Gingival Recession and Localized Aggressive Periodontitis Among HIV-infected Children and Adolescents Receiving Antiretroviral Therapy

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Abstract

Background: Limited information is available on gingival recession or localized aggressive periodontitis among HIV-infected children and adolescents. This study reports on the prevalence of these conditions among children and adolescents receiving antiretroviral therapy (ART).

Methods: A cross-sectional study on HIV-infected children and adolescents attending a Pediatric HIV clinic in Gauteng, South Africa, between January 2013 and June 2016. Patients received an oral examination and oral hygiene instructions, irrespective of oral- or dental-related complaints. Hard and soft tissue pathology was managed and recorded, together with relevant demographic and clinical data. Statistical analysis was performed in Stata 14 with $P < 0.05$ as significant.

Results: A total of 554 children and adolescents 5-19 years of age (median age: 12.2 years; interquartile range: 10.3-14.9) were included, of whom 78 (14.1%) presented with gingival recession on permanent mandibular incisors and/or localized aggressive periodontitis of molar teeth. Multivariable logistic regression revealed that patients with gingival recession and aggressive periodontitis had a significantly shorter duration of ART and were more likely to have suboptimal HIV control (CD4 count <=500 cells/[micro]L and/or HIV viral load >=50 copies/mL) and be on advanced ART regimens after virologic failure on first- and second-line treatment.

Conclusions: The results emphasize the importance of oral health care among HIV-infected children and adolescents from the onset, to prevent and manage conditions that could result in tooth loss and permanent disfigurement. This is of particular importance in the presence of virologic failure and immunosuppression.

Keywords: HIV infection; children; adolescents; aggressive periodontitis; South Africa

Periodontal disease (PD) involves the breakdown of connective tissue and alveolar bone that support teeth, resulting in mobility and tooth loss. Chronic periodontitis progresses slowly with no specific tooth pattern, while aggressive periodontitis (AP) affects young people with the localized subtype having a distinct incisor/first molar disease pattern.[1,2] AP also has a

race predilection with young individuals from African descent more prone to this aggressive subset of PD than Caucasian children.[3] Gingival recession (GR), another subtype of PD, presents as apical migration of the gingival margin, exposing the cementum that covers the root of the tooth, increases in frequency with increased age and has no distinct ethnic association.[4] While 2 recent publications provide information on chronic PD among American and Puerto Rican HIV-infected youth,[5,6] there is paucity of information on the prevalence of AP among HIV-infected children and adolescents. This is true globally, but of particular importance in sub-Saharan Africa, where the majority of HIV-infected children reside. To our knowledge, this cross-sectional study is the first to report on GR occurring in isolation on mandibular incisors and in combination with localized aggressive periodontitis (LAP) involving incisor and molar teeth among HIV-infected children and adolescents receiving antiretroviral therapy (ART).

MATERIALS AND METHODS

Study Design and Patients

A cross-section of data was selected from information gathered between January 2013 and June 2016 on HIV-infected children and adolescents, between 5 and 19 years of age attending the pediatric HIV clinic at Kalafong Provincial Tertiary Hospital, Gauteng, South Africa. Patients were of periurban, low- to middle-income sociodemographic background and reported monthly or 2 monthly for medical care as per routine follow-up protocol in the clinic depending on the disease severity and treatment success. Included into the analysis data set were data from a single visit for any given patient. In particular, control group (CG) patients were those who never developed any PD, and data from their last visit were included, while for periodontal disease group (PDG) patients data from the visit of diagnosis were included. By the above inclusion criteria, along with the specified age range of 5-19 years, data for 554 patients from records of approximately 1100 patients were included.

Oral Examination

Irrespective of any oral or dental complaints, each patient received oral hygiene instructions and a comprehensive extra- and intraoral examination of soft and hard tissue, excluding routine periodontal probing, according to generally accepted criteria.[7,8] While the vast majority of patients reported for an oral examination at every visit to the clinic, all patients did so at least every 6 months. Observations were recorded, discussed with patients and/or caregivers and managed accordingly. GR was noted when the gingival margin was located apical to the cemento-enamel junction exposing the cementum covering the root of the tooth. It was measured by placing a Williams periodontal probe against the exposed cementum and recording the distance between the cemento-enamel junction and the free gingival margin (to nearest 1 mm). When GR was identified, tooth mobility was assessed in a horizontal plane on incisors and mandibular and maxillary first and second molars and recorded as 1 (movement 1-2 mm) and 2 (movement >2 mm).[9] Incisor malocclusion and possible gnashing were also assessed. Information on mobile or missing teeth (excluding normal exfoliation) was obtained from patients and parents/caregivers. Patients with GR of the mandibular incisors were advised to brush with an upward, sweeping motion [10] and afterwards rinse with a salt and bicarbonate solution. When molar teeth were affected, in addition to mandibular incisors, patients were prescribed amoxicillin, metronidazole and 0.2% chlorhexidine oral rinse for 5 days.[11] This was repeated once a year, while proper oral hygiene measures were emphasized at every visit, together with a recommendation to

regularly rinse with salt and bicarbonate of soda after completion of the antibiotic and chlor hexidine regimen.

Patient Records

Relevant information, extracted from clinic folders, included demographic data, ART initiation date, ART regimens and most recent $CD4^+$ T-cell counts/percentages and HIV viral loads (VL).

Statistical Analysis

Data were analyzed using Stata 14 (StataCorp LLC, TX), with statistical methods selected based on data distribution. A P value <0.05 was deemed significant. Bivariate statistical analysis included Pearson $[chi]^2$ and Fisher exact (categorical variables) and Kruskal-Wallis rank-sum tests (continuous variables). Multivariable logistic regression was performed and results tested for collinearity. ART regimens were divided into nonnucleoside reverse transcriptase inhibitor-based, protease inhibitor-based and advanced regimens (third-line or holding regimens). Patients were categorized as immunocompetent if the latest $CD4^+$ count was >=500 cells/[micro]L and a VL of >50 copies/mL was used to define virologic failure. A category was created to describe suboptimal HIV-disease control using the combined immunologic and virologic responses of $CD4^+$ count <500 cells/[micro]L and/or VL >50 copies/mL.

Ethical Clearance

Written permission was obtained from the Kalafong Hospital management and the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria (74/2004), to publish data obtained during routine clinical care, observing patient anonymity.

RESULTS

A total of 554 patients were included with a median of 12.2 years of age [interquartile range (IQR): 10.3-14.9] and 297 (53.6%) were female. They started ART at a median age of 4.7 years (IQR: 1.9-7.9) and were on treatment for an average of 7.6 years (IQR: 5.3-9.6). While a total of 4511 dental visits were recorded for the 554 patients, for the purpose of this study, only data from a single visit per patient were included, as well as only observations pertaining to GR and LAP. GR and/or LAP involving incisor and/or molar teeth (PDG) was diagnosed in 78 (14.1%) patients, while 476 had no evidence or history of gingival or periodontal disease (CG). Demographic and clinical data of these groups are summarized in Table 1. Except for the gender distribution, the PDG was significantly different from the CG. Children in the PDG were older but had also started ART at an older age and hence had a shorter duration of ART and were more likely to be on advanced ART regimens. They had lower median $CD4^+$ counts/percentages and higher median VLs and were more likely to have virologic failure and/or be immunocompromised, regardless of whether the latter was defined at $CD4^+$ <500 or <=350.

TABLE 1. Demographic and Health Characteristics of CG and PDG Patients

	CG (n = 476)	PDG (n = 78)	*P* Value
Female, n/N (%)	256/476 (53.8)	41/78 (52.6)	0.84
Age at visit (yr), median (IQR)	12.0 (10.2–14.8)	13.1 (11.6–15.1)	0.04
Antiretroviral therapy (ART), median (IQR)			
Age at ART start (yr)	4.4 (1.8–7.5)	7.0 (2.9–10.0)	0.0003
Duration ART (yr)	7.8 (5.8–9.6)	6.6 (3.6–9.5)	0.01
ART regimens, n/N (%)			
First-line	259/472 (54.9)	46/78 (59.0)	<0.001
Second-line	203/472 (43.0)	23/78 (29.5)	
Advanced regimen	10/472 (2.1)	9/78 (11.5)	
†Immunologic status			
CD4⁺ (cells/μL), median (IQR)	797 (580–1080)	635 (392–804)	0.0002
CD4⁺%, median (IQR)	31.5 (24.8–37.5)	27.6 (19.2–34.6)	0.008
No immunosuppression (CD4⁺ ≥ 500), n/N (%)	373/476 (78.4)	53/78 (67.9)	0.04
Immunosuppressed (CD4⁺ < 500), n/N (%)	103/476 (21.6)	25/78 (32.1)	
HIV VL			
VL (copies/mL), median (IQR)	50 (50–150)	130 (50–3997)	0.0004
≤50 copies/mL, n/N (%)	308/469 (65.7)	37/78 (47.4)	0.002
>50 copies/mL, n/N (%)	161/469 (34.3)	41/78 (52.6)	
‡Combined CD4⁺ and VL category, n/N (%)			
CD4⁺ ≥ 500 and VL ≤ 50	279/469 (59.5)	32/78 (41.0)	0.002
Either/both CD4⁺<500 and VL > 50	190/469 (40.5)	46/78 (59.0)	

*First-line ART = abacavir (ABC) + lamivudine (3TC) + efavirenz (EFV) or emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF) + EFV; second-line ART = ABC, 3TC and lopinavir/ritonavir; holding therapy = either 3TC monotherapy or zidovudine (AZT) + ABC + 3TC; third-line ART = individualized drug regimen chosen according to genotyping.

†Based on the WHO immunologic classification with a CD4⁺ count of 500 cells/μL as cutoff point.

‡Categories created for no immunosuppression and virologic failure versus any immunosuppression or virologic failure.

IQR indicates interquartile range.

Identification of LAP was based on recession, mobility and/or loss of molar and/or incisor teeth. Sixty-eight patients (87.1%) presented with varying degrees of recession, from an insidious onset (Fig. 1) to recession masked by gingivitis and gingival hypertrophy (Fig. 2). Nine patients (11.5%) fitted the case definition of LAP. Three patients had lost one or more teeth of whom a 16 year-old female had lost both mandibular central incisor and first molars (Fig. 3). Another 2 patients presented with recession and mobility of maxillary molars only and 1 with primary molars and incisors affected. The remaining 3 patients presented with advanced recession, calculus and mobility of >2 on affected teeth (Fig. 4). These 9 patients with LAP did not differ significantly from the other PDG patients in terms of immunologic and virologic failure (P = 0.542). In another 6 patients with GR only, calculus was present on the mandibular incisors. One patient presented with an edge-to-edge incisor occlusion and another with an anterior cross-bite, with none displaying evidence of gnashing. One patient was referred for a frenectomy.

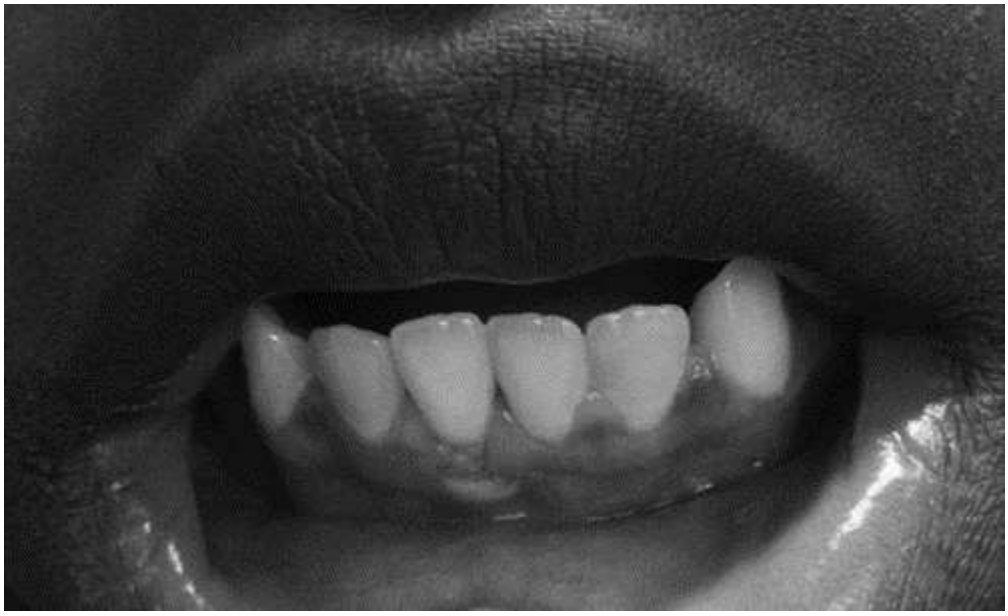

FIGURE 1. Eleven-year-old female with insidious onset of gingival recession on mandibular incisors without gingivitis.

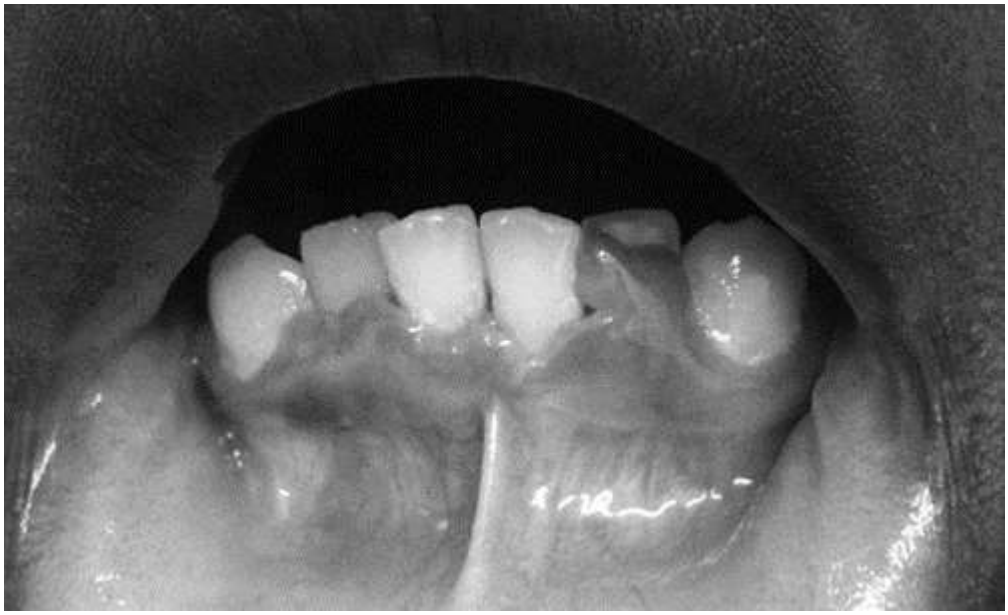

FIGURE 2. Sixteen-year-old female with gingival hypertrophy, masking initial recession on mandibular incisors.

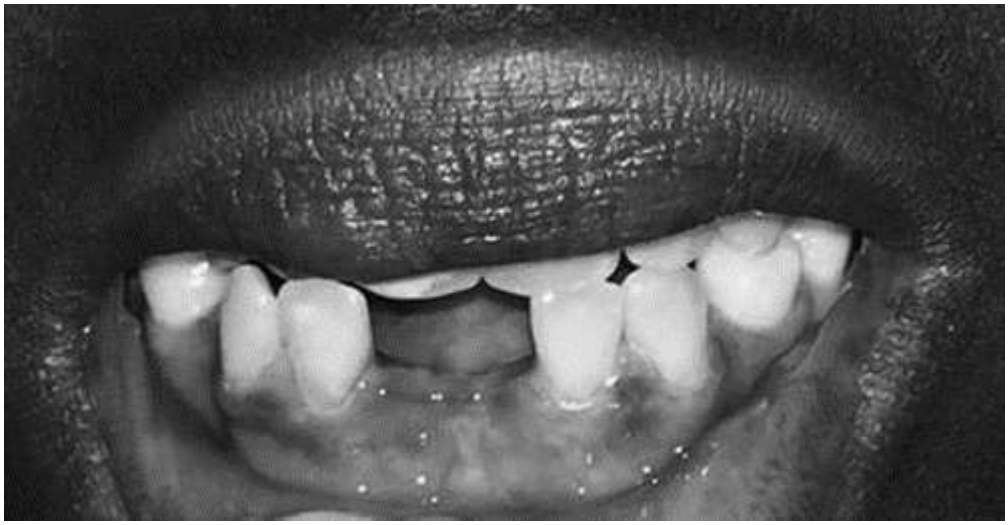

FIGURE 3. Sixteen-year-old female with loss of both central mandibular incisors and calculus but no recession on remaining incisors.

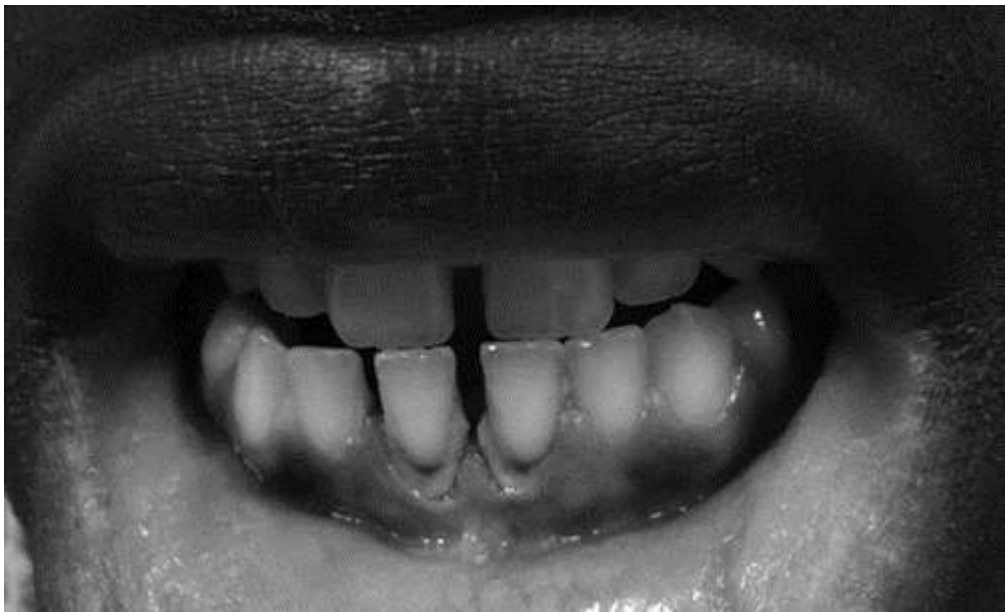

FIGURE 4. Fourteen-year-old male with marked recession and calculus on mandibular central incisors.

DISCUSSION

This study is the first to describe GR and LAP among HIV-infected children and adolescents. Data were obtained during an oral health service to HIV-infected youth and is, therefore, not a dedicated PD survey like that of Ryder et al.[6] Statistically significant associations between PD and suboptimal HIV-disease control (immunocompromise and/or virologic failure) as well as advanced ART regimens were demonstrated. Patients on advanced ART regimens had a history of immunosuppression and high VLs before switching and were more likely to still have an inadequate treatment response at time of study. Furthermore, the significant association between longer ART duration and absence of GR and LAP strengthens the motivation for early ART.[12,13]

Theoretically, the observed LAP should be referred to as "periodontal disease as a manifestation of systemic disease," although forcing observed conditions into an existing

classification system may be clinically unhelpful, an approach that Ryder et al also selected by merely referring to PD.[6]

Not having performed periodontal probing may be regarded as a shortcoming of the study, with possible underestimation of periodontal destruction in the absence of visible GR. It is, however, not recommended to perform routine probing on children 15 years of age or younger,[8] and probing depths would not have influenced the available treatment modalities. With their extensive phlebotomy history, these children are, understandably, fearful of sharp instruments, and patients' willingness to return for dental visits and maintain good oral hygiene was of greater priority.

Both GR and LAP have multifactorial etiologies that encompass microbiologic, immunologic/inflammatory and genetic mechanisms as well as factors affecting bone mineralization,[14,15] while the role of medication, such as frequent antibiotic use and ART, seemingly remains unexplored. Except for immunosuppression and high VL, it is not possible from this descriptive study to identify specific etiologic factors. Globally, there is a lack of information on the prevalence of GR and LAP among HIV-infected children and adolescents. A control group is equally problematic due to limited information in healthy children, and in South Africa, information regarding these conditions is not included in national oral health surveys.[16]

The problem is, however, significant. Of the 9 patients diagnosed with LAP, 3 had already lost teeth and another 3 had teeth with extreme mobility. Again, this may be an underestimation because obtaining an accurate history of missing teeth proved difficult, as children often attended clinic visits unaccompanied (age-permitting) or accompanied by adults other than their biologic parents. Longitudinal studies would provide more accurate information on the progression of GR and impact of aggressive PD.

The importance of optimal oral health in the management of systemic disease, including HIV,[17,18] is evident; yet calls for inclusion of oral health as a component of general health services have gone unheeded.[19] No professional oral hygiene services are available to these patients, and extractions remain the only treatment modality. Limited health resources in developing countries do not allow for extensive microbiologic, sophisticated immunologic and genetic analysis, thereby preventing the implementation of affordable treatment, including antimicrobial agents or mineral and vitamin supplementation for bone density augmentation.[20,21] In the absence of professional oral hygiene services, patients with GR are advised to brush their teeth with an upward sweeping motion [10] and subsequent salt-bicarbonate rinsing. Patients presenting with molar involvement are prescribed antibiotic treatment, with emphasis on oral hygiene, although in the absence of professional oral hygiene treatment, the effectiveness thereof in curbing disease progression remains unclear.[11] The tooth loss already observed in some patients is alarming, particularly as they enter adulthood disfigured, with currently no prospect of prosthetic treatment within the South African public sector dental services.

In conclusion, this study found a significant association between suboptimal HIV-disease control and GR and LAP. The prevalence of these conditions may even have been underestimated, further strengthening the motivation for the earliest possible identification and treatment of HIV infection and ART treatment failure, as well as the inclusion of oral health services in the management of pediatric HIV infection.

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REFERENCES

[1.] Albandar JM. Aggressive periodontitis: case definition and diagnostic criteria. Periodontol 2000. 2014;65:13-26

[2] Armitage GC, Cullinan MP. Comparison of the clinical features of chronic and aggressive periodontitis. Periodontol 2000. 2010;53:12-27.

[3.] Susin C, Haas AN, Albandar JM. Epidemiology and demographics of aggressive periodontitis. Periodontol 2000. 2014;65:27-45.

[4.] Stoner JE, Mazdyasna S. Gingival recession in the lower incisor region of 15-year-old subjects. J Periodontol. 1980;51:74-76.

[5.] Moscicki AB, Yao TJ, Ryder MI, et al; Shiboski. The burden of oral disease among perinatally HIV-infected and HIV-exposed uninfected youth. PLoS One. 2016;11:e0156459.

[6.] Ryder MI, Yao TJ, Russell JS, et al; Pediatric HIV/AIDS Cohort Study. Prevalence of periodontal diseases in a multicenter cohort of perinatally HIV-infected and HIV-exposed and uninfected youth. J Clin Periodontol. 2017;44:2-12.

[7.] Shiboski CH, Patton LL, Webster-Cyriaque JY, et al; Oral HIV/AIDS Research Alliance, Subcommittee of the AIDS Clinical Trial Group. The Oral HIV/AIDS Research Alliance: updated case definitions of oral disease endpoints. J Oral Pathol Med. 2009;38:481-488.

[8.] World Health Organization. Oral Health Surveys: Basic Methods - 5th ed. 2013. Geneva, Switzerland: WHO; Available at: http://www.who.int/oral_health/publications/978924154869/en/. Accessed December 12, 2016.

[9.] Feldman RS, Douglass CW, Loftus ER, et al. Interexaminer agreement in the measurement of periodontal disease. J Periodontal Res. 1982;17:80-89.

[10.] Levi PAJ, Rudy RJ, Jeong YN, Coleman DK. Methods of Plaque Removal by the Patient. In: Non-surgical Control of Periodontal Disease. 2016.1st ed. Berlin, Heidelberg: Springer-Verlag; 37-70.

[11.] Teughels W, Dhondt R, Dekeyser C, et al. Treatment of aggressive periodontitis. Periodontol 2000. 2014;65:107-133.

[12.] Heidari S, Mofenson LM, Hobbs CV, et al. Unresolved antiretroviral treatment management issues in HIV-infected children. J Acquir Immune Defic Syndr. 2012;59:161-169.

[13.] Geretti AM, Tsakiroglou M. HIV: new drugs, new guidelines. Curr Opin Infect Dis. 2014;27:545-553.

[14.] Dominiak M, Gedrange T. New perspectives in the diagnostic of gingival recession. Adv Clin Exp Med. 2014;23:857-863.

[15.] Khocht A, Albandar JM. Aggressive forms of periodontitis secondary to systemic disorders. Periodontol 2000. 2014;65:134-148.

[16.] van Wyk P. Report: National Children's Oral Health Survey South Africa, 1999 - 2002. 2003.Pretoria. Department of Health.

[17.] Berquist V, Hoy JF, Trevillyan JM. Contribution of common infections to cardiovascular risk in HIV positive individuals. AIDS Rev. 2017;19:72-80.

[18.]Valentine J, Saladyanant T, Ramsey K, et al. Impact of periodontal intervention on local inflammation, periodontitis, and HIV outcomes. Oral Dis. 2016;22(suppl 1):87-97.

[19.]Petersen PE. World Health Organization global policy for improvement of oral health-World Health Assembly 2007. Int Dent J. 2008;58:115-121.

[20.]Jepsen K, Jepsen S. Antibiotics/antimicrobials: systemic and local administration in the therapy of mild to moderately advanced periodontitis. Periodontol 2000. 2016;71:82-112.

[21.]Barlow-Mosha L, Eckard AR, McComsey GA, et al. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. J Int AIDS Soc. 2013;16:18600.