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Oral lesions among HIV-infected children on antiretroviral treatment in West Africa

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Abstract

Objectives—To estimate the prevalence of oral mucosal diseases and dental caries among HIV-infected children receiving antiretroviral treatment (ART) in West Africa, and to identify factors associated with the prevalence of oral mucosal lesions.

Methods—Multi-center cross-sectional survey in 5 pediatric HIV clinics in Côte d'Ivoire, Mali and Sénégal. A standardized examination was performed by trained dentists on a random sample of HIV-infected children aged 5 to 15 years receiving ART. The prevalence of oral and dental lesions and mean number of decayed, missing/extracted and filled teeth (DMFdefT) in temporary and permanent dentition were estimated with their 95% confidence interval (95%CI). We used logistic regression to explore the association between children's characteristics and the prevalence of oral mucosal lesions, expressed as prevalence odds ratio (POR).

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Results—The median age of the 420 children (47% females) enrolled was 10.4 years (interquartile range [IQR]=8.3–12.6). The median duration on ART was 4.6 years (IQR=2.6–6.2); 84 (20.0%) had CD4 count<350 cells/mm^3. 35 children (8.3%; 95%CI: [6.1–11.1]) exhibited 42 oral mucosal lesions (24 were candidiasis); 86.0% (95%CI=82.6–89.3) of children had DMFdefT≥1. The presence of oral mucosal lesions was independently associated with CD4 count<350 cells/mm^3 (POR=2.96, 95% CI=1.06–4.36) and poor oral hygiene (POR=2.69, 95%CI=1.07–6.76).

Conclusions—Oral mucosal lesions still occur in HIV-infected African children despite ART, but rarely. However, dental caries were common and severe in this population, reflecting the need to include oral health in the comprehensive care of HIV.

Keywords

Oral Health; HIV; Child; antiretroviral therapy; Africa; Côte d'Ivoire; Mali; Sénégal

INTRODUCTION

Oral mucosal lesions are among frequent opportunistic infections that occur in people living with HIV (1). The most common HIV-associated lesions are oral candidiasis, and oral hairy leukoplakia (2, 3). In children, the types of oral lesions observed are similar to those found in adults except for the higher frequency of chronic parotid enlargement (4). Furthermore, there is a lower frequency of Kaposi's sarcoma, non-Hodgkin lymphoma and hairy leukoplakia (5, 6). In children, oral lesions are associated with HIV-infection and disease progression due to their opportunistic nature, and are therefore a part of the WHO classification to determine the clinical stage of pediatric HIV disease (7).

More than 90% of HIV-infected children in the world live in sub-Saharan Africa (8). However, most studies describing oral disease in children living with HIV are from industrialized countries or from Brazil (1, 6, 9). The few studies conducted in sub-Saharan pediatric populations are from Southern and Eastern Africa and report prevalence figures of oral lesions from 10% to 77% (4, 10–15). Investigators have reported a lower prevalence of oral lesions in African children receiving ART, corroborating outcomes reported in pediatric patients from other settings and in African adult patients (1). Furthermore, most oral health studies among HIV-infected children focus on oral mucosal lesions without considering the prevalence of dental caries. HIV-infected children are thought to be at high risk for dental caries in industrialized as well as resource-limited countries (11, 13, 15–18)**,** where access to dental care is difficult, oral health manpower is limited and cost of care is relatively high (19). A substantial fraction of the higher frequency of caries in HIV-infected children may be attributed to more frequent intake of carbohydrate- and sucrose-rich foods and of sucrose or fructose-containing medications (11, 16, 17, 19–21).

Few data on oral lesions and dental caries exist in HIV-infected pediatric populations in West Africa where access to ART has increased since 2004 (22). In order to develop and plan appropriate comprehensive care, the objectives of this study were to (1) estimate the prevalence of oral mucosal diseases, parotid enlargement, and dental caries among HIV-

infected children receiving ART in West Africa, and (2) identify factors associated with the presence of oral mucosal lesions.

METHODS

Study design and population

We conducted a multi-center cross-sectional survey between April and October 2011 among HIV-infected children. Our eligibility criteria were: age 5 to 15 years, currently receiving ART, being followed in a pediatric HIV clinic participating in the International epidemiological database to Evaluate AIDS (IeDEA) West Africa collaboration (Appendix 1), and willingness to participate in the study.

A total of five centers participated, representing 1260 children potentially meeting eligibility criteria; three in Abidjan, Côte d'Ivoire (pediatric ward of the Teaching Hospital of Yopougon [n=366], Centre Intégré de Recherches Biocliniques [CIRBA, n=162], Centre de Prise en charge de Recherche et de Formation [CePReF, n=246]); one in Bamako, Mali (pediatric ward of Gabriel Touré Hospital, n=354), and one in Dakar, Sénégal (Albert Royer Children's Hospital, n=132).

Sample size estimations revealed that 400 participants were needed to allow the estimation of a prevalence of oral mucosal lesions of 10% with a precision of 3%. The expected prevalence was determined based on a study conducted in Brazil reporting a 16% prevalence of oral lesions (parotid enlargement excluded) in 6–12-year children on highly active antiretroviral therapy (23). The expected prevalence was reduced to 10% for calculation in a worst case scenario. We enrolled 420 children to allow for the possibility of 5% missing data.

The sample was constituted by using a stratified random method without replacement: the number of participants recruited from each center was proportional to the number of children meeting selection criteria in each center (about 30%).

The study was approved by the ethics committees of each participating country: Comité National d'Ethique et de la Recherche in Côte d'Ivoire, Comité d'Ethique de la Faculté de Médecine, de Pharmacie et d'Odonto-stomatologie in Mali and Comité National d'Ethique pour la Recherche en Santé in Senegal. Before data collection, informed written consent to participate in the study was obtained from children's caregivers as well as an assent from children aged 10 years or older. Children found to have an oral mucosal lesion were provided with care free of charge in the facility according to the local standard. Children with dental caries were given a referral for care to a provider with negotiated rates.

Variables and Measures

Data collection was performed through face-to-face interview and oral examination (performed by trained and calibrated dentists) and medical record retrieval (performed by site pediatricians who also obtained informed consent). A standardized questionnaire created for the purpose of the study was administered to obtain data on dietary intake, oral hygiene and oral care habits. The dentist-examiners, one per participating site, performed a

standardized examination of the oral soft tissue and teeth using a mouth mirror, #6 explorer and gauze, and an overhead dental light. Their findings were recorded on a standardized form by an assistant (dental student).

The main outcomes were presence of (i) oral mucosal lesions associated with HIV infection (2), specifically, oral candidiasis (pseudomembranous or erythematous candidiasis, or angular cheilitis), hairy leukoplakia, oral warts, primary herpertic gingivo-stomatitis, recurrent herpes simplex infection, aphthous ulcers, necrotizing stomatitis, necrotizing ulcerative gingivitis/periodontitis, Kaposi's sarcoma, or non Hodgkin's lymphoma; (ii) parotid enlargement; and (iii) dental caries experience assessed using the decayed, filled and missing/extracted surface index in permanent dentition (DMFS), in temporary dentition (defs), and in mixed dentition (DMFdefS) (24). These indices were recorded according to the WHO criteria and method (25). The decayed, filled and missing teeth (DMFT) index (and deft, DMFdefT) were derived from the surface indices for some of our analyses, and prevalence of caries experience was defined as DMFdefT≥1. Oral hygiene was recorded using the Oral Hygiene Index–Simplified (OHI-S) described by Greene and Vermillion (26).

In addition to the record of these clinical outcomes, the following data were extracted from the children's medical charts by the pediatricians: demographics (date of birth, gender); ART regimen (date of initiation, drug combination at the time of the study); biological and clinical data at treatment initiation within the past six months: CDC or WHO clinical stage, CD4 cell count (also recorded at time of the survey); cotrimoxazole prophylaxis; adherence to ART. Immunosupression was defined as CD4 count <350 cells/mm3 (7). Severe clinical stage was defined as WHO clinical stage=4 or CDC clinical stage=C depending on the site. No reported missing dose during the four past days defined good adherence to ART.

A general in-person training session led by the dental epidemiologists was conducted for pediatricians and dentists from all sites before the start of the study. For the clinical diagnosis of oral lesions, the training consisted in the viewing of a narrated slide presentation, using the Oral HIV / AIDS Research Alliance (OHARA)'s training module, (2). The Oral Medicine specialist who developed the OHARA training module also attended part of the training session through videoconferencing to answer questions about clinical slides presented to the group. Pre- and post-tests based on clinical slides of oral lesions with brief description of symptoms were administered, and dentists had to score at least 80% of correct answers on the post test to be considered calibrated with respect to the oral mucosal lesion assessment.

For the dental examination, procedures were reviewed as part of the general training session, and subsequently, the project manager (a dentist epidemiologist) visited each site and provided individual training on the WHO criteria and methods to collect dentition status and oral hygiene indices (25, 26). Convenience samples of 8–10 children per site were examined both by the project manager and the examiner dedicated to the site to assess the inter-examiner reliability. Then, the children were re-examined by the site examiner one week later to assess the intra-examiner reliability. The intra- and inter-examiner (between examiner and project manager) reliability was assessed for the experience of decay per tooth, with Cohen's Kappa values varying between 0.65 and 0.74, and between 0.58–0.81,

respectively. These values indicated strong intra-examiner reliability and moderate to almost perfect inter-examiner reliability (27).

After the study visit, each child received information about dental caries and their associated etiology, instructions on effective tooth brushing, and appropriate diet practices. The participating children were also given a brochure, a toothbrush and toothpaste.

Statistical analysis

We used standard summary statistics to describe sample characteristics: counts and frequencies for the categorical variables, and median and interquartile range (IQR) or mean and standard deviation (std) for the quantitative variables. Prevalence of oral and dental lesions and the mean DMFdefS and the mean DMFdefT were estimated with 95% confidence interval (CI). Chi^2 and Kruskal-Wallis tests were used to compare characteristics between children included in the study and those who were approached but could not participate for any reason. Chi^2 test was used to explore association between parotid enlargement and immunosupression. Logistic regression was used to study the association between children's characteristics and the prevalence of oral lesions, expressed as prevalence odds ratio (POR). For theses analyses, children with missing data on CD4 count or on clinical stage were combined with children not presenting severe immunological or clinical condition, respectively, as we have shown previously that they have the same risk of death or loss-to-follow-up (28). Variables with p-value ≤.25 in univariable analysis were considered for the multivariable analysis. Goodness of fit of the model was assessed with Hosmer and Lemeshow test. Data were processed and analyzed using the statistical software SAS 9.2.

RESULTS

Characteristics of the participants

A total of 530 children were screened to obtain a final sample of 420 who agreed to participate in the study, corresponding to a 79% participation rate. When comparing enrolled and nonenrolled children (due to caregivers' inability to be contacted by the medical team or refusal to participate), we found no difference with respect to gender, age and length of follow-up on ART at the time of the study. Of the 420 participants, 224 (53.3%) were males and 307 (73.1%) under 12 years old. The median age (IQR) of the study participants was 10.2 [7.9–12.2] years. At ART initiation, 100 children (23.8%) were at WHO stage 4 or CDC stage C (N=402). The median CD4 T lymphocyte count was 409 [190–602] cells/mm^3 (N=409); 24% received protease inhibitor (PI)-based ART regimen. Children had a median duration of ART of 4.5 [2.6–6.2] years, a median CD4 T lymphocyte count of 663 [412–950] cells/mm^3 (N=417); 82 (19.5%) received protease inhibitor (PI)-based ART regimen; 412 (98.1%) were reported to be adherent to ART. More than half of the children (55.0%) were on cotrimoxazole prophylaxis (including all children from Mali and Senegal and 27.3% from Côte d'Ivoire).

Prevalence of oral lesions

At the time of the survey, 35 children presented with at least one oral mucosal lesion, yielding a prevalence of 8.3% (95% CI: 6.1–11.1). A total of 42 lesions were diagnosed among the 35 children, of whom 7 children (20%) had 2 lesions and 4 had 2 types of oral candidiasis. The most frequent lesion was candidiasis, ie pseudo membranous candidiasis, or erythematous candidiasis and angular cheilitis (Table 1). The most frequent location for oral mucosal lesions included the tongue (36%), the lips (21%) and the gingiva (19%). Parotid enlargement was found in 68 (16.4%) children (95% CI=13.0–20.3), of whom 56 (82%) had bilateral enlargement. It was not associated with immunosupression (p=0.444).

Dental caries experience

Permanent teeth were present in 407 children and temporary teeth in 286 children. The prevalence of caries experience (DMFdefT≥1) was 86.0% (95% CI=82.6–89.3) when considering both temporary and permanent teeth. The mean DMFdmfS was 10.6 (95% CI=9.5–11.7) and the mean DMFdefT was 4.9 (95% CI=4.4–5.3) (Table 2). Decayed teeth accounted for 97.3% of the total number of DMFdefT.

Dietary intake, oral hygiene, and oral care habits

At the time of the study, only 54 (12.9%) participants were receiving a liquid form of medication; 65% reported between four and six meals per day. 389 children (92.6%) reported tooth brushing, with 381 (98%) using a toothbrush, and 378 (97.2%) reported using toothpaste. 237 (61%) brushed their teeth only once a day. Of those using a toothbrush, 368 (96.6%) reported to brush their teeth in the morning and before breakfast, and only 97 (25.5%) in the evening after dinner. Only 99 (23.6%) had ever been examined by a dentist.

Factors associated with oral mucosal lesions

Presence of oral lesions was independently associated with immunosupression (POR=2.96, 95% CI=1.06–4.36) and poor oral hygiene as reflected by an increased OHI-S (POR=2.69, 95% CI=1.07–6.76) (Table 3). Goodness of fit was verified (p-value for Hosmer and Lemeshow=0.779). To be more specific, 15.5% of children with immunosupression (n=13/84) and 18.9% with poor oral hygiene (7/37) had oral lesions compared to 6.5% of children with no immunosuppression (n=22/336) and 7.3% of children with OHI-S≤3 (28/383).

DISCUSSION

In this sample of West African HIV-infected children on ART, we found a low prevalence of oral mucosal lesions but a high prevalence of dental caries. Despite a relatively well-controlled HIV infection owed to effective ART, oral lesions were still associated with immunosupression.

The prevalence of mucosal oral lesions in HIV-infected children in resource limited areas varies across settings from more than 60% in most of the studies we reviewed, to about 30% in Brazil (23) or 13% in Mozambique (13). African studies with higher reported prevalence of oral lesions are from Nigeria or Uganda (Table 4). Our study showed a much lower

prevalence of oral lesions, which can be explained by the fact that all children were on ART while, in the other studies, the proportion on ART varied from 50% to 70% and the prevalence included salivary gland diseases and cervical lymphadenopathy. Our findings with respect to parotid enlargement corroborate studies conducted in Mozambique and Uganda with about 23–25% of parotid enlargement (13, 15). However, it was much lower in the Nigerian study with a prevalence of 3.8% (29), or in the Ugandan one (5.5%) (14).

While our sample may not be representative of all West African HIV-infected children on ART, it is likely to be representative of HIV-infected children on ART in Côte d'Ivoire, Mali and Senegal owing to our random sampling from referent structures for pediatric HIV treatment in these countries.

As all children enrolled in our study were on ART, we could not assess the association of ART with reduced prevalence of oral lesions, particularly candidiasis and ginigivitis, contrary to other studies (13, 15, 23, 29). Also, we found no relationship between the prevalence of oral lesions and the nature of ART regimen; it has been hypothesized that it would be lower in children on protease inhibitors because these drugs may inhibit a fungal protease implied in the adherence of the *Candida albicans* to the mucosal cells (30). Indeed, the most common lesion was oral candidiasis, as found in other studies (15, 23, 29, 31, 32).

A higher prevalence of oral lesions was associated with poor oral hygiene corroborating another study from Uganda (15). One explanation may be that opportunistic pathogens such as *Candida albicans* thrive in dental plaque or in the presence of sucrose-containing medication that will adhere to tissues more readily in the absence of good oral hygiene. We also demonstrated an association with immunosupression as in Mexico (33) and South Africa (10).

We report a high proportion of children presenting with severe patterns of dental caries, the majority of whom were untreated. Indeed, in resource-limited countries, access to dental care is difficult because of low oral health manpower and high relative cost in the absence of dental insurance (19). Fewer than one quarter of the children had consulted a dentist at least once since the diagnosis of HIV infection. In the scientific literature, caries prevalence in HIV-infected children ranges from 11 to 96.7% and mean DMFT from 0.2 to 5.1 according to the dentition type, with more severe disease in primary dentition (13, 15, 17, 34–36). A substantial fraction of the increased caries among HIV-infected children may be attributed to more frequent feeding with carbohydrate- and sucrose-rich foods and more frequent sweetener-containing medications (16, 35). Furthermore, HIV-infected children may have increased levels of cariogenic bacteria, and may have salivary hypofunction associated with medication or salivary gland disease. One limitation of many studies of caries prevalence in HIV-infected children, including the present study, is the absence of an HIV-negative control group. Thus we could not assess the effect of HIV status on caries prevalence or severity. However, oral data collected in the general population (37) showed that 62.4% of 12-year old children were affected by dental caries in Côte d'Ivoire, with a DMFT of 1.8 in 1996, a DMFT of 2.2 at 12 years in Mali in 1983. In Senegal, 52% of 12-year old children were affected by dental caries with a DMFT of 1.2 in 1994 while it was 82% in a group aged 6–7 years, with a deft of 3.9 in 2000.

In conclusion, while oral mucosal lesions were observed in a small proportion of our study population, parotid enlargement appears to be common despite ART use. Furthermore, the prevalence of dental caries was high in this group of children infected with HIV in West Africa. These data reflect the need for comprehensive care of HIV, including oral health. HIV care would benefit from the inclusion of a multipliciplinary team of dental professionals to prevent, detect, treat and control oral and dental lesions. Further research is needed to evaluate the effect of theses lesions on the general health-related quality of life, to better understand the role of HIV infection in the development of dental caries, as well as the best approach to oral prevention and care after immune restoration on ART.

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Appendix 1

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Table 1

Distribution of HIV-related oral lesions diagnosed among 5–15 year old HIV-infected children on antiretroviral treatment in Côte d'Ivoire, Mali, Senegal. IeDeA West Africa Collaboration 2011.

Lesion type	n	%sample (N=420)	% lesions (N=42)
Oral candidiasis	20*	4.8	52.6**
Pseudomembranous	*10*	*2.4*	*23.8*
Erythematous	*8*	*1.9*	*19.0*
Angular cheilitis	*6*	*1.4*	*14.3*
Necrotizing ulcerative gingivitis/periodontitis/stomatitis	7	1.7	16.7
Herpes simplex lesion	5	1.2	11.9
Aphtous stomatitis	4	1.0	9.5
Wart	2	0.5	4.8

* Four children had two types of oral candidiasis

** N=38 lesions for this line only to take into account the four children with two types of oral candidiasis

Table 2

Dental status 5–15 year old HIV-infected children on antiretroviral treatment in Côte d'Ivoire, Mali, Senegal. IeDeA West Africa Collaboration 2011

	Total sample N=420	**<12 years N=307**	**≥12 years N=113**
Temporary teeth	**n=286**	**n=267**	**n=19**
Prevalence with deft≥1: n (%)	220 (76.9)	78.3	57.9
Mean deft (std)	4.0 (3.9)	4.2 (4.0)	1.6 (1.9)
Mean defs (std)	10.1 (12.3)	10.5 (12.5)	4.2 (7.1)
Permanent teeth	**n=407**	**n=294**	**n=113**
Prevalence with DMFT≥1: n (%)	268 (65.8)	57.1	88.5
Mean DMFT (std)	2.2 (2.5)	1.5 (1.8)	4.1 (3.0)
Mean DMFS (std)	4.0 (6.3)	2.6 (4.1)	7.8 (8.9)
Permanent and temporary teeth	**n=420**	**n=307**	**n=113**
Prevalence with DMFTdeft≥1: n (%)	361 (86.0)	84.6	91.1
Mean DMFdefT (std)	4.9 (4.0)	5.0 (4.2)	4.3 (3.1)
Mean DMFdefS (std)	10.8 (12.1)	11.6 (12.8)	8.5 (9.6)

Table 3

Correlates of prevalence of oral mucosal lesions in 5–15 year old HIV-infected children on antiretroviral treatment in Côte d'Ivoire, Mali, Senegal. IeDeA West Africa Collaboration 2011.

			Univariable analyses			Mulivariable analyses		
		n (%)	POR	[CI]	p-value	POR	[CI]	p-value
Country (ref. Côte d'Ivoire)	Mali	120 (28.6)	0.94	0.43–2.04	0.721			
	Sénégal	40 (9.5)	0.54	0.12–2.40				
Gender (ref. Female)	Male	224 (53.3)	1.04	0.52–2.09	0.906			
Age (ref. <12 years)	≥12 years	113 (26.9)	1.09	0.50–2.36	0.816			
Clinical stage at ART initiation (ref.: Not severe or missing)	Severe	100 (23.8)	1.12	0.50–2.48	0.782			
CD4 at ART initiation (ref.: ≥350 cells/mm^3 or missing)	<350	181 (43.1) (45.7)	1.27	0.63–2.55	0.495			
CD4 at study visit (ref.: ≥350 cells/mm^3 or missing)	<350	84 (20.0)	2.61	1.25–5.44	0.010	2.16	1.06–4.36	0.032
ARV regimen at the study period (ref. NNRTI or NRTI-based)	IP-based	82 (19.5)	1.48	0.66–3.30	0.337			
Dental caries at study period	One unit increase		0.95	0.86–1.05	0.294			
OHI-S (ref: ≤3)	>3	37 (8.8)	2.96	1.19–7.34	0.019	2.69	1.07–6.76	0.035
Parotid enlargement (ref.: No)	Yes	68 (16.4)	1.91	0.85–4.29	0.115			
Previous dental consultation (ref.: No)	Yes	99 (23.6)	1.13	0.51–2.51	0.762			

CI= 95% Confidence interval; POR= Prevalence Odd Ratio

ART= antiretroviral therapy; PI=protease inhibitors ; NNRTI=non nucleosidic reverse transcriptase inhibitors; NRTI=nucleosidic reverse transcriptase inhibitors;

OHI-S=Oral Hygiene Index - simplified

Table 4

Studies presenting prevalence of oral lesions in HIV-infected children on antiretroviral therapy in Sub-Saharan Africa

Reference	Country	N	Age group	% on ART	Prevalence
Olaniyi, *et al.* (2005)	Nigeria	36	18–168 months	38.9	41.7% had at least one oral lesion (including parotid enlargement accounting for 16.7%)
Hamza *et al*. (2006)	Tanzania	51	2–17 years	43.1	41.2% had at least one oral lesion (including parotid enlargement accounting for 19.6%)
Duggal *et al.* (2010)	South Africa	56	0–4 years	100%	mucosal lesion in 51.8%
Rwenyonyi *et al.* (2011)	Uganda	237	1.5–12 years	50%	one or more oral lesions in 73% (including salivary gland diseases accounting for 5.5% and cervical lymphadenopathy for 60.8%)
Sale-Peres *et al*. (2012)	Mozambique	90	1.7–16 years	81%	mucosal lesion in 13.3% and parotid enlargement in 23.3%
Adebola *et al.* (2012)	Nigeria	105	2–156 months	65%	62%, had at least one orofacial lesion (including parotid enlargement accounting for 3.8%)
Nabbanja *et al*. (2013)	Uganda	368	1.5–17 years	67.4%	77.4% had at least one orofacial lesion associated with HIV (including parotid enlargement accounting for 25% and cervical lymphadenopathy for 28.5%)
Present study	Côte d'Ivoire, Mali, Senegal	420	5–15 years	100%	mucosal lesion in 8.3% and parotid enlargement in 16.4%