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ABSTRACT

To determine the frequency of Enamel Development Defects (DDE) and associated factors in children and adolescents infected with HIV. A case-control study was conducted in HIV-infected patients (n = 52), aged 3 to 15, and a control group formed by preschool and schoolchildren (n = 104) matched according to gender, age and household income. Data on medical history, neonatal and maternal conditions were obtained. For diagnosis of enamel defects was used modified DDE Index. DDE frequency was 61.5% in the case group and 58.7% in the control group (p = 0.569). Infection of the genitourinary tract and maternal hemorrhage were factors associated with DDE in the case and control groups, respectively. An association was observed between the use of antiretroviral regimens with protease inhibitors or efavirenz and DDE in the permanent dentition. Children and adolescents HIV-infected showed a DDE frequency similar to healthy patients, but factors associated with this condition were different between the groups.

KEY WORDS: dental enamel, children, adolescents, acquired immune deficiency syndrome, antiretroviral agents

Dental enamel development defects in children and adolescents with HIV infection: case-control study

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Introduction

During odontogenesis, many factors can affect the ameloblastic function and interfere with the enamel organ formation process, triggering anomalies called Developmental Defects of Enamel.[1] Such changes are irreversible and are risk factors for the installation of dental caries, dentinal sensitivity and commitment esthetic.[2,4–7]

The DDE etiology is unclear, however, nutritional deficiencies, infections in early childhood, prematurity, low birth weight and the use of antibiotics such as penicillin and cephalosporin, have been associated with condition.[8–10] In children infected with Human Immunodeficiency Virus (HIV), pre-, peri- and postnatal changes are often described.[11,12]

The HIV infection compromises the immune system and causes systemic repercussions in children and adolescents, and can affect the development of dental enamel.[13] To control the infection, treatment with antiretroviral drugs are started at an early age and, while effective, may have adverse effects on certain cellular mechanisms, such as those involved in osteogenesis.[14,15]

Few studies correlate HIV infection with the presence of DDE.[13,16] Exposure to risk factors such as pregnancy complications, infectious processes and medications in children and adolescents infected with HIV are conditions that support the formulation of the hypothesis that these patients are more susceptible to the development of DDE. The aim of this study was to determine the frequency of enamel defects and associated factors in children and adolescents infected with HIV.

Materials and methods

This case-control study was approved by the Ethics Committee of the Federal University of Piauí (CEP/UFPI) (Protocol N° 920.248), and it met the ethics recommendations dictated by the Declaration of Helsinki.

The population of the case group consisted of children and adolescents infected with HIV, treated at the referral hospital of the state of Piauí, Institute of

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Tropical Diseases Nattan Portella (ITDNP). Children and adolescents infected with HIV and treated at ITDNP in the period from November 2014 to September 2015 were consecutively included.

The control group consisted of preschool children and children enrolled in public schools in the city of Teresina, Piauí, Brazil. The sample was randomly stratified and matched with individuals in the case group for age, gender, and socioeconomic conditions with a ratio of two individuals not infected with HIV to an individual infected with HIV.

The case group included patients infected with HIV through vertical channels, ranging in age from 3 to 15 years. In both groups, patients were excluded if they were using a fixed orthodontic appliance.

Control subjects were selected from five schools and a day-care center in the city of Teresina, PI, from a list provided by the Municipal Education. After contact with the kindergartens and schools and access to nominal lists with the age and gender of students, those preschool and school children eligible for the study were selected.

The calibration of the examination was performed in two steps: the first training was performed *in lux*, consisting of slide projection images of different kinds of enamel defects. After a week, the photographs were restated and the examiner had to identify at least 80% of clinical diagnoses.[17] In the second stage, 10 patients not participating in the research were examined independently by an experienced examiner ($\kappa > 0.9$) and the examiner of the study. After two weeks the same patients were reexamined. The inter ($\kappa = 0.818$) and intrarater concordances ($\kappa = 0.863$) were determined by κ index.

The pilot study was conducted with 10 subjects, randomly selected, frequenters of Federal University of Piauí dental clinics not involved in the research. The aim of the pilot study was to evaluate the proposed methodology. The results indicated that there was no need to make changes in the methodology.

Data collection was carried out in three stages: (1) Evaluation of the medical records of patients in the case group—data were collected concerning HIV infection and viral load, CD4 and CD8 T-cell counts after the start of antiretroviral therapy regimens; (2) application questionnaire to parents or guardians—the questionnaire contained questions related to pregnancy, neonatal conditions, dental trauma, drug use, oral hygiene habits and the occurrence of primary diseases of childhood; (3) dental clinical examination.

The patients were examined in a conventional dental office under direct lighting reflector using dental mirror and probe. The diagnosis of enamel defects was performed using the modified DDE Index recommended by the World Dental Federation, which evaluates the presence of marked opacity, diffuse opacity, hypoplasia or combinations thereof, beyond the location and extent of these defects.[1]

Opacities are defects involving changes in enamel translucency and it can be classified as demarcated or diffuse. When there was a limit between the adjacent normal enamel and the opacity, it was classified as a demarcated opacity. When there was no limit between the normal enamel and the opacity, it was classified as a diffuse opacity. Hypoplasia was quantitative defect associated with localized reduction in thickness. Defects measuring less than 1 mm in diameter were not considered.[1] Tooth surfaces with carious lesions, restorations and/or fractures involving more than two-thirds of the surface were excluded.[1]

Data were analyzed in the *Statistical Package for the Social Science* (SPSS® for Windows, versão 20.0, SPSS Inc., Chicago, IL, USA). Descriptive analysis using frequencies was performed. In the bivariate analysis, we used the chi-square test and Fisher's exact test to determine associations between pre-, peri-, and postnatal conditions and the presence of DDE. The $p \leq 0.2$ variables were included in the multivariate logistic regression by stepwise backward method, which only selects the significant variable of each test step. The results were expressed as odds ratio (OR) and 95% confidence interval and remained in the model if associations reached $p < 0.05$. In all analyses, significance level was $\alpha = 5\%$.

Results

Fifty-seven individuals were identified as meeting the inclusion criteria for the study group, of which 52 agreed to participate and 5 did not agree. In the case group the mean age was 8.44 years (minimum of 3 and maximum of 15 years). The control group consisted of 104 individuals who agreed to participate.

Table 1 describes the socioeconomic and demographic characteristics and clinical data of the population. Of those children and adolescents infected with HIV, 32 (61.5%) were diagnosed with DDE. In the control group, the DDE rate was 58.7%.

In the case group, of the 3,561 examined tooth surfaces, 366 (10.3%) were excluded due to extensive carious lesions, and 83% of these surfaces were excluded from deciduous teeth. In the control group, 6,195 dental surfaces were examined, among which 168 (2.7%) were excluded due to carious lesions that prevented the examination (81 surfaces of permanent teeth and 75 surfaces of deciduous teeth).

Demarcated opacities were the most frequent defects in permanent teeth among individuals in the case group. No statistically significant difference was observed between the groups (Table 2).

In the bivariate analysis, associations were observed between infection of the genitourinary tract in pregnancy and the presence of DDE in HIV-infected patients ($p = 0.013$) (Table 3). In the control group, a positive association was observed between bleeding during pregnancy and enamel defects in both dentitions ($p = 0.021$). There was no association between postnatal conditions and the presence of DDE in permanent teeth of both groups (Table 4).

A positive association was found between the type of anti-retroviral regimen and frequency of enamel defects ($p = 0.039$) (Table 5).

In the adjusted multivariate regression model, urinary tract infection (OR: 5.4; IC 95%: 1.3 to 21.7) and bleeding

Table 1. Characterization of socioeconomic variables and the presence of DDE in the study population.

Variáveis	Case group n (%) (n = 52)	Control group n (%) (n = 104)	*p**
Gender			
Male	27 (51.9)	54 (51.9)	1.000*
Female	25 (48.1)	50 (48.1)	
Age			
3 to 6 years	19 (36.5)	38 (36.5)	1.000*
7 to 15 years	33 (63.5)	66 (63.5)	
Family income (minimum wage)			
<2 SM	22 (42.3)	57 (54.8)	0.532*
≤2 SM	30 (57.7)	37 (35.6)	
Education of charge (years of formal study)			
≤8 anos	26 (51.0)	30 (28.8)	0.146*
>8 anos	25 (49.0)	65 (62.5)	
DDE frequency			
Yes	32 (61.5)	61 (58.7)	0.569*
No	20 (38.5)	43 (41.3)	
*Chi-square test of Pearson.			

Table 2. Frequency and type of enamel developmental defects in primary and permanent dentition.

	Case group N(%)	Control group N(%)	*p**
Primary tooth			
DDE frequency			
Yes	5/22 (22.7)	13/44 (29.5)	0.523*
No	17/22 (77.3)	31/44 (70.4)	
Type defects			
Opacity Demarcada	2/5 (40.0)	8/44 (61.5)	0.681**
Diffuse opacity	1/5 (20.0)	1/44 (7.7)	
Hypoplasia	2/5 (40.0)	4/44 (30.8)	
Permanent tooth			
DDE frequency			
Yes	26/33 (78,8)	49/66 (74.2)	0.447*
No	7/33 (21.2)	17/66 (25.8)	
Type defects			
Opacity Demarcada	16/26 (61.5)	15/49 (30.6)	0.123**
Diffuse opacity	7/26 (27.0)	33/49 (67.3)	
Hypoplasia	3/26 (11.5)	1/49 (2.1)	
*Chi-square test of pearson. **Fisher's exact test.			

during pregnancy (OR: 9.8, IC 95%: 1.1 to 84.6) were associated with the presence of DDE in the case and control groups, respectively (Table 6). In the permanent dentition, in HIV-infected patients, there was an association between DDE and antiretroviral therapy (OR: 6.3, 95%, 1.1 to 40.1) (Table 7).

Discussion

This is the first study to investigate pre-, peri-, and postnatal conditions associated with enamel developmental defects in children and adolescents infected with HIV compared with uninfected individuals.

Despite the high frequency of DDE in children and adolescents infected with HIV, it is not possible to consider that these patients are at increased risk of DDE, considering that there was no statistically significant difference in the presence of enamel defects between the groups. Other studies have analyzed enamel defects in HIV-infected patients, but the results were mixed for the occurrence of DDE in these patients due to the discrepancy between the values observed.[16,18]

In this study, the frequency of DDE was higher in permanent teeth, a result that can be explained by the fact that children with deciduous dentition presented more decayed teeth compared to those with permanent teeth, reducing the number of surfaces for the diagnosis of DDE, especially in the case group. The results are consistent with those presented by Lunardelli *et al.*[19]

Systemic conditions can alter the normal function of ameloblasts and consequently trigger DDE.[20] In general, clinical aspects of enamel defects do not accurately reflect the etiology of the disorder. Furthermore, other systemic origin factors may occur simultaneously.[7]

In the permanent dentition, the opacity of the enamel was a prevalent defect in both groups. However, HIV-infected patients had a higher frequency of demarcated opacities, while in the control group diffuse opacities were predominant. Both defects result from disturbances during the enamel

Table 3. Association between pre- and perinatal conditions and DDE in children and adolescents infected with HIV and the control group.

Pre- and perinatal conditions	Case group (n = 52)		*p**	Control group (n = 104)		*p**
	With DDE	Without DDE		With DDE	Without DDE	
Fever and/or infection during pregnancy						
Yes	8 (25)		0.408*	8 (13.1)	6 (15.4)	0.553**
No	20 (62.5)	8 (40.0)		48 (78.7)	33 (84.6)	
No information	4 (12.5)	12 (60.0)		5 (8.2)	4 (9.3)	
Urinary tract infection						
Yes	4 (12.5)	9 (47.4)	0.013*	11 (18.0)	8 (19.0)	0.992*
No	24 (12.5)	10 (52.6)		47 (77.0)	34 (81.0)	
No information	24 (75.0)	1 (5.0)		3 (4.9)	1 (2.3)	
Use of antibiotics						
Yes	7 (25.0)	9 (47.4)	0.112*	12 (19.7)	8 (19.5)	0.886*
No	21 (75.0)	10 (52.6)		46 (75.4)	33 (80.5)	
No information	4 (12.5)	1 (5.0)		3 (4.9)	2 (4.6)	
Bleeding during pregnancy						
Yes	1 (3.2)	2 (10.5)	0.355**	1 (1.7)	6 (14.3)	0.021**
No	27 (65.6)	17 (89.5)		57 (93.4)	36 (85.7)	
No information	4 (12.5)	1 (5.0)		3 (4.9)	1 (2.3)	
Premature birth						
Yes	1 (3.2)	2 (10.0)	0.373**	8 (13.1)	4 (9.5)	0.420*
No	27 (65.6)	18 (90.0)		50 (82.0)	38 (90.5)	
No information	4 (12.5)			3 (4.9)	1 (2.3)	
Fetal distress						
Yes	3 (9.4)	1 (5.3)	0.448**	9 (14.8)	8 (18.6)	0.247*
No	24 (75.0)	18 (94.7)		47 (77.0)	32 (74.4)	
No information	5 (15.6)	1 (5.0)		5 (8.2)	3 (7.0)	
Hypoxia						
Yes	1 (3.2)	2 (10.5)	0.355**	4 (6.6)	1 (2.4)	0.300**
No	27 (65.6)	17 (89.5)		53 (86.9)	40 (93.0)	
No information	4 (12.5)	1 (5.0)		4 (6.5)	2 (4.6)	
Difficulties respiratory						
Yes	2 (7.4)	3 (15.0)	0.356**	4 (6.6)	4 (9.3)	0.376**
No	25 (92.6)	17 (85.0)		48 (78.7)	31 (72.1)	
No information	5 (15.6)			9 (14.7)	8 (18.6)	
Need incubator						
Yes	2 (6.3)	3 (15.0)	0.340**	7 (11.5)	3 (7.0)	0.403**
No	26 (78.2)	17 (85.0)		48 (78.7)	32 (74.4)	
No information	4 (12.5)			6 (9.8)	8 (18.6)	
Birthweight						
>2.500 g	14 (43.7)	11 (61.1)	0.252**	28 (45.9)	19 (44.1)	0.929*
<2.500 g	16 (50.0)	7 (38.9)		23 (37.7)	15 (34.9)	
No information	2 (6.3)	2 (10.0)		10 (16.4)	9 (21.0)	

*Chi-square test of Pearson.
**Fisher's exact test.

Table 4. Association between postnatal conditions and DDE in children and adolescents infected with HIV and the control group.

Post-natal factors						
	Case group (n = 52)			Control group (n = 104)		
	With DDE	Without DDE	*p**	With DDE	Without DDE	*p**
History of sepsis						
Yes	5 (12.2)	1 (14.3)	0.656**	3 (31.2)	1 (2.1)	0.059**
No	19 (73.1)	5 (71.4)		14 (68.8)	44 (89.7)	
No information	2 (7.7)	1 (14.3)		–	4 (8.2)	
Diarrhea/dehydration						
Yes	13 (50.0)	3 (42.9)	0.537**	5 (29.4)	12 (24.5)	0.443**
No	13 (50.0)	4 (57.1)		11 (64.7)	35 (71.4)	
No information	–	–		1 (5.9)	2 (4.1)	
Varicella						
Yes	5 (19.2)	1 (14.3)	0.624**	0	2 (4.1)	0.547**
No	21 (80.8)	6 (85.7)		16 (94.1)	44 (89.8)	
No information	–	–		1 (5.9)	3 (6.1)	
Pneumonia						
Yes	13 (50.0)	3 (42.9)	0.537**	2 (11.8)	3 (6.1)	0.376**
No	13 (50.0)	4 (57.1)		14 (82.3)	44 (89.8)	
No information	–	–		1 (5.9)	2 (4.1)	
Asthma						
Yes	1 (3.8)	2 (28.6)	0.106**	1 (5.9)	0	0.254**
No	25 (96.2)	5 (71.4)		15 (88.2)	47 (95.9)	
No information	–	–		1 (5.9)	2 (4.1)	
Bronchitis						
Yes	3 (11.5)	1 (14.3)	0.635**	2 (11.8)	2 (4.1)	0.265**
No	23 (88.5)	6 (85.7)		14 (82.3)	45 (91.8)	
No information	–	–		1 (5.9)	2 (4.1)	
Sinusitis						
Yes	2 (7.7)	1 (14.3)	0.523**	2 (11.8)	4 (8.2)	0.481**
No	24 (92.3)	6 (85.7)		14 (82.3)	43 (87.7)	
No information	–	–		1 (5.9)	2 (4.1)	
Rhinitis						
Yes	2 (7.7)	1 (14.3)	0.523**	0	5 (10.2)	0.218**
No	24 (92.3)	6 (85.7)		16 (94.1)	42 (85.7)	
No information	–	–		1 (5.9)	2 (4.1)	
Renal disorders						
Yes	1 (3.8)	0	0.788**	0	2 (4.1)	0.554**
No	25 (96.2)	7 (100.0)		16 (94.1)	45 (91.8)	
No information	–	–		1 (5.9)	2 (4.1)	
High fever						
Yes	17 (65.4)	3 (42.9)	0.256**	9 (52.9)	19 (38.7)	0.373*
No	9 (34.6)	4 (57.1)		8 (47.1)	28 (57.1)	
No information	–	–		–	2 (4.1)	

Continued

Table 4. Continued.

Post-natal factors						
	Case group (n = 52)			Control group (n = 104)		
	With DDE	Without DDE	*p**	With DDE	Without DDE	*p**
Malnutrition						
Yes	6 (23.1)	0	0.208**	2 (11.8)	3 (6.1)	0.401**
No	20 (76.9)	7 (100.0)		15 (88.2)	44 (89.8)	
No information	–	–		–	2 (4.1)	
Ear inflammation						
Yes	11 (42.3)	3 (42.9)	0.652**	5 (70.6)	9 (18.4)	0.289**
No	15 (57.7)	4 (57.1)		12 (29.4)	38 (77.5)	
No information	–	–		–	2 (4.1)	
Antibiotics						
Yes	16 (61.5)	4 (66.7)	0.601**	10 (58.8)	16 (32.7)	0.123*
No	10 (38.5)	2 (33.3)		7 (41.2)	26 (53.0)	
No information	–	–		–	7 (14.3)	
Fluoridated water intake						
Yes	13 (50.0)	2 (28.6)	0.283**	17 (100.0)	47 (95.9)	0.548**
No	13 (50.0)	5 (71.4)		0	2 (4.11)	
No information	–	–		–	–	

*Chi-square test of Pearson.
**Fisher's exact test.

Table 5. Aspects association between infection and antiretroviral therapy in children and the presence of DDE.

	Case group (n = 33)		
Variables	Sem DDE	Com DDE	*p**
Lymphocytes T CD4			
≤500 cells/μl	3 (42.9)	6 (20.8)	0.374*
>500 cells/μl	5 (57.1)	19 (79.2)	
Lymphocytes T CD8			
≤500 cells/μl	0 (0.0)	1 (4.8)	0.759**
>500 cells/μl	7 (100.0)	21 (79.2)	
Viral charge			
Indetectável	4 (57.1)	13 (56.5)	0.760**
50 to 10.000 cópias/ml	3 (28.6)	9 (34.8)	
>10.000 cópias/ml	1 (14.3)	2 (8.7)	
Antiretroviral regimens			
2ITRN[a]/3ITRN	5 (57.1)	4 (17.4)	0.039*
2 ITRN + 1 IP[b]/2 ITRN + EFV[c]	4 (42.9)	20 (82.6)	

[a]Nucleoside inhibitor reverse transcriptase.
[b]Protease inhibitor.
[c]Efavirenz inhibitor (non-nucleoside reverse transcriptase).
*Chi-square Test of Pearson.
**Fisher's exact test.

maturation phase, which may interfere with the growth of crystals and the replacement of the organic matrix by mineral content.[21,22] However, diffuse and demarcated opacities are associated with different causal factors.[7,22,23]

Demarcated opacities are associated with local factors, such as trauma or infection in primary teeth predecessors, while diffuse opacity is the type of enamel defect observed more in the permanent dentition in communities with a fluoridated public water supply.[21–24] In this study, most of the children in the control group reside in a municipality with a fluoridated public water supply. In contrast, more than half of the patients in the case group reported living in cities without access to fluoridated water, a condition that may explain the difference in the types of defects between the two groups.

The intake of other chemical elements may cause an adverse effect on dental enamel formation.[25] Exposure to substances such as lead, mercury, bisphenol A and other drugs, such as anticancer

Table 6. Associations between DDE and prenatal conditions.

Groups	Variables	OR (aj)*	IC 95%		*p*
			LI	LS	
Case	Urinary tract infection during pregnancy**	5.4	1.3	21.7	0.017
Control	Bleeding during pregnancy**	9.8	1.1	84.6	0.038

*Multivariate logistic regression.
**Reference category: no DE.
OR (aj) = adjusted odds ratio, IC 95% = confidence interval, *p* = significance of the multivariate logistic regression model. LI: lower limit, LS: upper limit

Table 7. Association between DDE and antiretroviral regimens.

Groups	Variables	OR (aj)*	IC 95%		*p*
			LI	LS	
Case	Antiretroviral Regimens** (2 ITRN + 1 IP[b] / 2 ITRN + EFV[c]	6.3	1.1	40.1	0.049

*Multivariate logistic regression.
**Reference category: no DE. [b]Protease inibidor. [c]Efavirenz inhibitor (non-nucleoside reverse transcriptase).
OR (aj) = odds ratio adjusted, IC 95% = confidence interval, *p* = significance of the multivariate logistic regression model. LI: lower limit, LS: upper limit

agents and antibiotics, have been identified as possible causative agents of DDE, depending on the enamel development phase in which the child was exposed, the general health of the same, and the time and duration of exposure.[10,26–28] In this study, a positive association was observed between antiretroviral triple-therapy regimens containing protease inhibitors (PI) or nonspecific inhibitor analogue reverse transcriptase, the efavirenz (EFV) and DDE in the permanent dentition.

Although there is no report in the literature on the effects of antiretroviral drugs on the formation of tooth enamel, studies show that the use of PI and EFV for children and adolescents causes reduced levels of calcium and Vitamin D, respectively.[29–31] These minerals are essential for the normal development of enamel.[32]

During amelogenesis, calcium ions regulate cellular activities, such as signal transduction and enzyme activation, and directly participate in the enamel-maturation phase.[33–35] As well as calcium, vitamin D plays an important role during amelogenesis, acting in cell differentiation and mineralization of dental enamel.[36] A study by Zerofsky[32] demonstrated that children with vitamin D deficiency had a higher frequency of enamel defects. Such arguments are supported by the results observed here, suggesting that the reduction of calcium and vitamin D caused by the use of PI and EFV may be associated with the development of DDE.

In this study, aspects related to pregnancy, neonatal and postnatal conditions were examined as possible factors associated with DDE, considering the different display windows for the development of the condition. However, determining the specific time of occurrence of injuries to the enamel development is difficult because of the difficulty in specifying the chronology of the various stages of amelogenesis as well as individual variations in the enamel development period.[2,3]

The amelogenesis in primary dentition begins in intrauterine life and ends around the birth, while the enamel of permanent teeth begins to develop during gestation and is completed in infancy.[37] Thus, associations were analyzed between pre- and perinatal conditions of both dentitions and postnatal conditions only with permanent dentition.

The development of DDE has been associated with factors such as pregnancy complications, low birth weight, prematurity and perinatal respiratory disorders.[8–10,38,39] In this study, only infection of the genitourinary tract during pregnancy was positively associated with the presence of DDE in the permanent teeth in HIV-infected patients.

Pregnant and HIV-infected women are more susceptible to the genitourinary tract infections due to impairment of the immune system.[11] Infectious processes during the prenatal and perinatal periods are identified as risk factors for the occurrence of demarcated opacities,[40] which was the most frequent type of DDE in the first permanent molars in this study. Such findings are consistent with molar-incisor hypomineralization, a condition characterized by the presence of structural enamel defects affecting at least one of the first permanent molars and commonly associated with changes in incisor permanent.[39,41]

Given the occurrence of DDE in children and adolescents infected with HIV and that such changes are considered a risk factor for the development of dental caries and periodontal disease,[3,6] it is recommended that these patients are monitored regularly and when dental treatment is indicated that is carried out early.

Due to the retrospective nature of the study, care should be taken regarding the analysis of the results, considering that research on factors associated with DDE is subject to a recall bias of parents/guardians. Moreover, the study of drug effects on DDE is not simple, considering that the condition for which the medication was prescribed might have caused the defect and thus serve as a confounding factor.

In conclusion, children and adolescents infected with HIV showed DDE frequency similar to uninfected patients. Prenatal factors associated with DDE

were genitourinary tract infection in the case group and bleeding in the control group in both dentitions. Exposure to antiretroviral regimens with efavirenz and protease inhibitors was a postnatal factor associated with DDE in permanent teeth in the case group.

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