Access this article online
Quick Response Code:
Website:
www.jorthodsci.org
DOI:
10.4103/jos.JOS_8_20

Craniofacial morphology of HIV-infected adolescents undergoing highly active antiretroviral therapy (HAART): An original research

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Submitted: 23-Feb-2020
Revised: 30-Mar-2020
Accepted: 15-May-2020
Published: 15-Jul-2020

Abstract:

OBJECTIVES: To analyze the craniofacial morphology in child patients and adolescents by evaluating the skeletal cephalometric profile of the HIV infected patients in this age group and comparing them with the HIV-negative controls.

MATERIALS AND METHODS: The present study was a planned case-control study which included 25 HIV-positive adolescent patients aged between 10 and 18 years (the study group) who were compared with 25 age- and sex-matched HIV-negative adolescent controls (the control group). All the patients had been HIV infected via a vertical transmission with positive serology confirmed in two different tests and had been kept on HAART since they were born. The diagnostic aids used for orthodontic documentation included facial photographs, digital orthopantomographs, lateral teleradiographs, and study models.

RESULTS: With reference to the methodologies used for taking the cephalometric values, all the methods used were in strong agreement with each other for almost all the variables studied and had high intra-class correlation coefficient values except Co-A, SN.ANSPNS, and SNB which, too, had a good agreement of 60%. Nevertheless, the agreement was positive for these variables, too, since the P values obtained were found to be statistically significant ($P < 0.05$).

CONCLUSION: Most of the measurements in the HIV-infected adolescents were found to be similar to the ones obtained for the HIV-negative controls, although, the study results highlighted the significance of further studies to be conducted in this regard, especially, the longitudinal study designs wherein the said variables can be studied on a follow-up basis in longitudinal studies to have an idea of the exact changes observed and their pattern in the included groups.

Keywords:

Craniofacial morphology, highly active antiretroviral therapy, HIV-positive adolescents

Introduction

With the advent of the highly active antiretroviral therapy (HAART) in the 1990s, patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) have undergone an increase in the quality and assumption of their life.[1-3] The adverse effects of the combination of these antiretroviral drugs started to be identified through compromised physiologic functions in various systems and organs much later. The changes identified in the pediatric group included mitochondrial toxicity, hepatic and renal toxicity, insulin resistance, hypertension, cardiac dysfunction with an increased risk for cardiovascular diseases, and decreased bone mineral density.[4-19]

How to cite this article: Neeraja M, Garabadu A, Nayak SC, Das M, Dash D, Tiwari A, *et al*. Craniofacial morphology of HIV-infected adolescents undergoing highly active antiretroviral therapy (HAART): An original research. J Orthodont Sci 2020;9:8.

Dental considerations in patients with HIV/AIDS have concentrated more on the prevalence, diagnosis, and treatment of the varied oral presentations seen due to immunocompromise.[20-23] Furthermore, such changes have been recognized not only in the teeth and their associated structures but also in the craniofacial growth pattern seen in the HIV-infected/AIDS patients in the younger age groups who are undergoing HAART.[24,25] Several studies and various authors have illustrated a plethora of chronic systemic diseases leading to changes in the craniofacial growth and development,[26-33] however, there has been a relative dearth of such studies on the HIV-infected/AIDS patients. Also, there is no way to estimate whether disease or its treatment does have an impact on craniofacial growth and development.

Recently, studies have pointed out that there are fewer studies about children and adolescents with HIV and most importantly, about the adverse effects of HAART on this age group of the population. In agreement with most of the recent concerns raised in this particular area of research, the present study was planned to analyze the craniofacial morphology in child patients and adolescents by evaluating the skeletal cephalometric profile of the HIV-infected patients in this age group wherein HIV was transmitted via vertical transmission, and hence, submitted to HAART and comparing them with the HIV-negative controls.

Materials and Methods

Study design, source of data, and selection criteria used in the study

The present study was a planned case-control study which included adolescent patients seropositive for HIV and the HIV-negative controls who attended the outpatient department for orthodontic treatment for 1 year. The protocol of the study was approved by the university research ethics committee. Twenty-five HIV-positive adolescent patients aged between 10 and 18 years (study group) were selected and then, compared with 25 age- and sex-matched HIV-negative adolescent controls (control group). All the patients had been HIV infected via a vertical transmission with positive serology confirmed in two different tests and had been kept on HAART since they were born. The patients were, also, categorized into three age ranges (10–12, 13–15, and 16–18 years). The patients who were undergoing any long-term systemic therapy for severe chronic diseases (except AIDS in the study group) and who had received radio-chemotherapy or, any previous orthodontic and orthopedic treatment in the past were excluded from the study.

Protocol of the study

The diagnostic aids used for orthodontic documentation included facial photographs, digital orthopantomographs, lateral teleradiographs, and study models. For the present study, teleradiographs were used, and over them, various cephalometric points of the hard profile were identified and used for evaluating the craniofacial morphology. Cephalometric tracings of 18 (linear and angular) measurements on teleradiographs were done. The mean values of each measurement were, then, compared between the two groups based on their specific age range. Overall, 14 points and 18 (linear and angular) measurements were used for the assessment of the craniofacial growth pattern, all based on the previous studies conducted by various authors in the past. To decrease the possibility of errors, cephalometric points, and measurements were traced with two different methods. In the initial (semi-automated) method, a dental radiologist used a Compaq Presario microcomputer (Specifications: 1.7 GHz, 768 Mb RAM, HD 30 GB, Windows XP SP3; Pentium 4; Hewlett Packard, Palo Alto, Ca) and Radiocef Studio Software (RadioMemory, Belo Horizonte). The cephalometric landmarks were marked manually while the software traced the said lines and angles including the relevant measurements. In the second (manual) method, for each radiograph, an orthodontist used a transparent acetate sheet (Specifications: Ultraphan; 3M Unitek, Monrovia, Calif) measuring 8-3-10 inches in dimensions and 0.003 inches in thickness with a propelling pencil with 0.5-mm thick graphite to mark the required points. All the measurements were listed into a spreadsheet (Specifications: Microsoft Office Excel 2007; Microsoft, Redmond, Wash) to get the mean values of each angle and linear measurement calculated by the semiautomated and manual methodologies. The data obtained for the study and control groups were, then, compared. It was hypothesized that pubertal growth spurt in girls occurred from 10 years of age reaching its maximum at 12 years of age whereas, in boys, it started from 9 years and reached its peak at 14 years of age. Hence, the time interval between 9 and 12 years was chosen as the main growth spurt period for both the sexes combinedly. Two other age ranges were, also, defined viz. before the growth spurt in the 6–8 years period and after growth spurt during the 13–17 years period.

Statistical analysis used

The data were analyzed by using the Epiinfo software while the Bartlett test was performed to verify the homogeneity of the variances ($P = 0.05$). For variables without a normal distribution, the Wilcoxon test was applied while to determine the reliability of the agreement between two measurement methodologies, an intra-class correlation coefficient test was used for the conduct of statistical analysis. The significance level was put at 0.05 or 5%. $P < 0.05$ was considered statistically significant.

Results

Twenty-five subjects were evaluated in the study group of which 10 were girls and 15 were boys, all aged between 10 and 18 years of age with a mean age of 14 years. All the study participants had been diagnosed with HIV since birth and were being treated with HAART from the first year of their lives. During clinical evaluation, a mean CD41 T lymphocytes count of 752 cells per cubic millimeter (minimum, 180 cells/mm^3 and maximum, 1727 cells/mm^3) was observed in the study group. Two patients had no detected viral load while the said patients were, also, the ones to have CD41 T lymphocyte counts within the normal range (273 and 180 cells/mm^3). Four of the patients used first-line drugs composed of two nucleoside reverse transcriptase inhibitors and 1 non-nucleoside reverse transcriptase inhibitor. Twelve patients used second-line combinations including 2 NRTIs with one protease inhibitor (PI) with ritonavir boosters. Two patients used two NRTIs plus one PI. Three patients used the following combinations as 2 NRTIs and 1 PI along with ritonavir boosters plus 1 PI; and 2 NRTIs with 1 PI and 1 integrase inhibitor; 3 NRTIs and 1 PI with ritonavir boosters in the 3rd patient.

With reference to the methodologies used for taking the cephalometric values, all the methods used were in strong agreement with each other for almost all the variables studied [Table 1] and had high intra-class correlation coefficient values [Table 2] except Co-A, SN.ANSPNS, and SNB which, too, had a good agreement of 60%. Nevertheless, the agreement was positive for these variables, too, since the P values obtained were found to be statistically significant ($P < 0.05$). The cephalometric measurements of the study and control groups were compared according to the age ranges included as 10–12 years, 13–15 years, and 16–18 years of age [Tables 3-5].

In the 10–12-year age group, when considering the mean values, positions of the maxilla, and mandible in the study group were found to be retruded in relation to the skull base when compared with the control group. Also, the growth pattern in the study group was seen as more horizontal with the effective size of the bone bases increased than as seen for the control group. Despite the same, though, the difference observed was not found to be statistically significant except for the palatal plane inclination as is seen in Table 3. With regard to the mean values in the 13–15-year age group, the maxilla was retruded slightly while the mandible was found to be protruded in the study group in relation to the base of the skull than as compared with the control group. Also, the former had a decreased effective size of the maxillary bone with an increased effective size of the mandible than the latter group.

Furthermore, in the 13–15-year age group, growth patterns were almost similar in both the study and the control groups. None of the variables related to the maxillary and mandibular positions in an anteroposterior direction, growth pattern, and effective linear measurements in this particular age group showed statistically significant differences between the study and control groups [Table 4].

With regards to the mean values in the 16–18-year age group, the position of the maxilla in the study group was, again, retruded while the mandible protruded in relation to the skull base than seen in the control group. Also, although, the former had an effective maxillary size smaller than that seen in the latter group, the effective mandibular size was similar between the two groups. Furthermore, the growth pattern was more horizontal in the study group than in the control group, though, the only statistically significant difference found was in the position of the maxilla in the anteroposterior direction (SNA) [Table 5].

Discussion

Adolescents seropositive for HIV, now, attend the dental hospitals and demand full treatment for their oral health conditions.[34-36] Studies evaluating growth and development of face have identified that up to 5 years of age, craniometric dimensions get established along with the maxillofacial skeleton and a significant increase in the height and width of the jaws is, also, observed.[26-33] However, the greatest gain in growth occurs only after 6 years of age with a continuous increase in jaw length and facial height, width, and depth observed until the craniofacial dimensions reach maturity and become more or, less stable during the adolescence between 13 and 15 years of age.[24,25] Because of the drawbacks inherent in a cross-sectional study, differences that could be found in different age groups in the present study suggested continuous craniofacial growth changes with the whole face growing vertically and horizontally in both the groups.

The results of the present study revealed that two of the measurements had statistically significant differences viz. the angle between the palatal plane and base of the skull (SN.ANSPNS) and the angle demonstrating the position of the maxilla in anteroposterior direction in relation to the base of the skull (SNA). Furthermore, in the 10–12 years of age range, the SN.ANSPNS values showed a rotation of the maxilla (palatal plane) which

Table 1: Linear and angular measurements used in cephalometric analysis

Variable	Definition/Description
S-N (mm)	Linear distance between points S and N. Length of the anterior cranial base.
S-Ba (mm)	Linear distance between points S and Ba. Linear size of the posterior base of the skull.
Ba-N (mm)	Linear distance between the points Ba and N. Linear size of the posterior base of the skull.
SNA (degrees)	Angle between the lines SN and NA. Anteroposterior projection of the maxilla.
SN.ANSPNS (degrees)	Angle formed between the lines from S to N in the palatal plane. Inclination of the palatal plane in relation to the base of the skull.
N-ANS (mm)	Linear distance between the points N and ANS. Antero-posterior linear facial height.
Co-A (mm)	Linear distance between the points Co and A. Effective maxillary length.
SNB (degrees)	Angle determined by the intersection of lines SN and NB: Antero-posterior projection of mandible.
PoOr.NPg (degrees)	Angle between Frankfort plane and facial line. Position of menton in a horizontal direction.
Co-Gn (mm)	Linear distance between the points Co and Gn. Effective mandibular length.
Co-Go (mm)	Linear distance between the points Co and Go. Height of mandibular ramus.
Go-Gn (mm)	Linear distance between the points Go and Gn. Length of mandibular body.
ANB (degrees)	Angle determined by the intersection of lines NA and NB: Relative position of mandible to the maxilla.
ANS.Me (mm)	Linear distance between the points ANS and Me. Anterior-inferior facial height.
ANSPNS.GoMe (degrees)	Angle between palatal and mandibular planes. Angular relationship between the palatal plane (ANS-PNS) and mandibular body (Go-Me).
PoOr.GoMe (degrees)	Angle between the Frankfort plane and line Go-Me. Mandibular plane angle indicates the growth vector
SN.GoGn (degrees)	Angle formed between line from points S to N and line from points Go to Gn. Degree of mandibular rotation in relation to the base of skull.
SN.Gn	Angle formed between the intersection of a line from points S to N and the line passing through points N and Gn. that Indicates growth vector.

Table 2: Intra-class correlation coefficient analysis showing a comparison between the two methods of cephalometric measurements

Variable	ICC	*P*	95% CI	
N-ANS	100%	0.0000	1.00	1.00
Co-Gn	93%	0.0000	0.85	0.94
Co-Go	65%	0.0000	0.44	0.81
S-N	99%	0.0000	0.96	0.99
S-Ba	74%	0.0000	0.55	0.85
Ba-N	92%	0.0000	0.88	0.96
ANS-Me	100%	0.0000	1.00	1.00
Co-A	25%	0.0550	0.06	0.50
Go-Gn	93%	0.0000	0.88	0.97
SNA	86%	0.0000	0.77	0.93
ANSPNS.GoMe	100%	0.0000	1.00	1.00
SN.ANSPNS	45%	0.0006	0.21	0.67
SNB	55%	0.0000	0.32	0.75
SN.GoGn	100%	0.0000	1.00	1.00
PoOr.NPg	75%	0.0000	0.62	0.87
PoOr.GoMe	90%	0.0000	0.82	0.94
SNGn	90%	0.0000	0.83	0.94
ANB	82%	0.0000	0.70	0.90

ICC=Intra-class correlation coefficient, CI=Confidence interval

was increased in the HIV-positive patients as against the HIV-negative age- and sex-matched controls wherein these values were seen to diminish. Also, angle SNA was shown to significantly decrease in the 13–15 and 16–18 years age groups wherein the reduction in measurements was interpreted as retrusion of the maxillary bone in accordance with the study conducted previously.[31]

Furthermore, although, the present study was not longitudinal, 3 interpretations could be perceived for this type of craniofacial change observed in the study group in the present study with reference from the previously conducted studies. The first and the most significant interpretation amongst them was that this type of change seen in the study group was a consequence of the respiratory pattern seen in the HIV positive adolescents which gets compromised in this group of patients due to recurrent airway infections.[24-33] Also, SNA may, also, decrease in patients with compromised respiratory function of upper airway due to habits such as mouth-breathing.[27,28]

HIV infection being associated or not associated with varying states of immune activation and inflammatory processes can, also, affect the process osteoclastogenesis increasing rate of apoptosis of primary osteoblasts, decreasing calcium deposition and alkaline phosphatase activity, diminishing specific bone proteins, and compromising the differentiation of the mesenchymal cells into active bone-forming osteoblasts.[7,8,11,15,16] The long-term use of HAART might, also, be responsible for the systemic changes that affect the growth of these seropositive individuals.[29,30]

HAART emerged as a solution to deleterious effects caused by the virus by lowering the circulating viral load. The immunologic reconstitution induced by the use of HAART, expressed by an increase in CD4 T lymphocytes, allows these patients to be clinically

Table 3: Comparison of cephalometric measurements of the study and control groups in the 10-12 years age groups

							95% CI												
	Study group (*n*=3)									Control group (*n*=3)									
Measurements	Mean	Median	SD	Q1	Q3	Inf	Sup	Min	Max	Mean	Median	SD	Q1	Q2	Inf	Sup	Min	Max	*P*
SNA	79.5	79.1	2.3	82.0	77.4	72.8	85.2	77.4	82.0	83.5	82.5	3.5	86.3	80.5	74.7	92.2	81.5	88.3	0.1267
SN.ANSPNS	10.1	10.3	0.4	10.4	9.7	9.3	11.0	9.7	10.4	6.6	7.0	1.1	7.4	5.4	3.9	9.3	5.4	7.4	0.0595
N-ANS	46.7	45.0	4.3	51.5	43.5	36.1	57.2	42.5	51.5	43.5	45.5	9.4	51.0	33.0	21.2	66.8	33.0	51.0	0.8373
Co-A	83.3	84.3	3.9	86.5	79.0	73.7	92.7	79.0	86.5	81.0	81.8	5.4	86.0	75.3	67.6	94.4	76.3	86.0	0.5127
SNB	33.3	31.5	6.4	40.5	28.0	17.3	49.4	29.0	40.5	34.3	33.0	2.8	37.5	32.5	27.5	41.2	32.5	37.5	0.8273
PoOr.NPg	24.4	23.3	5.6	30.5	19.4	10.4	37.4	19.4	30.5	24.8	26.1	2.3	26.1	22.2	19.2	30.4	22.2	26.1	0.8273
Co-Gn	105.7	103.8	3.8	110.1	103.3	96.3	125.2	103.3	110.1	99.1	103.5	11.1	109.4	86.5	71.5	126.8	86.5	107.4	0.5127
Co-Go	48.9	48.8	0.3	49.2	0.3	48.8	49.6	47.6	49.2	45.8	47.5	6.1	50.9	39.1	30.7	61.0	39.1	50.9	0.5127
Go-Gn	68.3	66.3	5.6	74.6	63.9	54.3	81.3	63.9	74.6	65.2	63.7	8.1	73.9	58.0	45.1	85.3	58.0	73.9	0.2752
S-N	66.1	67.6	4.6	69.8	61.0	54.8	77.5	60.0	69.8	62.6	64.0	5.4	67.1	56.6	49.2	75.9	56.6	67.1	0.2752
Ba-N	100.0	103.5	7.1	104.7	91.8	82.3	118.7	91.8	104.7	93.4	99.2	10.6	99.9	81.2	67.0	119.9	81.2	99.9	0.2752
S-Ba	39.8	38.8	3.3	43.5	37.2	31.6	48.0	37.2	43.5	38.2	40.8	5.2	41.6	32.2	25.3	51.1	32.2	40.6	0.8273
ANB	77.9	79.3	4.5	81.6	72.9	66.7	89.2	72.9	81.6	77.9	79.6	3.6	80.3	73.7	69.0	86.8	74.7	80.3	0.2652
ANS-Me	62.5	58.5	7.4	71.0	58.0	44.2	80.8	58.0	71.0	60.3	63.5	6.4	64.5	53.0	44.5	76.2	53.0	64.5	0.8273
ANSPNS.GoMe	27.7	26.0	6.2	34.5	34. 0	22. 5	12.3 31.5 27.5	43.0 27.5	22.5 27.5	34.5	29.8	30.5	31.5	27.5	24.7	35.0	27.5	31.5	0.5127
PoOr.GoMe	77.3	79.8	4.9	80.5	66.1	71.7	80.5	71.7	80.5	76.8	77.3	3.7	80.2	72.9	67.7	85.9	72.9	80.2	0.8273
SN.GoGn	89.4	91.0	3.3	91.7	85.7	81.3	96.6	85.7	91.7	89.8	89.7	4.3	94.2	85.5	79.0	100.6	85.5	94.2	0.5027
SN.Gn	1.6	6.2	5.3	6.2	14.8	−4.3	−11.7	14.8	−4.3	6.2	5.6	2.9	7.8	2.3	−1.7	12.9	2.3	7.8	0.8273

SD=Standard deviation, Q1=First quartile, Q3=Third quartile, Inf=Inferior, Sup=Superior, Min=Minimum, Max=Maximum

Table 4: Comparison of cephalometric measurements of the study and control groups in the 13-15-year age groups

	95% CI																		
	Study Group (n=10)									Control Group (n=10)									
Measurements	Mean	Median	SD	Q1	Q3	Inf	Sup	Min	Max	Mean	Median	SD	Q1	Q2	Inf	Sup	Min	Max	*P*
SNA	81.6	81.2	3.8	83.6	77.1	77.9	83.3	72.0	84.8	82.0	80.9	4.2	84.2	79.6	79.0	85.0	76.9	90.9	90.9
SN.ANSPNS	9.6	9.4	2.1	11.9	8.9	8.1	11.1	6.5	12.4	9.0	8.3	3.4	12.8	6.7	6.5	11.4	4.2	14.3	14.3
N-ANS	52.1	53.0	4.7	54.5	47.0	47.7	55.5	43.0	58.0	51.9	52.3	5.6	53.5	48.5	47.8	55.9	43.5	60.0	60.0
Co-A	85.7	89.3	15.8	94.0	86.0	75.4	97.0	42.7	98.4	88.5	86.5	6.7	93.2	85.2	83.7	93.3	77.6	102.0	102.0
SNB	33.0	31.5	3.0	35.0	31.0	30.8	35.2	29.0	38.0	32.1	30.5	6.5	36.0	26.5	27.4	36.8	25.5	43.5	43.5
PoOr.NPg	25.2	26.8	2.4	26.8	23.5	22.5	26.9	20.7	29.3	25.1	24.2	5.7	27.9	22.8	21.0	29.3	17.1	36.2	36.2
Co-Gn	114.1	112.8	5.3	118.0	111.3	110.3	118.0	104.0	121.3	112.9	113.1	6.3	114.5	110.4	108.4	117.5	98.8	122.1	122.1
Co-Go	55.2	53.6	6.9	57.9	50.5	50.2	60.1	48.7	71.9	50.4	51.5	4.0	53.4	46.8	47.5	53.3	42.8	55.2	55.2
Go-Gn	74.6	76.1	3.6	77.0	72.3	72.0	77.1	67.1	78.6	75.0	73.8	5.4	79.8	73.2	71.2	78.9	64.3	83.9	83.9
S-N	70.6	70.5	3.6	73.0	67.4	68.1	73.2	66.0	76.6	69.9	68.3	4.5	74.0	66.3	66.6	73.1	64.1	76.2	76.2
Ba-N	105.8	106.4	7.2	109.6	100.8	100.7	111.0	95.3	117.6	104.0	103.3	6.8	107.2	98.5	99.3	108.8	96.7	114.2	114.2
S-Ba	42.6	41.9	3.9	46.2	39.7	39.8	45.3	36.7	49.6	42.8	42.2	4.2	46.9	40.0	39.7	45.8	36.7	49.8	49.8
ANB	77.8	78.5	4.0	82.0	74.8	74.9	80.7	71.4	82.5	79.6	79.4	3.3	82.6	76.8	77.3	82.0	75.5	85.6	85.6
ANS-Me	66.5	67.3	4.9	70.0	62.0	63.0	70.0	57.5	73.0	65.4	65.8	7.8	70.0	60.0	59.8	71.0	53.0	80.0	80.0
ANSPNS.GoMe	25.9	26.8	5.1	31.5	22.5	23.3	30.5	20.0	35.0	25.7	25.5	6.2	30.5	21.5	22.2	31.1	17.5	36.5	36.5
PoOr.GoMe	77.4	77.2	3.7	81.3	73.4	74.8	80.1	72.8	82.7	79.4	79.7	3.8	82.6	76.3	76.7	82.1	74.2	84.3	84.3
SN.GoGn	89.1	88.4	2.9	91.6	87.1	87.0	91.2	83.0	92.3	89.0	89.2	2.1	90.2	88.3	87.5	90.5	84.7	92.7	92.7
SN.Gn	2.3	1.6	2.6	4.6	0.7	0.5	4.2	−1.3	6.3	2.5	2.5	2.6	4.7	0.0	0.6	4.3	−1.5	6.4	6.4

SD=Standard deviation, Q1=First quartile, Q3=Third quartile, Inf=Inferior, Sup=Superior, Min=Minimum, Max=Maximum

Table 5: Comparison of cephalometric measurements of the study and control groups in the 16-18 year age groups

	95% CI																		
	Study Group (*n*=8)									Control Group (*n*=8)									
Measurements	Mean	Median	SD	Q1	Q3	Inf	Sup	Min	Max	Mean	Median	SD	Q1	Q2	Inf	Sup	Min	Max	*P*
SNA	81.2	82.8	3.2	84.1	82.1	79.5	84.9	75.4	86.0	85.7	85.2	2.7	86.6	84.3	82.5	87.0	77.6	87.2	0.0460
SN.ANSPNS	7.4	8.7	2.2	9.1	5.6	5.6	9.3	3.5	9.3	8.1	6.8	2.2	10.4	6.6	6.3	9.9	5.9	11.3	0.4623
N-ANS	54.1	54.0	5.6	57.5	49.5	49.4	58.8	47.0	63.5	57.4	57.3	6.8	62.3	52.5	51.7	63.1	47.5	67.5	0.2261
Co-A	90.0	94.1	9.6	96.7	84.6	82.0	98.0	71.3	97.7	92.4	98.5	18.5	103.7	88.8	77.0	107.9	50.2	107.2	0.2698
SNB	33.4	31.5	6.1	38.0	29.3	28.3	38.5	25.0	43.5	30.4	27.5	5.8	36.3	25.3	25.5	35.2	24.5	38.5	0.8336
PoOr.NPg	26.0	26.9	5.0	28.5	22.3	21.8	30.2	18.4	32.3	23.3	20.9	7.2	29.8	18.4	17.2	29.4	13.2	34.0	0.9164
Co-Gn	120.5	126.6	12.3	128.6	109.3	110.2	130.8	101.3	133.5	123.8	123.0	9.4	126.9	120.9	115.9	131.6	107.4	141.3	0.9164
Co-Go	59.8	61.7	7.5	64.1	54.6	53.5	66.0	47.6	69.7	59.8	47.5	7.8	64.1	56.7	53.3	66.3	44.8	70.9	0.635
Go-Gn	77.9	80.6	9.8	84.8	71.2	69.7	86.0	60.2	89.8	82.5	63.7	7.1	85.8	76.3	76.6	88.5	74.0	96.4	0.4623
S-N	73.1	76.1	7.8	78.0	68.7	66.6	79.7	59.8	79.7	75.9	64.0	5.1	78.2	72.8	70.6	79.1	64.3	78.8	0.6744
Ba-N	107.6	110.9	10.1	114.6	99.4	99.1	116.1	91.7	117.4	110.6	99.2	7.3	114.8	108.4	104.5	116.7	93.7	115.2	0.8336
S-Ba	44.1	45.8	5.0	47.9	41.0	39.9	48.3	35.3	49.8	45.7	40.8	3.3	47.0	43.7	41.9	47.4	37.4	47.5	0.9164
ANB	78.6	79.0	2.4	80.6	76.4	76.5	80.6	75.2	81.3	79.0	79.6	2.9	81.1	77.7	76.5	81.4	73.9	83.1	0.1722
ANS-Me	75.8	77.5	10.1	83.5	65.5	67.3	84.3	63.5	90.0	74.1	63.5	6.8	80.5	68.3	68.4	79.8	64.5	84.0	0.7128
ANSPNS.GoMe	28.3	26.8	4.9	32.5	24.0	24.2	32.4	24.0	36.0	26.5	29.8	6.3	32.3	21.8	21.3	31.7	19.5	36.5	0.3994
PoOr.GoMe	78.0	77.2	3.1	80.7	75.4	75.4	80.6	73.4	81.7	78.9	77.3	4.5	83.2	76.9	75.1	82.6	70.1	84.2	0.5286
SN.GoGn	88.9	88.1	4.6	92.0	87.2	85.2	92.7	80.9	96.0	89.5	89.7	3.7	92.2	86.1	86.5	92.6	85.0	95.0	0.247
SN.Gn	3.8	3.8	2.3	5.3	2.2	1.9	5.7	0.6	7.4	5.2	5.6	2.0	6.7	4.1	3.6	6.9	1.7	7.9	0.4008

SD=Standard deviation, Q1=First quartile, Q3=Third quartile, Inf=Inferior, Sup=Superior, Min=Minimum, Max=Maximum

stable with reductions in the incidence of opportunistic infections that, further, compromise the nutritional status of these group of individuals and bring malnutrition.[24] Although gains in height and weight among the HIV patients on HAART are vital and calculable, these gains are relatively less marked than the respective gains seen in the HIV-negative controls.[25]

The results of the present study were not supportive of changes in the other linear and angular values included which were found to be statistically insignificant when compared with the control group, however, it was possible to identify a trend toward a decrease in the linear measurements of the maxilla and mandible along with the base of the skull in the study patients, especially, in the age groups of 13–15 and 16–18 years. In the present study, among the said variables in the mentioned age groups, 14 angular and linear measurements were found to be lower than those seen in the HIV-negative controls. This type of difference could, also, be observed in five of the measurements in the 10–12-year age group as against in seven of the measurements in the 13–15-year age group.

Conclusion

The results of the present study highlighted the significance of further studies to be conducted in this regard, especially, the longitudinal study designs wherein the said variables can be studied on a follow-up basis in longitudinal studies to have an idea of the exact changes observed and their pattern in the included groups. The differences, though, in the majority of the measurements made in the HIV infected and control groups in the present study were not found to be significant enough to generate a statistically significant difference in the craniofacial growth pattern studied. Although 18 comparisons were studied in the included study and control groups in the present study, only two of the measurements had statistically significant differences with marginally significant *P* values. Since no overall differences could be observed between the two groups in the present study, it could be hypothesized that the beneficial effects of HAART overcome the associated adverse effects of the said therapy.

Limitations of the present study

Nevertheless, the present study was based on cross-sectional study design and could not establish a cause and effect relationship which can be considered as the major limitation of the present study. Another limitation and confounding factor in the present study was that only teleradiographs of adolescents who were referred for orthodontic treatment were included in the present study and consequently, they had some amount of deviation from normality in both the groups included. On the contrary, an ideal study design would include all adolescents in the said age groups irrespective of their need for orthodontic treatment. Also, ethical concerns can be raised and are a major constraint due to exposure of young adolescents to ionizing radiation not only during the growth periods but, also, at various times throughout their lives only to check for the possible changes in their craniofacial growth pattern. Furthermore, it is difficult to correctly predict whether such changes are seen as a result of the active disease process and the reactive immune activation and inflammatory processes seen due to HIV infection or, due to HAART since most of the HIV infected patients who are under medical treatment are already under HAART.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Chiappini E, Galli L, Tovo PA. Cancer rates after year 2000 significantly decrease in children with peri-natal HIV infection: A study by the Italian Register for HIV Infection in Children. J Clin Oncol 2007;25:97-101.
2. De martino M, Tovo PA, Balducci M. Reduction in mortality with availability of anti-retroviral therapy for children with peri-natal HIV-1 infection: Italian register for HIV infection in children and the Italian national AIDS registry. J Am Med Assoc 2000;248:190-7.
3. Gortmaker S, Hughes M, Cervia J. Effects of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. N Engl J Med 2001;345:1522-8.
4. Jain RG, Furfine ES, Pedneault L, White AJ, Lenhard JM. Metabolic complications associated with anti-retroviral therapy. Antiviral Res 2001;51:151-77.
5. Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of peri-natally HIV infected adolescents. J Int AIDS Soc 2013;16:18600.
6. Orellana RV, Fonseca HA, Monteiro AM, Ortega KL, Gallottini MH, Gidlund M, *et al*. Association of auto-antibodies anti-OxLDL and markers of inflammation with stage of HIV infection. Int J Cardiol 2013;168:1610-2.
7. Liu K, Sun Y, Liu D, Yin J, Qiao L, Shi Y, *et al*. Mitochondrial toxicity studied with the PBMC of children from the Chinese national pediatric highly active anti-retroviral therapy cohort. PLoS One 2013;8:e57223.
8. Miro O, Villarroya J, Garrabou G, Lopez S, Rodriguez de la Concepcion M, Pedrol E, *et al*. In-vivo effects of highly active anti-retroviral therapies containing the protease inhibitor nelfinavir on mitochondrially driven apoptosis. Antivir Ther 2005;10:945-51.
9. Abrescia N, D'Abbraccio M, Figoni M, Busto A, Maddaloni A, De Marco M. Hepatotoxicity of anti-retroviral drugs. Curr Pharm Des 2005;11:3697-710.
10. Aurpibul L, Bunupuradah T, Sophan S, Boettiger D, Wati DK, Nguyen LV, *et al*. TREAT Asia pediatric HIV observational database: Prevalence and incidence of liver dysfunction and assessment of biomarkers of liver disease in HIV-infected Asian children. Pediatr Infect Dis J 2015;34:e153-8.
11. Fortuny C, Deyà-Martínez Á, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of

anti-retroviral therapy in HIV-infected children and adolescents. Pediatr Infect Dis J 2015;34:S36-43.

12. Innes S, Abdullah KL, Haubrich R, Cotton MF, Browne SH. High prevalence of dyslipidemia and insulin resistance in HIV-infected pre-pubertal African children on anti-retroviral therapy. Pediatr Infect Dis J 2016;35:e1-7.
13. Bwakura-Dangarembizi M, Musiime V, Szubert AJ, Prendergast AJ, Gomo ZA, Thomason MJ, *et al*. ARROW trial team: Prevalence of lipodystrophy and metabolic abnormalities in HIV-infected African children after 3 years on first-line anti-retroviral therapy. Pediatr Infect Dis J 2015;34:e23-31.
14. Chatterton-Kirchmeier S, Camacho-Gonzalez AF, McCracken CE, Chakraborty R, Batisky DL. Increased prevalence of elevated blood pressures in HIV-infected children, adolescents and young adults. Pediatr Infect Dis J 2015;34:610-4.
15. Noguera A, Fortuny C, Munoz-Almagro C. Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to anti-retrovirals. Pediatrics 2004;114:e598-603.
16. Giaquinto C, Rampon O, Torresan S. Lactic acid levels in infant exposed to anti-retrovirals during fetal life [Abstract 941]. 11th Conference on retroviruses and opportunistic infections, San Francisco, USA, 2004.
17. Namuyonga J, Lubega S, Musiime V, Lwabi P, Lubega I. Cardiac dysfunction among Ugandan HIV-infected children on anti-retroviral therapy. Pediatr Infect Dis J 2016;35:e85-8.
18. Sainz T, Alvarez-Fuente M, Navarro ML, Dıaz L, Rojo P, Blazquez D, *et al*. Subclinical atherosclerosis and markers of immune activation in HIV-infected children and adolescents: The CaroVIH study, Madrid cohort of HIV-infected children and adolescents integrated in the pediatric branch of the Spanish national AIDS network (CoRISPE). J Acquir Immune Defic Syndr 2014;65:42-9.
19. Guerreiro da Silva Júnior N, Pedreira EN, Tuji FM, Warmling LV, Ortega KL. Prevalence of calcified carotid artery atheromas in panoramic radiographs of HIV-positive patients undergoing anti-retroviral treatment: A retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:67-74.
20. Ortega KL, Vale DA, Magalhães MH. Impact of PI and NNRTI HAART-based therapy on oral lesions of Brazilian HIV-infected patients. J Oral Pathol Med 2009;38:489-94.
21. Ortega KL, Rezende NP, Magalhães MH. Diagnosing secondary syphilis in a patient with HIV. Br J Oral Maxillofac Surg 2009;47:169-70.
22. Ortega KL, Rezende NP, Lotufo MA, Magalhães MH. Mandibular lesion in HIV-positive patient. J Oral Maxillofac Surg 2008;66:2140-4.
23. Francischini E, Martins FM, Braz-Silva PH, Magalhães MH, Ortega KL. HIV-associated oral plasmablastic lymphoma and role of adherence to highly active anti-retroviral therapy. Int J STD AIDS 2010;21:68-70.
24. Cruz ML, Cardoso CA. Peri-natally infected adolescents living with human immunodeficiency virus (peri-natally human immunodeficiency virus). World J Virol 2015;4:277-84.
25. Stagi S, Galli L, Cecchi C, Chiappini E, Losi S, Gattinara CG, *et al*. Final height in patients peri-natally infected with human immunodeficiency virus. Horm Res Paediatr 2010;74:165-71.
26. El-Bialy T, Aboul-Azm SF, El-Sakhawy M. Study of craniofacial morphology and skeletal maturation in juvenile diabetics (Type I). Am J Orthod Dentofacial Orthop 2000;118:189-95.
27. Sadeghianrizi A, Forsberg CM, Marcus C, Dahllöf G. Craniofacial development in obese adolescents. Eur J Orthod 2005;27:550-5.
28. Orup HI Jr, Holmes LB, Keith DA, Coull BA. Craniofacial skeletal deviations following in-utero exposure to the anti-convulsant phenytoin: Monotherapy and polytherapy. Orthod Craniofac Res 2003;6:2-19.
29. Amini F, Jafari A, Eslamian L, Sharifzadeh S. A cephalometric study on craniofacial morphology of Iranian children with beta thalassemia major. Orthod Craniofac Res 2007;10:36-44.
30. Gjorup H, Kjaer I, Sonnesen L, Haubek D, Beck-Nielsen SS, Hintze H, *et al*. Craniofacial morphology in patients with hypophosphatemic rickets: Cephalometric study focusing on differences between bone of cartilaginous and intra-membranous origin. Am J Med Genet A 2011;155A: 2654-60.
31. Fjeld MG, Arvidsson LZ, Stabrun AE, Birkeland K, Larheim TA, Ogaard B. Average craniofacial development from 6 to 35 years of age in mixed group of patients with juvenile idiopathic arthritis. Acta Odontol Scand 2009;67:153-60.
32. Al-Thomali Y, El-Bialy TH. Cephalometric craniofacial features of growing patients with chronic renal failure. Arch Oral Biol 2012;57:257-63.
33. Niles DG, Rynearson RD, Baum M, Neufeld RD, Caruso JM. A study of craniofacial growth in infant heart transplant recipients receiving cyclosporine. J Heart Lung Transplant 2000;19:231-9.
34. Oliveira MA, Gallottini M, Pallos D, Maluf PS, Jablonka F, Ortega KL. The success of endosseous implants in human immunodeficiency virus-positive patients receiving anti-retroviral therapy: A pilot study. J Am Dent Assoc 2011;142:1010-6.
35. Trigueiro M, Tedeschi-Oliveira SV, Melani RF, Ortega KL. An assessment of adverse effects of anti-retroviral therapy on development of HIV positive children by observation of dental mineralization chronology. J Oral Pathol Med 2010;39:35-40.
36. Hsieh YJ, Darvann TA, Hermann NV, Larsen P, Liao YF, Bjoern- Joergensen J, *et al*. Facial morphology in children and adolescents with juvenile idiopathic arthritis and moderate to severe temporomandibular joint involvement. Am J Orthod Dentofacial Orthop 2016;149:182-91.