Comparative study of the effect of antiretroviral therapy on benign lymphoepithelial cyst of parotid glands and ranulas in HIV-positive patients

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Abstract

Objective. This study's aim was to assess the effect of highly active antiretroviral drugs (HAART) on benign lymphoepithelial cysts (BLEC) of the parotid and ranulas.

Study design. The records of 10 HIV-positive patients who presented with BLEC were reviewed, and 14 HIV-positive patients who presented with ranulas were prospectively enrolled. Patients in

both groups received the same combination of HAART and were clinically evaluated for the first three months. Patients with ranulas were followed up for an additional three months. A clinical reduction in the size of the lesions was considered to be a positive outcome.

Results. All parotid glands with BLEC resolved within three months. No positive results were observed in ranulas during the first three months. However, some of the ranulas displayed a positive result after the initial three months of HAART.

Conclusion. In contrast to BLEC, ranulas in HIV-positive patients seem to present a mixed and delayed response to HAART.

Numerous publications report about HIV-related salivary gland disease (HIV-SGD). HIV-related enlargement of the parotid salivary gland, particularly benign lymphoepithelial cysts (BLEC), remains the most reported form of HIV-SGD.[1-6] Other salivary glands are affected as well[1]. However, little has been reported about ranulas as being part of HIV-related salivary gland disease, in particular. The prevalence and the exact etiopathogenesis of BLEC in HIV-positive patients are still unclear, as are the reasons for the frequent observation of ranulas in HIV-positive individuals in Southern Africa.

Different modalities of treatment were previously used for BLEC management: repeated fine needle aspiration (FNA), surgery, radiotherapy, and sclerotherapy.[1,4,6-9] All of these modalities were forms of local and symptomatic treatment. They neither addressed the overall and systemic context of the HIV infection, nor stopped the progression of HIV disease. The advent of highly active antiretroviral therapy (HAART) dramatically changed the way BLEC was managed. Not only did HAART improve the overall quality of life of HIV-infected patients, but HAART

indirectly reduced parotid gland swelling.[10-12] The effect of HAART on parotid gland swelling represents a great achievement regarding cosmetic and HIV-related stigma for patients. HAART has also reduced the need for surgery as a symptomatic treatment of BLEC.

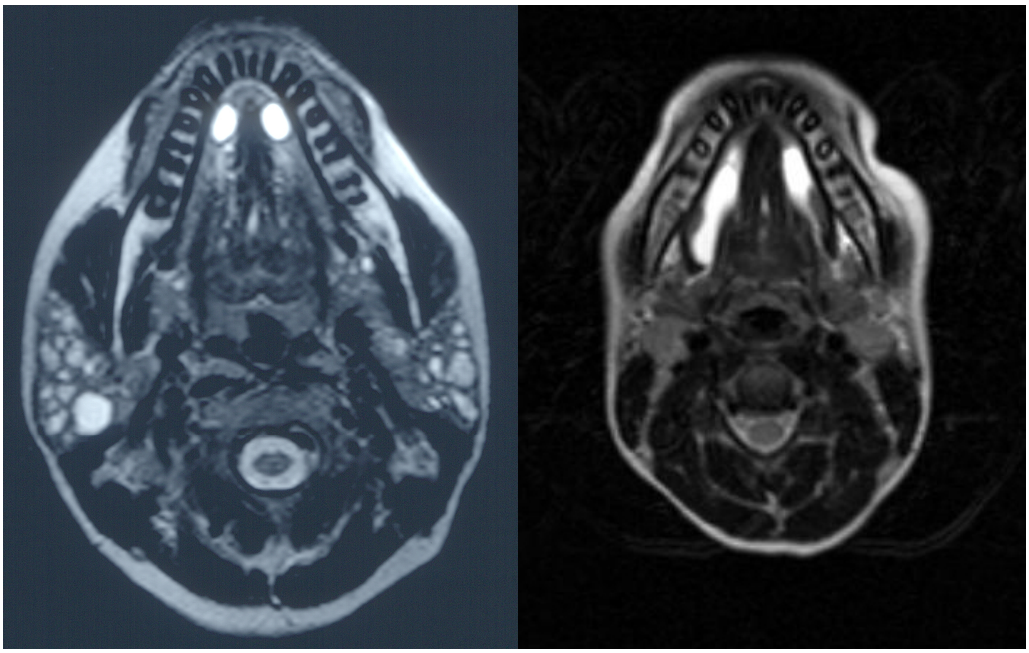

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Fig.1. MRI imaging (axial view) of multiple lymphoid infiltrations with bilateral ranulas and HIV-related parotid cysts (1A), and bilateral plunging ranulas (1B).

Currently, the generally accepted standard mode of treatment for ranulas is surgical removal of the offending ipsilateral salivary gland either with or without the attached cystic lesion.[13-15] However, this radical surgical approach might face limitations in the current clinical presentations of some cases of ranulas in HIV-positive patients. Current cases seem to include more cases of plunging and bilateral ranulas (Fig. 1). More importantly, there are reported cases of BLEC co-existing with ranulas in the same subject and in multiple sites (Fig. 1A). This clinical presentation of both pathologies is of great etiological importance and presents therapeutic implications in the context of HIV-SGD. The quest for a less invasive modality of

treatment for ranulas in HIV-positive patients might, therefore, become a greater challenge. To date, there is no evidence-based proof of treatment for ranulas with HAART.[12] The well-documented benefit of HAART for BLEC in HIV-positive patients has led these authors to hypothesize that the very same drugs may positively affect ranulas in the context of HIV-SGD. A comparative approach has not been performed before.

The aim of this study is, therefore, to assess how ranulas in HIV-positive patients respond to HAART, and compare the results with those of BLEC in parotid salivary glands in the context of HIV-SGD. Furthermore, a secondary objective is to define the time-frame within which to assess the effectiveness of the therapy in both groups.

PATIENTS AND METHODS

This was a clinical study with both retrospective and prospective components. It involved both pediatric and adult HIV-positive patients who presented with either an enlargement of the parotid glands or a ranula. In both components of the study, every patient acted as his/her own control. This reduced the effect of other confounding factors such as age, gender, CD_4^+ cell count, and blood viral load.

Retrospective study

This retrospective study was based on an audit of charts of 10 HIV-positive patients who presented with an enlarged parotid gland.

The criteria for selection were as follows:

- Patients diagnosed as HIV positive. An HIV-1 antigen (p24) / antibody combination assay was used to establish each patient's HIV status.
- Patients not on HAART at the time of the first consultation.

The diagnosis of a lymphoepithelial cyst of the parotid was made on clinical grounds and supported by computed tomography (CT). A fine needle aspiration was also performed.[1,2]

Clinical monitoring was performed over a three month period by means of comparative clinical photographs and/or CT scan imaging. Complete or partial reduction in parotid gland swellings was considered to be a positive result.

Prospective study

The prospective component consisted of 14 HIV-positive patients who qualified for the study. The criteria for patient selection were as follows:

- Patients presenting with a simple or plunging ranula.
- Patients tested for HIV infection if they were unaware of their HIV status.
- Patients not on HAART at the time of consultation.

The diagnosis of ranulas was based on clinical exam. However, CT scan and/or MRI scan imaging were requested in cases of plunging ranulas. Comparative clinical photographs were again used for monitoring purposes at the start of HAART and for a subsequent period of more than three months. Patients who agreed to participate in the study were requested to remain on HAART until three months prior to performing any surgical treatment. Due to the unstable and cystic nature of ranulas, it was not practical to express measurements in centimeters. The effect of HAART on ranulas was assessed clinically by monitoring any reduction in the size of the ranula. As above, a complete or partial size reduction of the ranula was considered to be a positive result.

The assessment included the first three months following the initiation of HAART, as well as a subsequent follow-up period of six months. The three month period provided an element of

comparison between the response of BLEC and that of ranulas. The three months also provided a time-frame to initiate further investigations, especially in the case of BLEC.

Antiretroviral drugs

The national antiretroviral treatment guidelines for South African's public health institutions recommend the following regimen: two nucleoside analog reverse transcriptase inhibitors (NRTIs) [stavudine (d4T) and lamivudine (3TC)] and one non-nucleoside reverse transcriptase inhibitor (NNRTIs) [efavirenz (EFV)]. This was the regimen for naïve adult and pediatric patients above three years of age. The first-line HAART regimen for pediatric patients below three years of age consisted of two NRTIs [stavudine (d4T) and lamivudine (3TC)] and one protease inhibitor [(PIs) lopinavir / ritonavir].[16]

Ethics and informed consent

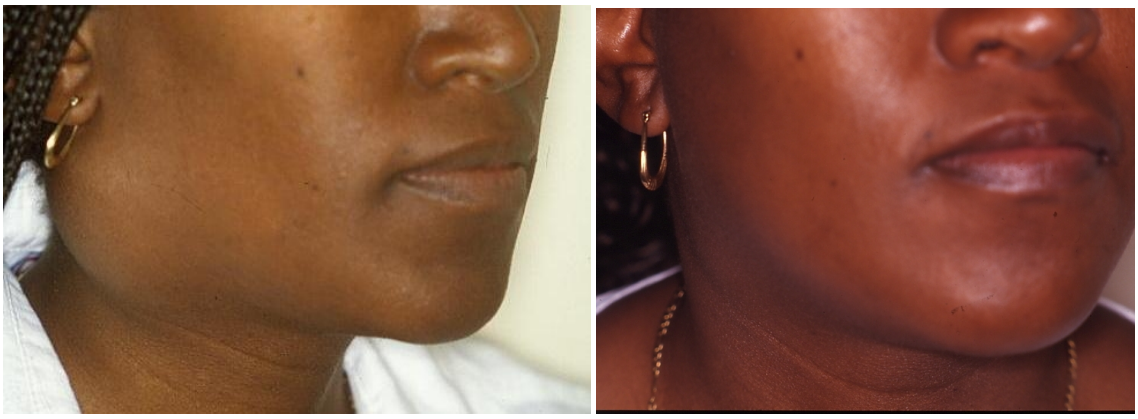
The prospective study was conducted with strict adherence to all regulations and guidelines governing the research and the management of HIV positive patients in South Africa. The protocol and informed consent documents were reviewed and approved by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

RESULTS

In Table 1, the socio-epidemiologic data and clinical results for the BLEC patients are summarized. In this retrospective study group, all ten patients with BLEC displayed a positive result. The parotid gland swelling was completely reduced to a fraction of their initial size in nine of the ten patients. Fig. 2 (A and B) represents the initial and final clinical status of the enlarged parotid gland in one of the adult HIV-positive patients on HAART.

Table 1. Socio-epidemiological data and clinical results for patients with BLEC

	SEX	*AGE*	*CD4x10^6/l*	*PROTID SWELLING*	*FNA*	*CT SCAN*	*ULTRA SOUND*	*HAART REGIMEN*	*(%) PAROTID REDUCTION*
1	*F*	*42*	*183*	*Bilateral*	*Compatible*	*Multicystic*		*D4T+3TC+EFV*	*100%*
2	*F*	*29*	*200*	*Bilateral*	*Not conclusive*	*Multicystic*		*D4T+3TC+EFV*	*100%*
3	*M*	*30*	*210*	*Unilateral*	*Compatible*	*Multicystic*		*D4T+3TC+EFV*	*100%*
4	*F*	*27*	*214*	*Bilateral*	*Compatible*	*Multicystic*	*Multicystic*	*D4T+3TC+EFV*	*100%*
5	*F*	*40*	*252*	*Bilateral*	*Not available*	*Multicystic*	*Multicystic*	*D4T+3TC+EFV*	*100%*
6	*M*	*7*	*260(13%)*	*Bilateral*	*Compatible*	*Multicystic*		*D4T+3TC+EFV*	*90%*
7	*M*	*12*	*374(18%)*	*Bilateral*	*Compatible*	*Multicystic*		*D4T+3TC+EFV*	*100%*
8	*F*	*10*	*387 (18%)*	*Bilateral*	*Compatible*	*Multicystic*		*D4T+3TC+EFV*	*100%*
9	*M*	*6*	*425 (15%)*	*Bilateral*	*Compatible*	*Multicystic*	*Multicystic*	*D4T+3TC+EFV*	*100%*
10	*F*	*2*	*1160 (20%)*	*Bilateral*	*Compatible*	*Multicystic*	*Multicystic*	*D4T+3TC+EFV*	*100%*



A B

Fig. 2. HIV-related parotid cysts in adult HIV-positive patient: (2A) before HAART, (2B) after HAART.

In the prospective study group (Table 2), all of the 14 selected cases of ranulas displayed a negative result after the first three month period. Neither a clinical reduction in size, nor a modification in radiological imaging of the cystic lesions was observed. There were no differences between simple and plunging ranulas (Figs. 3A and 3B) or between adults and pediatric patients. However, in the subsequent follow-up after the first three month term, ranulas displayed mixed results. Among patients that could not immediately undergo an operation, three

Table 2. Socio-epidemiological data and Clinical results for patients with ranulas

	SEX	*AGE*	*CD4x10^6/l*	*VIRAL LOAD RNA copies/l*	*RANULA TYPE*	*MRI OR CT SCAN*	*HAART REGIMEN*	*RESULTS AFTER 3 MONTHS*	*RESULTS BEYOND 3 MONTHS*
1	*M*	*13*	*31*	*73000*	*PLUNGING*		*D4T+3TC+EFV*	*No change*	*NO change*
2	*F*	*39*	*54*	*17000*	*SIMPLE*		*D4T+3TC+EFV*	*No change*	
3	*F*	*31*	*92*	*24000*	*PLUNGING*		*D4T+3TC+EFV*	*No change*	
4	*M*	*39*	*121*	*46000*	*PLUNGING*		*D4T+3TC+EFV*	*No change*	
5	*F*	*29*	*207*	*20000*	*PLUNGING*	*YES*	*D4T+3TC+EFV*	*No change*	
6	*F*	*50*	*251*	*93000*	*SIMPLE*		*D4T+3TC+EFV*	*No change*	
7	*F*	*32*	*287*	*74*	*PLUNGING*	*YES*	*D4T+3TC+EFV*	*No change*	*+ CHANGE*
8	*F*	*27*	*302*	*5500*	*PLUNGING*		*D4T+3TC+EFV*	*No change*	
9	*F*	*23*	*324*	*130000*	*SIMPLE*		*D4T+3TC+EFV*	*No change*	*NO change*
10	*F*	*42*	*339*	*8300*	*PLUNGING*	*YES*	*D4T+3TC+EFV*	*No change*	*NO change*
11	*F*	*32*	*357*		*PLUNGING*	*YES*	*D4T+3TC+EFV*	*No change*	
12	*M*	*6*	*400*	*290*	*SIMPLE*		*D4T+3TC+EFV*	*No change*	
13	*F*	*6*	*521*	*<25*	*SIMPLE*		*D4T+3TC+EFV*	*No change*	*+ CHANGE*
14	*F*	*2*	*972*	*150000*	*SIMPLE*		*D4T+3TC+EFV*	*No change*	*+ CHANGE*

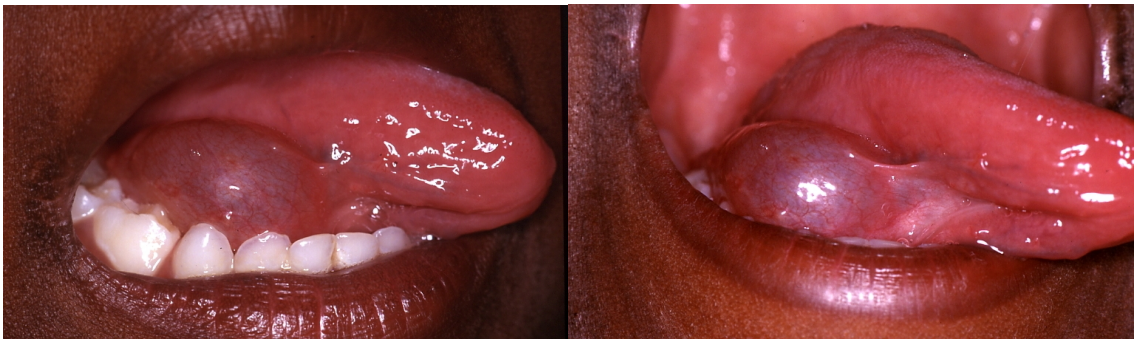


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Fig. 3. Simple ranula in the floor of the mouth: No clinical change in the size before (4A) and after three months of HAART (3B).

cases continued to display a “no-change” result, while three cases with ranulas presented with a slow but noticeable positive result (Figs. 4A and 4B).

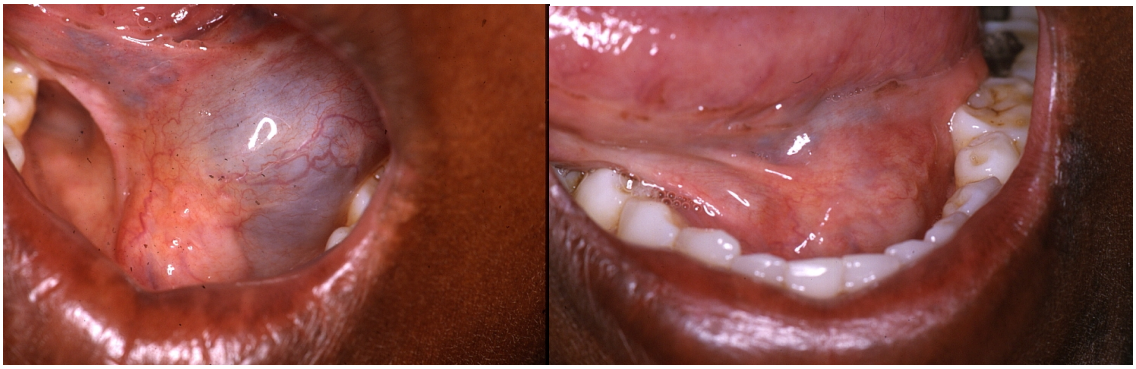

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Fig. 4. A case of simple ranula in the floor of the mouth: (4A) before HAART, and (4B) after treatment with HAART for up to six months, without any FNA performed.

DISCUSSION

Enlargement of the parotid salivary glands, secondary to benign lymphoepithelial cysts, is the most described form of HIV-SGD. Not only is it a lesion frequently associated with HIV infection, but it is also a presumptive sign of a possible underlying HIV infection in both pediatric and adult patients. The prevalence of ranulas in HIV-positive patients is not well defined. In the specific context of the Southern Africa region, where the prevalence of HIV infection is recognized to be particularly high, the association between HIV infection and oral mucoceles or ranulas is more frequently observed.[12,17] In the context of HIV-SGD, oral mucoceles and ranulas could, therefore, also be considered an oral lesion frequently associated with HIV.

It is well documented that HAART has a beneficial effect on BLEC in HIV-positive patients.[11,12] Currently there is no need for aggressive treatment such as surgery or radiotherapy to treat this disease. However, the exact mechanism of HAART's action on BLEC remains to be elucidated.

Two main theories have been postulated as to the exact etiopathogenesis of BLEC. Some writers have advocated for an HIV-related reactive lymphoproliferation of glandular epithelium trapped

in normal intraparotid lymph nodes. Others researchers have advocated for an obstructive theory that assumes that ductal obstruction by lymphoid proliferation might lead to ductal dilatation that mimics a true cyst.[1,3,4,18-21] Based on the latter theory, it is possible to elaborate on two possible mechanisms for HAART's action on BLEC. It is reported, on one hand, that HAART decreases the diffuse infiltrative lymphocytosis syndrome (DILS).[22] It is also suggested that DILS is an antigen-driven response, possibly by a viral antigen, and the primary treatment for it is HAART.[22] On the other hand, HAART is credited with an increase in the $CD4^+$ cell count as well as a decrease in the blood viral load.[23] The two actions combined might correlate with the obstructive physiopathogenesis theory, whereas the diminution of DILS due to HAART might subsequently lead to the re-opening of previously obstructed salivary gland ducts. The results observed in the retrospective component of this study continue to support what has been already reported in the literature about the effect of HAART on BLEC. The effect of HAART on BLEC may be assessed between four weeks and three months. However, no complications in the parotid gland were observed with the use of HAART in this study, contrary to reports by some researchers.[24,25]

Mixed results were observed during the prospective component of the study. The results seem to suggest that ranulas in HIV-positive patients in particular and probably oral mucoceles in general, do not respond to HAART as fast as BLEC of the parotid gland. In some cases, no change in the lesion's size was observed between three and six months, and these patients subsequently required an operation. Other patients presented with a slow but noticeable reduction in the size of the cystic lesion. These results raised the following questions: Why do ranulas and BLEC respond differently to the same medication and in the same context of HIV-SGD? Are these two pathologic entities both HIV-related salivary gland lesions?

From a physiopathogenic point of view, ranulas are believed to derive from a traumatic mechanism. Post-traumatic damage to the minute excretory duct of minor or small major salivary glands (sublingual) may lead to the extravasation of mucus. In addition to the rupture of the glandular duct, obstructive factors are also evoked: sialolith, stenosis, periductal fibrosis, and periductal post-traumatic scarring.[26] The obstruction is, in fact, irreversible, which explains why surgical intervention remains the mainstream treatment of ranulas. The question remains: aside from the traditional hypothesis of traumatic damage to the excretory apparatus, what may be the cause of duct obstruction and/or saliva stasis that leads to the formation of ranulas in HIV-positive patients? Ductal obstruction by lymphoid proliferation due to DILS might, once again, be the most probable cause. It must be emphasized that lymphoepithelial lesions or cysts are not phenomenon exclusive to HIV-infected patients. They have been described in other autoimmune sialadenitis in immunologically competent patients (i.e., Sjögren's syndrome). [18,27,28] The main histological difference between the lymphocytic proliferation in non-HIV patients and that of HIV-associated lymphoepithelial lesions is the predominance of CD_8+ cells in the latter group.[18,28] In HIV-positive patients, the lymphoid infiltration may not only involve all the salivary glands, but may also involve all other lymphoid tissues surrounding the oral cavity and the oropharynx. The MRI imaging shown in Fig. 1A is testimony of a widespread lymphoid proliferation in all salivary glands as well as the lymphofollicular hyperplasia of the nasopharyngeal adenoid tissue in an HIV-infected patient. Cystic formation can already be seen in the parotid and sublingual glands. Clinically, this patient presented with bilateral enlargement of the parotid and submandibular salivary glands with bilateral ranulas in the floor of mouth. The co-existence of BLEC with ranulas in one HIV-positive subject, as shown in Fig. 1A, is not a rare phenomenon, and it may be related to the possibility of a common and systemic etiological

factor (HIV). Ranula in HIV-positive patients may be, most probably, an HIV-related salivary gland disease. These authors believe that the lack of or the slow response to HAART observed by ranulas may be explained by the glandular anatomical differences between major and minor salivary glands (minute ducts).

The results observed in this study need to be considered with its inherent limitations and weaknesses. The small size of both samples and the use of non metric criteria for the evaluation of size reduction, are some of those limiting factors and weakness.

The current clinical presentation of bilateral ranulas, as well as larger and plunging ranula, highlights the need for a new therapeutic approach to these diseases. The traditional surgical approach which consists of radical removal of the involved salivary gland may not necessarily be the ideal solution to all cases of ranula in HIV-positive patients. The removal of one or more salivary gland may, most probably exacerbate xerostomia that is already common in these patients. The earlier suggestion of a systemic etiological factor for ranula in HIV-positive patients, implies also that the lesion may affect in any other salivary gland, despite previous aggressive surgical procedure.

CONCLUSION

The retrospective component of this clinical study supports what has already been reported in the literature about the beneficial effect of HAART on HIV-related parotid cysts. The need for parotid gland surgery has been reduced, especially for patients who qualify for HAART.

The results observed in the prospective component of this study suggest, with great caution, that HAART does not equally influence the course of ranulas in HIV-infected patients. One should be patient and first implement HAART before contemplating a more aggressive approach.

Finally, this study has highlighted few clinical and radiological features that support further, the inclusion of ranula in the HIV-SGD group.

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