spanish guidelines, nor a definition of immunological failure in North American guidelines[11, 12].

After a paraclinical median follow-up period of 378 days (ICR: 310 to 459), changes in count and percentage of CD4 lymphocytes, viral load (figure 1) and CDC category (supplementary figure 3) were explored. In table 2, several important outcomes are compared at the program entry and after the follow-up period had elapsed. It is noteworthy, that 18 pairs of data were processed for analysis of immuno-virological outcomes shown in table 2. Pairs of data with missing values at baseline or during follow-up, were excluded from the analysis. As a result, relative risk (RR) and absolute risk reduction (ARR) statistics were calculated based on proportions of patients that differ from those shown in baseline and follow-up columns of table 3. In such columns, the percentage of the totality of available patients at a time is shown.

Baseline anthropometrical evaluation revealed that 4 out of 28 patients were stunted (14,3%; 95%CI: 1,3 – 27,2), 2 of them severely stunted (HAZ < -3); 2 out of 7 patients were wasted (28,6%; 95%CI: 0 – 62), 1 of them severely wasted (WHZ < -3); and 5 out of 17 patients were underweight (27,8%; 95%CI: 7,1 – 48,5), 1 of them severely underweight (WAZ < -3). According to BAZ, 4 out of 28 patients suffered thinness (29,6%; 95%CI: 12,4 – 46,8), 1 of them was severely thin (BAZ < -3). Changes in anthropometrical variables after clinical follow-up interval are shown in figure 2.

Anemia was found in 2 out of 8 girls and 11 out of 17 (64,7%) boys, adopting hemoglobin cut-off points from a reference laboratory (<12 g/dL for girls and <14 g/dL for boys). Considering reference values for diagnosis of dyslipidemia in children[13], baseline elevations in total cholesterol (TC), LDL cholesterol (LDLc) and triglycerides (TG) in 2 out of 22 (9,1%), 1 out of 22 (4,6%) and 16 out of 22 (72,7%) patients, respectively. A low HDL cholesterol (HDLc) value was found in 10 out of 21 (47,6%) patients. No patients had an estimated glomerular filtration rate (eGFR) below 60 mL/min, making use of the last update of Schwartz formula[9].

After a paraclinical follow-up interval, an increment in mean value of TC, mainly due to LDLc was found (p=0,0063), with no significant changes in HDLc, TG or hemoglobin. Serum creatinine increased during paraclinical follow-up interval (p=0,0019), parallel to a decrease in mean eGFR from 116 mL/min to 105 mL/min (p=0,0109). Finally, mean changes of several clinical-anthropometrical and paraclinical nutritional diagnosis are shown in table 2.

Discussion

In this work, malnutrition was found to be a frequent comorbidity in pediatric patients living with HIV in Bogota, Colombia. The WHO Nutritional Landscape Information System has defined prevalence cut-off points to stablish the impact that several nutritional diagnosis have on the public health of a nation[14]. According to this information, the prevalence of wasting found in this work is categorized as critic (≥15%), proportion of patients with underweight is catalogued as high (20-29%), while the percentage of patients with stunting seems to be

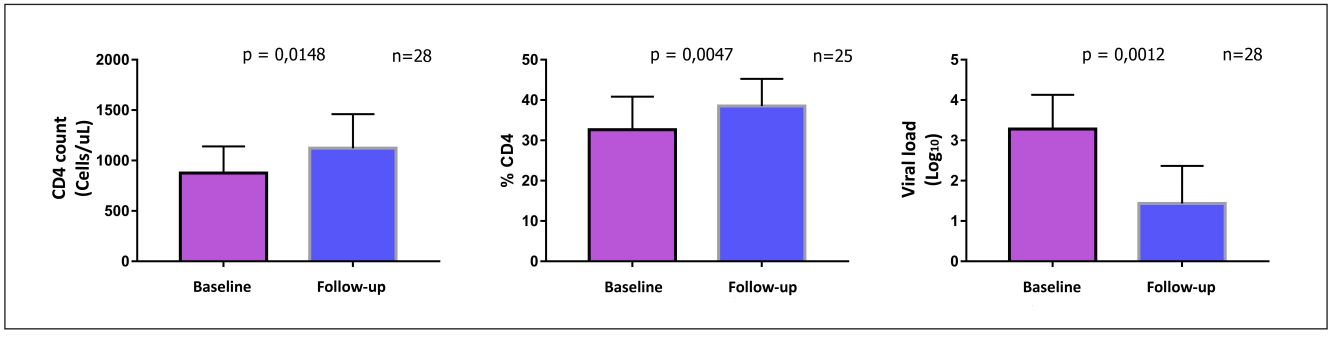

Figure 1. Immuno-virological control marker changes in pediatric patients of an HIV program in Bogota, Colombia.
Changes in immuno-virological control markers are observed during follow-up period. Bars represent means and corresponding 95% confidence intervals. n: number of pairs of observations.

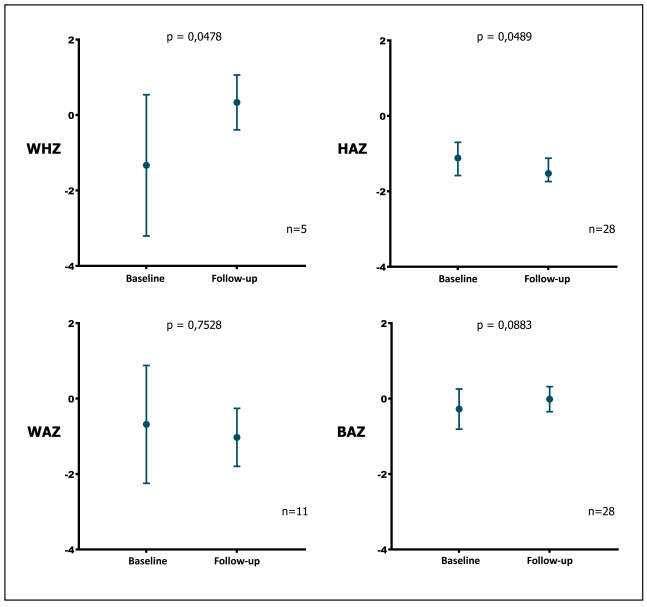

Figure 2. Changes in Z scores of different anthropometrical indices during clinical follow-up of pediatric patients of an HIV program in Bogota, Colombia. Changes in Z scores during follow-up are plotted for each anthropometrical index. For HAZ, median was used instead of mean. WHZ and WAZ can only be calculated for children under 5 and 10 years of age, respectively. Bars represent 95% confidence intervals for each measure. WHZ: Weight for height Z score; HAZ: Height for age Z score; WAZ: Weight for age Z score; BAZ: BMI for age Z score; n: number of pairs of data.

low (<20%). In contrast, after a comparison with previous data from other Colombian studies, it is likely that nutritional panorama of those patients may have improved over time.

The percentage of children with underweight that was found more than a decade ago in different Colombian cities (70,4 – 72%)[4, 5] is high in comparison with the upper limit of the confidence interval found in the present study (27,8%; 95%CI: 7,1 – 48,5). Likewise, a previous proportion of children with stunting of 67% in 2005[4], is high in comparison with the currently found one (14,3%; 95%CI: 1,3 – 27,2). Nonetheless, a prevalence of wasting found in that same work from Cali[4] seems to be similar to the one reported in this research (28,6%; 95%CI: 0 – 62). Several reasons explain this improvement in the nutritional status. According to the Nutritional Situation National Survey of Colombia (ENSIN, from its Spanish initials), Between years 2005 to 2015 pediatric chronic malnutrition decreased 5,2% for children under 5 years and 6,5% for children between 5 and 12 years of age[15]. In the same way, between years 2017 and 2018 there was a paramount 24% increment in ART national coverage for children between 0 and 14 years[16]. In view of the above, it is plausible that malnutrition prevalence in children living with HIV in Bogotá may be decreasing, although further research is required to confirm such assertion.

In the present research there were no clinically significant longitudinal changes in anthropometrical markers, which is in contrast with previous findings from published cohort studies that show a sustained improvement of every Z score (WHZ, HAZ, WAZ and BAZ) throughout the first year from start of ART, with a subsequent stabilization of the markers during the following 5 years of follow-up[17, 18]. In this way, the current work is consistent with previous findings because of, except for ART naive patients, 18 out of 21 patients (85,7%) were already receiving ART with a therapy duration greater or equal to one year, and therefore they were out of the nutritional benefit window of the first year from ART starting point.

There was no significant variation in the percentage of patients with therapeutic failure during follow-up and the proportion was comparable with the one found in two Thai prospective cohorts and a study from Netherlands, notwithstanding the use of different definitions[19, 20]. However, it is noteworthy that the percentage of patients with undetectable viral load was so low even after the paraclinical time interval had elapsed (35,7% 95%CI: 18-53,5). A meta-analysis of 12 publications, with a total of 1497 patients from developing countries, estimated in 70% (95%CI: 67 - 73) the proportion of patients with undetectable viral load at one year from ART start[21]. One possible explanation of this contrast is the detection limit of viral load assay, which is < 20 copies/mL for the present study. If the cut-off point from the above cited studies (< 50 copies/mL) is used instead, the proportion of patients with viral suppression increases to 53,6%. The reason for the finding of a low proportion of patients with undetectable viral load could be explored in future local studies.

The fact that the finding of a percentage CD4 increment (ΔCD4) of 5,9% (95%CI: 1,6 - 10) was inferior to the 14% (95%CI: 12 – 16) reported in the Ciaranello, *et al* meta-analysis, is explained because of the exclusion of studies with ART experienced patients in the cited meta-analysis, which stand for the majority of the studied population in the present work. Previous research has confirmed a marked increase in CD4 percentage throughout the first year of ART, a change that is much lower and seems to stabilize in subsequent years of therapy continuation[19, 20]; as observed in this work, whose ART experienced population had a median therapy duration of 5,5 years (ICR: 1,6 – 9,1) at HIV program entry.

It is well known that protease inhibitors (PI) increase very low density lipoprotein cholesterol (VLDLc) production in the liver and decrease peripheral retrieval of triglycerides[22]. Despite that in the present work, more than 80% of patients received LPV/r (supplementary figure 1), It is remarkable that the percentage of patients with hypertriglyceridemia and total hypercholesterolemia is similar to the one found in an observational study, whose children population received treatments without PI in 100% of cases[23]. It is likely that, because of the use of different cut-offs for diagnosis of dyslipidemia[13], It may not be possible to draw valid conclusions from this comparison. In contrast, a previously found prevalence of low HDLc of 3,7% in patients treated with nevirapine (NVP) based regimens[24] is much lower than the one found in this study, which was estimated around 50%. Anti-atherogenic properties attributed to NVP-based regimens lead to an

Table 2. HIV program follow-up effect on different nutritional outcomes of pediatric patients in Bogota, Colombia.

	Baseline	Follow-up	ARR (95%CI)	RR (95%CI)	NNT (95%CI)	p (one tail)*
Immunovirological outcomes according to WHO (baseline n= 18; follow-up n=28)¥						
Virological failure	5 (27,8)	6 (21,4)	-0,167 (-0,453_ 0,120)	0,4 (0,100_1,6)	NS	0,219
Immunological failure	1 (5,6)	5 (17,9)	0,222 (-0,025_0,470)	5 (0,866_28,9)	NS	0,062
Clinical failure	1 (5,6)	2 (7,1)	0,056 (-0,053_0,171)	2 (0,5_8)	NS	0,5
Anthropometrical nutritional outcomes (n varies across categories §)						
Stunting (HAZ < -2) (n=28)	4 (14,3)	4 (14,3)	0 (-0,207_0,207)	1 (0,301_3,32)	NS	0,688
Underweight (WAZ < -2) (baseline n =17; follow-up n =11)£	5 (27,8)	3 (27,3)	-0,091 (-0,352_0,17)	0,75 (0,426_1,32)	NS	0,5
Wasting (WHZ < -2) (baseline n=7; follow-up n=5) £	2 (29,4)	1 (20)	-0,2 (-0,751_0,351)	0,5 (0,125_2)	NS	0,5
Thinness (BAZ < -2) (n=28)	4 (14,3)	0 (0)	-0,143 (-0,308_0,022)	0	NS	0,062
Paraclinical nutritional outcomes (n varies across categories §)						
Anemia (baseline n=25; follow-up n=26)π	13 (52)	11 (42,3)	-0,087 (-0,246_0,072)	0,83 (0,647_1,07)	NS	0,25
High total cholesterol (baseline n=22; follow-up n=23) π	2 (9,1)	9 (39,1)	0,167 (-0,167_0,5)	2,5 (0,485_12,9)	NS	0,289
High LDL cholesterol (baseline n=22; follow-up n=24) π	1 (4,5)	8 (33,3)	0,2 (-0,025_0,425)	5 (0,866_28,9)	NS	0,062
Low HDL cholesterol (baseline n =21; follow-up n=23) π	10 (47,6)	8 (34,8)	-0,111 (-0,428_0,206)	0,78 (0,425_1,42)	NS	0,453
Hipertriglyceridemia (baseline n=22; follow-up n=24) π	16 (72,7)	20 (83,3)	-0,053 (-0,282_0,177)	0,94 (0,753_1,17)	NS	0,625

Effect size of HIV program on different clinical and paraclinical outcomes. ¥: Baseline n is lower because of exclusion of ART naive patients; however, for ARR and RR estimating purposes, the number of pairs of data was 18. £: Baseline n is lower because patients exited the age group they belonged to during follow-up. §: Pairs of data with missing values at baseline or during follow-up were excluded from analysis. π: Baseline and follow-up n differ because of missing data. *A mid-p value of McNemar test was used, because the number of discordant pairs was lower than 25. ARR: Absolute risk reduction; RR: Relative risk; NNT: Number needed to treat; n: number of observations.

associated increase of HDLc, in comparison with other ART regimens[25]. After paraclinical follow-up interval had elapsed only LDLc increased significantly, which is explained because of the frequent use of PI; being this pharmacological group an independent predictor of hypercholesterolemia[26].

Prevalence of anemia found in the current study seems to be high, but this is related with the chosen analytical cut-off point. If a lower diagnostic cut-off of 10 g/dL is selected and cautious interpretation of confidence intervals is given, then the proportion of anemic children results comparable (8%; 95%CI: 0 – 18,6) with a 22,3%% (95%CI: 18,5 – 26%) found in a meta-analysis of 3524 Ethiopian children with HIV[27]. In contrast, a high prevalence of anemia between 62,2 and 70% has been reported in African HIV-positive and ART-naive children[28, 29]. The above supports the concept that ART contributes to improve anemia, as was evidenced in EuroSIDA cohort, that detected a 19,3% decrease in the proportion of anemic patients at one year from ART starting[30].

Among limitations of this work, a low number of patients is highlighted; which notwithstanding, does not hinder the hypothesis-generating capacity of a study designed with an exploratory nature. Numerous nutritional, anthropometrical and paraclinical variables were not found in accessed clinical records, which limits the descriptive potential of the whole nutritional panorama. As a retrospective study, the possibility of a confusion bias is not excluded, and a multivariable analysis to deal with that systematic error was not considered appropriate due to a low number of patients. A selection bias is possible, given that all patients belong to a subsided insurance regimen and come from a unique HIV program in the city, which must be kept in mind for generalization of the findings. Finally, an information bias in clinical records is also possible, although paraclinical information was corroborated directly in the clinical laboratory database and a double audit to typed information was done. In the same way, it is stressed that there were no missing data in the principal variables; by which, it is not probable that the conclusions of the current work may be affected because of missing values.

In conclusion, undernutrition is frequent among children living with HIV in Bogotá and it is plausible that its prevalence had decreased through time, hand-in-hand with a change in other development indices of the country. Inclusion of patients in an HIV program was associated with an improvement in medical control of the disease, with stable therapeutic failure rates that are comparable to what has been found

in other parts of the globe. However, frequent problems such as anemia and dyslipidemia remain being a therapeutic challenge for this group of patients in Colombia.

Ethical disclosures

Protection of human and animal subjects. No experiments were performed in animal nor humans.

Confidentiality of data. Patient´s data were anonymized

Competing interests. None declared.

Ethical approval. This research was approved by the Ethics Committee of the University.

Conflict of interest. The authors have no conflicts of interest to declare.

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