Original Article

Effect of anti-retroviral treatment on tooth size of first premolars in children with human immunodeficiency virus

Priya Subramaniam*, Krishna Kumar
Department of Pedodontics and Preventive Dentistry, The Oxford Dental College, Hospital and Research Centre, Bommanahalli, Bengaluru, Karnataka, India

ABSTRACT

Children infected with human immunodeficiency virus (HIV) receive anti-retroviral therapy (ART) quite early in life. These drugs could possibly have an effect on tooth development. A group of 221 HIV-infected children in the age group of 6-18 years (mean 11.62 ± 3.30 years) were examined for any tooth anomalies. Only 109 children were on ART and they were divided into three groups based on the anti-retroviral regimen they received. Twenty percent of children on ART had microdontia of the first premolars, with a mean age of drug onset 3.2 ± 0.8 years. Type of anti-retroviral regimen and age of administration appears to have an effect on developing teeth. There is a need for further research on the possible effects of anti-retroviral medications on tooth mineralization.

Key words: Antiretroviral Treatment, Antiretroviral Therapy, Drug, Microdontia, Premolar, Side Effect

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INTRODUCTION

Human immunodeficiency virus (HIV) affects people of all countries of the world, but the greater majority of affected individuals live in the developing world. The National Acquired Immune Deficiency Syndrome (AIDS) Control Organization estimated that the number of people living with HIV in India in 2011 was 2.08 (1.72-2.53) million.[1] While children accounted for approximately 6.3% of the total HIV infections in 2007, this proportion increased to approximately 7% in 2011. The estimated number of children (<15 years) living with HIV in India was 0.145 million in 2011.[1]

The history of the HIV/AIDS epidemic over the last two decades has been marked by constant advances in the discovery and development of new antiretroviral drugs. In India, the guidelines for antiretroviral therapy (ART) eligibility in children that is based on the CD4 count threshold has been revised. Briefly, the threshold was CD4 count <200 cells/mm^3 up to the year 2008 and at CD4 count <250 cells/mm^3 from 2009 to 2011.[1] HIV attacks a type of immune system cell called the T-helper cell. The T-helper cell plays an essential role in the immune system by helping to co-ordinate with all other cells in order to fight disease. HIV damages and destroys T-helper cells. Therefore, any condition that results in a major reduction in the number of T-helper cells can have a serious effect on the immune system. A CD4 test measures the number of T-helper cells (in a cubic millimeter of blood) and is known as CD4 count. An individual who is not infected with HIV normally has a CD4 count between 500 and 1200 cells/mm^3. In a person infected with HIV, the CD4 count often declines over a number of years.

With the commencement of new therapies, there have been benefits such as an increase in cellular immunity, which is reflected by an increase in life expectancy for patients. At the end of 2011, more than 8 million HIV-infected people have received ART in low-income and middle-income countries.[2] Since the approval of zidovudine (ZDV) by the US Food and Drug

***Address for correspondence**
Dr. Priya Subramaniam, Department of Pedodontics and Preventive Dentistry, The Oxford Dental College, Hospital and Research Centre, Hosur Road, Bommanahalli, Bengaluru - 560 068, Karnataka, India. E-mail: drpriyapedo@yahoo.com

Administration (FDA) in 1987, it has been widely used for the treatment of HIV infection. In developing countries, highly active antiretroviral therapy is usually composed of ZDV or stavudine (d4T) + lamivudine (3TC) plus nevirapine (NVP) or efavirenz (EFV).[3]

During the course of administration, patients may experience side-effects of the drugs. Oral health and general well-being are well inter-related. Many commonly prescribed medications are known to be associated with oral manifestations.[4] Like all other body tissues, dental tissues may also be affected by using certain drugs during their developmental stages or given during pregnancy. Oral and dental structures are frequently the sites of adverse drug reactions. A range of drugs can affect the teeth.[5] Drugs that have the potential to induce changes in teeth can be classified as those leading to: Tooth discoloration (intrinsic and extrinsic), physical damage to tooth structure (enamel, dentin, and cementum); and alteration in tooth sensitivity.[6]

Drugs used for the treatment of childhood cancer and leukemia have consistently shown that children younger than 5 years at diagnosis and the start of treatment exhibit abnormal dental development.[7] The severity of dentofacial-developmental and tooth-related abnormalities secondary to the therapy are related to the age of the child, the dosage, and the duration of treatment.[7]

Several adverse effects have been noted in patients who use ART such as; metabolic, hematologic, liver, cardiac, neurological, pancreas and bone disorders.[8] Oro-facial effects of ART include oral ulcers, xerostomia, erythema multiformae, cheilitis, perioral paresthesia, angioedema, and taste alteration.[9] The hypothesis was that drugs used in ART could have an effect on developing the dentition. Hence, the purpose of this study was to examine the teeth of HIV-infected children for dental anomalies and its association with exposure to ART.

MATERIALS AND METHODS

The study protocol was approved by the Ethical Committee of the Institution (Ref. No. 712/10-11; dated: November 29, 2010). Information was obtained regarding the number of HIV-infected children from various centers. Prior to conducting the study, the nature of the study was explained and written permission was obtained from the authorities of various HIV center. An undertaking was given to the authorities stating that the identity of the children will not be disclosed.

A group of 221 HIV-infected children aged 6-18 years (mean 11.62 ± 3.30 years) were initially examined. Inclusion criteria: Children on ART and cooperative children. Children who were not on ART were excluded. Only 109 children were on ART and formed the study group. These 109 children were divided into three groups based on the drug regimen to which they were exposed:

- Group 1: 65 children on ZDV + 3TC + NVP.
- Group 2: 29 children on ZDV + didanosine + NVP.
- Group 3: 15 children on d4T +3TC + NVP.

A questionnaire cum patient data sheet was used to record child's age, gender, CD4 cell count, drug regimen, age of initiation of ART, medical history, extra oral and intra-oral examination. Presence for any dental anomalies was noted. On visual examination, the first premolars in both arches appeared to be smaller in size than a normal premolar. The average mesio-distal diameter of the crown of upper and lower first premolars is 7 mm.[10]

The mesi-odistal width of the first premolars was measured using a pair of sliding digital calipers (Mitsutoyo Co. Ltd., Kawasaki, Japan) with a precision of ±0.01 mm. The measuring tips of the calipers were specially pointed to carry out accurate measurements. The sliding calipers were held parallel to the occlusal and vestibular surfaces of the crown to measure mesio-distal crown diameter of the tooth. Measurement in millimeters was taken at the greatest distance between the approximate surfaces of the clinical crown. In the case of a rotated or malposed tooth, the measurement was taken between the points on the approximate surface of the crown, where it was judged that normal contact should have occurred with the adjacent teeth. The measurements were performed by a single examiner, and each measurement was taken twice. The average of two values was obtained to minimize intra-examiner error. The data was subjected to statistical analysis using software (SPSS version 16.01, SPSS. Inc., Chicago, IL, USA, 1989-2007).

The mean intra observer error, as calculated, was 0.080 mm for mesio-distal width. Pearson correlation between respective first and second measurements was highly significant at the 0.01 level (P = 0.000); Pearson r is 0.931 for mesio-distal width.

RESULTS

The maximum number of children on ART was in Group 1 [Table 1]. Twenty percent of children on ART were observed to have microdontia of all their four first premolars, and they belonged only to Group 1 [Table 2]. The mean mesio-distal width of the affected teeth was 3.2 ± 0.3 mm for upper first premolars and 3.4 ± 0.3 mm for lower first premolars [Table 3].

Microdontia was seen in children in whom ART was initiated at a mean age of 3.2 ± 0.8 years.

Table 1: Distribution of children according to ART drug regimen

Groups	Drug combination	Number
Group 1	ZDV + 3TC + NVP	65
Group 2	ZDV + ddI + NVP	29
Group 3	d4T + 3TC + NVP	15
	Total	109

ART: Antiretroviral therapy, ZDV: Zidovudine, 3TC: Lamivudine, NVP: Nevirapine, ddI: Didanosine, d4T: Stavudine

Table 2: Children affected with microdontia of all four first premolars

Groups (*n* = 109)	Onset of ART (years)	Duration of ART (years)	Number of children with microdontia of four first premolars *n* (%)
Group 1	3.2±0.8	9.3±1.3	22 (20.18)

ART: Antiretroviral therapy

Table 3: MD width of upper and lower first premolars

Upper 1st premolars (MD width in mm)			Lower 1st premolars (MD width in mm)		
Right side	Left side	Average	Right side	Left side	Average
3.4	3.4	3.4	3.6	3.6	3.6
3.6	3.6	3.6	3.4	3.4	3.4
3.2	3.0	3.1	3.4	3.2	3.3
3.6	3.6	3.6	3.8	3.8	3.8
3.4	3.2	3.3	3.3	3.1	3.2
3.2	3.2	3.2	4.3	4.3	4.3
3.8	3.8	3.8	3.8	3.8	3.8
3.1	3.1	3.1	3.2	3.2	3.2
3.6	3.6	3.6	3.1	3.1	3.1
3.9	3.7	3.8	3.3	3.1	3.2
3.2	3.2	3.2	3.8	3.8	3.8
3.1	3.1	3.1	3.5	3.5	3.5
2.9	2.9	2.9	3.6	3.6	3.6
3.2	3.2	3.2	3.1	3.1	3.1
2.8	2.8	2.8	2.8	2.8	2.8
3.1	3.1	3.1	3.1	3.1	3.1
3.8	3.8	3.8	2.9	2.9	2.9
3.0	3.2	3.1	3.0	3.2	3.1
2.6	2.6	2.6	3.8	3.8	3.8
3.6	3.6	3.6	3.3	3.3	3.3
3.2	3.2	3.2	3.7	3.7	3.7
3.2	3.2	3.2	4.1	4.1	4.1
Mean±SD=3.2±0.3			Mean±SD=3.4±0.3		

MD: Mesio-distal, SD: Standard deviation

DISCUSSION

In the last 10 years, ART has had a major impact on mortality and morbidity associated with HIV in children. According to Foster and Lyall,[11] the cumulative effects of ART on HIV-positive children are becoming more apparent, and their effect on mitochondrial toxicity needs further research.

Introduction of ART to children at an early age has been associated with impaired somatic growth. A Brazilian study[12] on HIV-vertically-infected adolescents on ART showed lower growth parameters in these individuals compared to that of the normal population. A correlation between the progression of HIV infection to pediatric AIDS and delayed tooth eruption has been observed.[13] Therefore, it is expected that dental development will also be altered in these children. It is more likely that a pediatric dentist would be the first health professional to recognize and diagnose the side-effects of a drug on both soft and hard tissues.[14]

In this study, 22 children were found to have smaller-sized upper and lower first premolars. Interestingly, these children belonged to Group I only. A sliding digital calipers was used to make intra-oral measurements of these premolars. Measurements from dental casts was with dividers were approximately 0.1 mm. Larger, on an average, than measurements made with sliding calipers.[15] Furthermore, measurements made intra-orally of maxillary teeth were seen to be almost 0.1 mm smaller than those made on plaster casts of the same teeth.[15]

Microdontia is a tooth that is much smaller than its contralateral homolog or tooth from the same group of the opposing arch (with exception of mandibular incisors), a tooth that does not "fill" its space in the dental arch, or a tooth that appears small because of absence of expected shape. Microdontia may affect a few teeth, usually homologous teeth or it may be generalized. It is a variable expression of tooth agenesis and is, therefore, multifactorial in etiology.[16] Microdontia is diagnosed by simple observation or measurement. Standards for tooth size have been published,[10] but microdontia is usually determined subjectively. For evaluating microdontia, only gross deviation in sizes easily discernible by clinical judgment have been accepted.[17]

There has been uncertainty about the role of specific ART drugs on mineral loss. Alterations in bone mass and metabolism have been found in HIV-infected children, adolescents, and adults. It could be due to the HIV infection *per se* and triggering bone mineral loss, as well as the cumulative exposure to antiretroviral drugs.[18,19] Since teeth are also calcifying structures, antiretroviral medication could also influence the different stages of dental mineralization.

ART regimes are based on nucleoside reverse transcriptase inhibitors (NRTIs). Therapy may combine three NRTI or two NRTI drugs with either HIV protease inhibitors (PI) or non-NRTIs. NRTIs can affect the function of the enzyme inside mitochondria, and this may

lead to depletion of mitochondrial DNA (mtDNA) or qualitative changes.[20] Evidence of mitochondrial toxicity associated with NRTIs has been identified *in vitro*, in animal models and in adults and children exposed to these drugs.[11]

The mitochondrial toxicity associated with NRTIs in children expresses itself in many ways and is comparable to children with mitochondrial congenital disorders.[11] As part of the national pediatric ART program in China, a study on mitochondrial toxicity and its potential mechanism in HIV-1-infected children found significant mtDNA loss in children on NRTI treatment.[21] Mitochondria play a major role in energy production and in glucose and fat metabolism. mtDNA is maternally inherited. There is a separate enzyme present inside the cell that replicates mtDNA, polymerase gamma.[22] The replication of mtDNA is independent of that of nuclear DNA synthesis, occurs throughout the cell cycle, and is required even in quiescent, nondividing cells. Basal mtDNA turnover rates vary in different cell types, and some tissues can increase their mtDNA content in response to energy demand or stress.

Mitochondrial toxicity is associated with NRTI therapy, and the incidence of symptomatic adverse effects rises with longer NRTI exposure. It is interesting to note that in the present study, microdontia of first premolars was seen in children who were introduced to ART at a very early age, with the mean age of administration being 3.2 ± 0.8 years. It is possible that mitochondrial toxicity plays a role in the delay of dental development of these children. According to Massler *et al.*,[23] formation of the crown tip of premolars is initiated at the age of 3 years. Exposure during early odontogenesis thus seems to cause microdontia, whereas later exposure seems to result in less damage to the tooth germ.

Although there are some known toxic effects of antiretroviral drugs, there is not enough evidence in the literature on their effect on the development of a permanent dentition. Within this context, further research is needed in order to identify better and recognize the changes that may be related to dental mineralization in children with HIV and on ART.

CONCLUSION

Microdontia of all first premolars was observed in 20% of HIV-infected children on ART. There is a need for further research on the possible effects of ART medications on developing teeth.

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