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ORIGINAL ARTICLE

An index for staging facial lipoatrophy and evaluation of the efficacy of the treatment with polymethylmethacrylate in HIV/AIDS patients: a pilot study

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Abstract

Background Treatment of facial lipoatrophy of HIV/AIDS patients is mandatory by law in Brazil due to its negative impact on their quality of life. The index for facial lipoatrophy (ILA) is used as one of the inclusion criteria for patient treatment.

Objectives To define a correct diagnosis and staging of facial lipoatrophy, by employing the ILA.

Patients and methods This is an observational study of a series of case reports from patients submitted to facial lipoatrophy evaluation through ILA and treated with polymethylmethacrylate (PMMA) fillers. Facial lipoatrophy was classified in grades from I to IV, corresponding to mild, moderate, severe and very severe stage, according to ILA. Response to the treatment was defined as excellent (≥91%), good (71–90%), moderate (51–70%) and insufficient (≤50%).

Results A total of 20 patients were included in this study: 18 men and two women. Median age was 49 years (35–61) and average ILA was 9.9 (7.2–16.8). Ten patients presented facial lipoatrophy grade II (moderate), 5 grade III (severe) and 5 grade IV (very severe). The average volume of PMMA used was 13 mL (5.5–22 mL). All patients showed good or excellent response, with a median of 86% (74–100%). The most typical adverse effect was local oedema but there were no late adverse effects.

Conclusion The ILA is an excellent method for evaluation of facial lipoatrophy and also for the assessment of the response to therapy. Facial filling with PMMA showed efficacy and safety in the treatment of facial lipoatrophy in HIV/AIDS patients.

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Conflict of Interest

None declared

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Introduction

Anti-retroviral (ARV) medications represent a significant impact in morbidity and mortality of HIV/AIDS patients, however, the need of their continuous use led to the occurrence of late collateral effects, such as facial lipoatrophy. This anaesthetic condition has a negative impact on the quality of life of these patients, affecting their personal and professional life, and often interfering in their adhesion to ARV treatment.[1]

The first studies on facial lipoatrophy treatment were presented in a workshop of adverse effects and lipodystrophy in HIV, in Canada in the year 2000, but included a limited number of patients and short follow-up periods.[2,3]

Since then, facial reconstruction therapy for those patients has been studied and, presently, several products and techniques are used as cutaneous fillers for facial lipoatrophy among which some are temporary, as polylactic acid,[4,5] and some permanent fillers, such as polyalkylamide[6] and polymethylmethacrylate (PMMA),[7] besides autologous fat transplants.[8] There are, however, no comparative studies showing long term aesthetic efficacy and/or collateral effects associated with these different types of fillers in HIV-infected patients.[8]

In Brazil, based on a series of case reports by experienced professionals in Dermatology, the use of colloidal solution with PMMA for correction of facial lipoatrophy has been proposed.[9] Based on these results, the National STD/Aids Program established a study group that developed a protocol for research and validation of the use of PMMA in facial lipoatrophy treatment. The index for facial lipoatrophy (ILA)[10] was created by this group and applied in this investigation. Despite being still somewhat subjective, ILA has the objective to quantify both the atrophy grades as the improvement after treatment.[11]

According to this methodology, facial areas are evaluated and the requirement for the use of fillers is assessed, with ILA as one of the inclusion criteria for the study.

Considering that the use of PMMA for treatment of facial lipoatrophy is already determined by law in Brazil,[12] evaluation methods for diagnosing and staging of facial lipoatrophy based on ILA are justifiable for giving less subjectivity to the evaluation.

To permit its use in the future as an indicator for assessing different therapeutical techniques, this study should have reproducible results for the staging of facial lipoatrophy and fillers' efficacy evaluation.

Patients and methods

This is an observational type of study, a compilation of a series of case reports of HIV-infected patients with facial lipoatrophy, who were submitted to facial lipoatrophy evaluation, by the facial lipoatrophy index – ILA (Table 1), and who were treated by a standardized use of PMMA on facial areas affected by lipoatrophy.

The study used data of the first 20 patients with intention to be treated, in the reference centre of Rio de Janeiro (Clementino Fraga Filho Hospital of the School of Medicine of the Federal University of Rio de Janeiro – UFRJ). Patients were included in the study according to the criteria of inclusion and exclusion established by the Ministry of Health (Table 2). They were all submitted to the standardized application of fillers to the affected facial regions by the same researcher, and were all evaluated regarding the grade of lipoatrophy by a second researcher, participant of the research protocol. This second researcher also evaluated the patients on all subsequent visits.

Facial lipoatrophy index

For the purpose of this study, the loss of facial fat was quantified based on the ILA Index (**I**ndex of facial **L**ipo**A**trophy). ILA consists on the assessment of the grade of severity of the affected area multiplied by the extension of that area, in all the three areas to be treated, malar, temporal and pre-auricular.

Areas of the face for ILA (Fig. 1)

Malar ILA (M) area corresponds to the zygomatic and buccal regions, having the infra-orbital border and the lower border of the mandible as limits. Temporal ILA (T) area corresponds to the frontal portion of the temporal fossa, limited by the temporal line of the frontal bone and zygomatic arch. Pre-Auricular (A) area for ILA corresponds to the portion located between the zygomatic arch, the angle and lower border of the mandible.

Classification of facial lipoatrophy

The criterion for diagnosis of facial lipoatrophy, utilizing ILA, was defined as a reduction of the fatty pads of three facial areas: malar, temporal and pre-auricular.

Facial lipoatrophy was classified in grades from I to IV, corresponding to a mild, moderate, severe and very severe stage, according to ILA. (Table 3).

The criteria for diagnosis for each stage are the following:

- *Mild facial lipoatrophy (grade I)*: corresponding to an ILA Index from zero to 5.9. There is a slight depression in the areas to be treated, without evidence of anatomic sites, nor loss of facial contour; and finger pressure of the skin is normal; (Fig. 2a).
- *Moderate facial lipoatrophy (grade II)*: ILA from 6.0 to 10. A little more visible depression of the areas to be treated is perceived; anatomic sites are beginning to be visualized, especially the zygomatic arch, and there is an increase of the nasolabial fold, without loss of facial contour or projection of the maxilla. Under finger pressure the skin depresses normally, but takes a little more than expected to return to its state of rest (Fig. 2b).
- *Severe facial lipoatrophy (grade III)*: ILA 10.1–15. Malar area anatomic accidents can be better seen, as the

Table 1 Facial lipoatrophy index (ILA) degree of depth

	0	1	2	3	4	
	None	Mild	Moderate	Severe	Very severe	
AFFECTED AREA						
DEGREE	0	1	2	3	4	5
AREA 100	0	<20	21 < 50	51 < 70	71 < 90	91<
REGION	MALAR (M)		TEMPORAL (T)		PRE-AURICULAR (A)	
DEPTH AREA						
DEPTH × AREA	[() × 0.7 =]		[() × 0.2 =]		[() × 0.1 =]	
M |_____|						
T |_____|						
A |_____|						
M + T + A + = TOTAL: |_____| Examiner's initials |___|___|___|						

Table 2 Inclusion and exclusion criteria

Inclusion criteria
HIV confirmed infection;
Age between 18 and 65 years;
ILA facial lipoatrophy score higher or equal to 6;
Referral by the involved centres' researchers;
Ability to understand and follow the team's instructions and ability to understand and sign the Free and Aware Consent Term (TCLE).
Exclusion criteria
Subject to opportunistic infections, neoplasia treatment or a rheumatic disease in development in the last 30 days;
T CD4+ cell count less than 200 cells/ml, obtained within 30 days of the exam;
Chemotherapy, immunomodulator, anabolic steroid and anticoagulant in the last 30 days.
Signs of bacterial infection in the area targeted for the filling;
Platelet count < 75,000/mL.

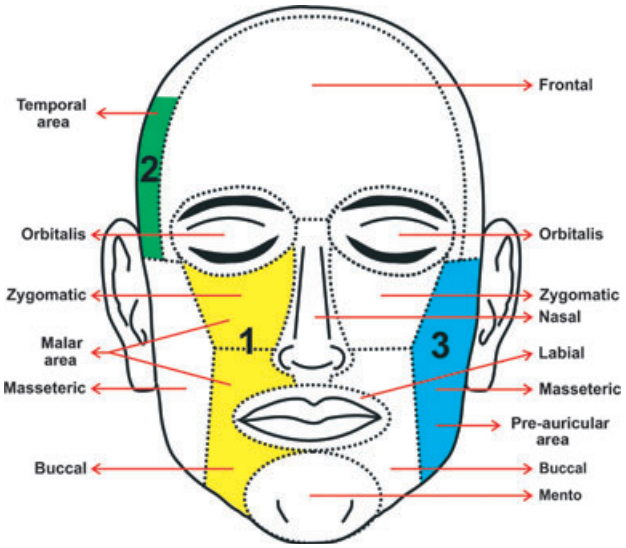

Figure 1 Areas of the face for index for facial lipoatrophy (ILA).

zygomatic arch; there is visualization of the canine fossa, partial visualization of the *musculus zygomaticus major* and a mild to moderate depression of the lower mandible border, in the temporal and pre-auricular regions. The zygomatic arch can be better seen; there is also an improved visualization of the zygomatic and frontal processes in the temporal region. Loss of facial contour and projection of maxilla can occur. With finger pressure, the skin depresses a little and takes a long time to return to its state of rest (Fig. 2c).

- *Very severe lipoatrophy (grade IV)*: ILA 15.1–20. This stage shows almost complete visualization of anatomic sites, revealing the facial bone and muscular structure. There is a projection of the zygomatic bone, visualization of the canine fossa with definition of the *musculus zygomaticus major* (dividing the malar area into two deep cavities), projection of the maxilla and depression in the lower border of the mandible area and angle with loss of facial contour. Moreover, there is visualization and definition of the upper and lower faces of the zygomatic arch in the temporal and pre-auricular regions. There is also a greater definition and visualization of the frontal and zygomatic processes, besides visualization of the frontal bone temporal lines. At finger pressure the skin actually does not depress, or, if it does, takes a very long time to return to its state of rest (Fig. 2d(i) and 2d(ii)).

Table 3 Facial lipoatrophy correlation grade × Classification × ILA

Grade	Classification	ILA
0	None	0
I	Mild	0.1–5.9
II	Moderate	6.0–10
III	Severe	10.1–15
IV	Very severe	15.1–20

Evaluation of patients

Patients were evaluated in five occasions, at the initial screening and visits 1, 2, 3 and 4.

At screening, the patients underwent a clinical and laboratorial evaluation, and those with a ILA >6 and who also filled out the other criteria for inclusion, without any for exclusion, were scheduled for Visit 1, where the first treatment for facial filling with PMMA was carried out. Patients would return 7 days after the procedure for Visit 2, when possible early adverse effects related to the procedure were assessed. In Visit 3, a month after Visit 1, patients were evaluated again regarding the grade of facial lipoatrophy (ILA) and, depending on the researcher's evaluation, were submitted or not to a new facial filling procedure with PMMA. During Visit 4, 6 months after visit 1, patients were submitted again to clinical and laboratorial evaluation and to the ILA once more, concluding their participation in the protocol (Fig. 3).

Treatment response evaluation

Four grades were considered for evaluation of the response to the treatment: insufficient (I); moderate (M); good (G); and excellent (E). To reach an (E) response, an ILA reduction of 90% was considered. For a (G) grade of improvement it was established that a patient with the highest facial lipoatrophy (ILA = 20) would have to reach the level of mild lipoatrophy as response (ILA = 5.9), thus representing an improvement above 70% of ILA reduction. The same calculation was used considering the patient who, after treatment, would reach the highest index of (M) lipoatrophy (ILA 9.9), whose calculation revealed being a reduction above 50%. A reduction equal to or less than 50% was considered as (I) (Table 4).

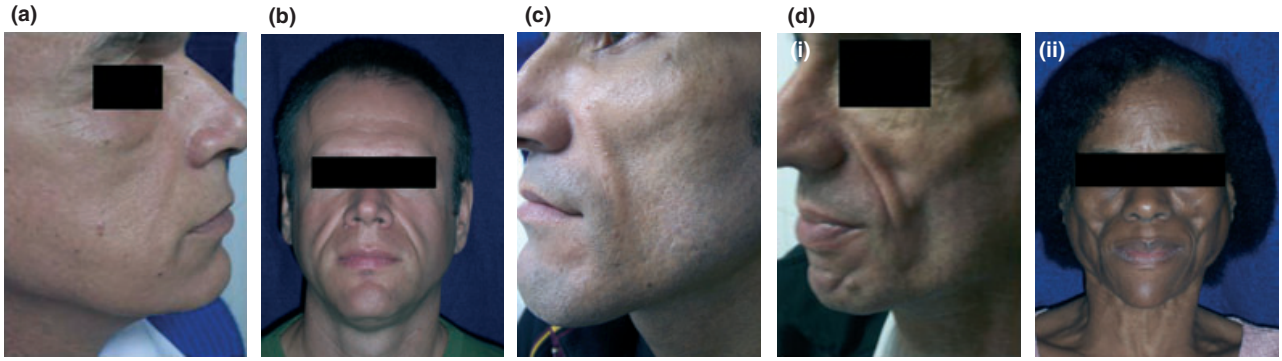

Figure 2 (a) Mild facial lipoatrophy (grade I). (b) Moderate facial lipoatrophy (grade II). (c) Severe facial lipoatrophy (grade III). d(i)Very severe lipoatrophy (grade IV). d(ii)Very severe lipoatrophy (grade IV).

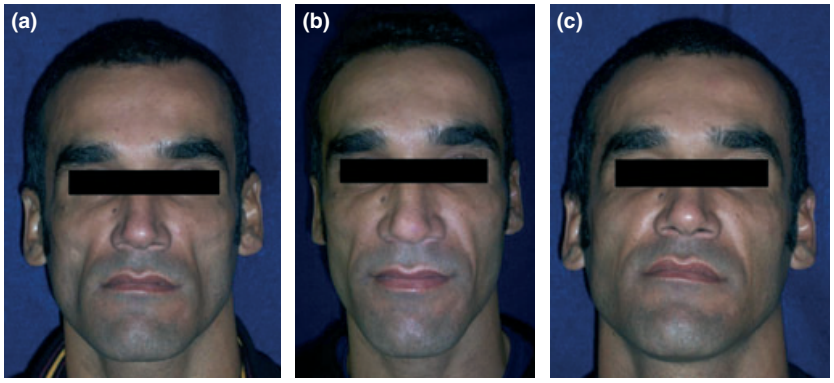

Figure 3 (a) Initial picture of a patient (V1). (b) Third visit picture of a patient (V3). (c) After picture of a patient (V4).

Table 4 Treatment response evaluation

Evaluation of the response to treatment	
Degree of improvement	(%)
Insufficient (I)	0–50
Moderate (M)	51–70
Good (G)	71–90
Excellent (E)	91–100

Results

Twenty patients were included in this study, 18 men and two women. Patients' median age was 49 years, ranging from 35 to 61 years.

Average ILA was 9.9, varying from 7.2 to 16.8, with 10 patients presenting moderate lipoatrophy, 5 presented severe lipoatrophy and 5 very severe lipoatrophy.

Of the 20 patients, only 17 finished the study: eight with moderate lipoatrophy, four severe and five with very severe lipoatrophy (Table 5).

The total volume of colloidal PMMA solution used per patient ranged from 5.5 mL to 22 mL, with average volume of 13 mL per patient.

All patients had either an excellent or good response to the treatment (Fig. 4), varying from 74 to 100%, with a median of 86%. Of these, 11 showed good response (74–89%; $m = 83\%$), and 6 had an excellent response to the treatment (91–100%; $m = 93\%$). Among the patients with good response, four presented moderate, four severe, and three very severe facial lipoatrophy. Of those with excellent response, four presented moderate facial lipoatrophy and two very severe.

Adverse effects and difficulties during the procedure

During or after the procedure the adverse effects were those expected and usual to the filler technique.

The most frequent was oedema, present in 13 of the 20 patients. Onset was during or soon after the procedure, with regression in all patients occurring within 3 days at most.

Five patients presented erythema that regressed in 24 h in all patients. Four patients mentioned local pain due to the procedure, which disappeared spontaneously without need of specific medication after the procedure. One patient complained about pain and mild discomfort in the treated area for 6 days, but this was also resolved without medication. One patient presented ecchymosis

Table 5 Patients submitted to polymethylmethacrylate (PMMA) facial filler

	I	G	A	ILA T	V1 vol. mL	ILA v3%	Impr	V3 vol. mL	ILA v4%	Impr	VOLt	Obs
600	JCM	M	37	8,9	8,4	5,5	38	1,3	2,3	74	9,7	M
601	DMS	M	43	13,7	8,7	3,6	74	2,3	1,8	87	11	S
602	JBS	M	59	16,8	18,9	3,8	80	3,1	1,1	94	22	VS
605	JCC	M	54	11	8,5	3,7	66	1,9	1,2	89	10,4	S
606	PEM	M	47	10,6	8,6	3,8	64	1,2	2,4	77	9,8	S
607	RAS	M	42	13,7	11	4,1	70	2,5	1,7	88	13,5	S
608	LRM	F	40	9,6	7,7	5,1	47	5,2	1,6	83	12,9	M
609	M-L	M	55	16,1	9,9	4,8	70	6,9	1,5	91	16,8	VS
610	JAC	M	50	7,2	7,8	4,4	39	4,4	0,9	93	12,2	M
613	IAS	F	57	15,2	6,8	4,2	72	3,8	2,2	86	10,6	VS
614	CPL	M	49	8,8	7,8	3,3	63	2	0,7	77	8,5	M
615	ACS	M	58	8,6	5,5	3,2	63	1,1	–	–	6,6	M
616	JMO	M	53	12,2	13,3	7,2	41	3,3	–	–	16,6	S
617	WDB	M	44	9,9	11,2	2,2	78	2,9	0,9	91	14,1	M
618	LGL	M	49	15,3	17,1	6,1	60	4,2	2,7	82	21,3	VS
620	ECM	M	61	9,9	14,1	2,4	76	3	1,1	89	17,1	M
621	HMB	M	35	7,2	5,5	0,7	90	0	0	100	5,5	M
622	JCS	M	47	15,3	10,5	4,8	69	2	2,7	82	12,5	VS
623	ADS	M	52	8,7	12,6	1,2	86	0,7	0,8	91	13,3	M
632	FCT	M	37	8,7	10,2	–	–	–	–	–	–	M

I, initials; G- gender; A, age; ILA T, lipoatrophy index used in the sample; V1 vol, quantity of PMMA used at visit 1; ILAv3, lipoatrophy index by visit 3; V3 vol, quantity of PMMA used at visit 3; ILAv4, lipoatrophy index by visit 4; VOLt, total quantity of PMMA used to treat the patient; OBS: M, Moderate lipoatrophy; S, Severe lipoatrophy; VS, Very severe lipoatrophy.

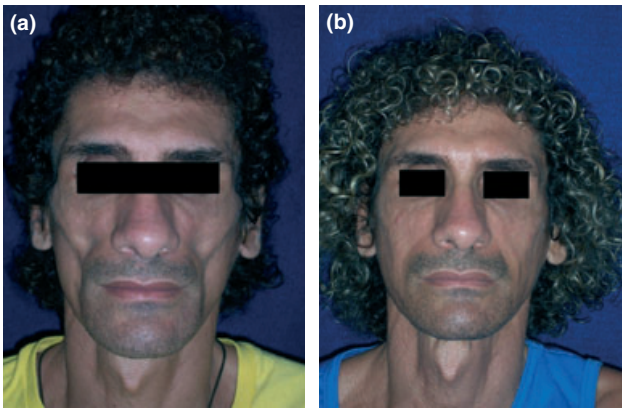

Figure 4 (a) Initial picture of a patient (V1). (b) After picture of a patient (V4).

that regressed in less than a week, and one patient mentioned local pruritus the day following the application.

At visit 2 all immediate adverse effects had already been completely resolved, and during visit 4 no late adverse effects were reported or observed.

Discussion

Current facial lipoatrophy staging proposals attempt to provide grades with descriptions of facial anatomic changes, as if the atrophy had the same pattern and was symmetrical.[13,14] However, it has been observed that lipoatrophy is not symmetrical or proportional, thus, when a numeric value is established for the facial lipoatrophy and detailed in the most affected areas on each side of the face, it becomes possible to have a better idea of the patient's lipoatrophy and to have a better visibility of their fascia.

Detailed perspective provided by ILA is very important for the patient's future follow-up, since the photographic documentation, being static and bi-dimensional, cannot always depict the true grade of lipoatrophy, or show the real improvements in some patients. Other factors influence the diagnosis and the evaluation of treatment response, as the intense elastosis in older patients, leading to a more difficult treatment and outcome, and the thickness of some patients' skin, which helps to dissimulate the degree of lipoatrophy. In this case, finger pressure associated with anatomic criteria for the evaluation of each ILA area to be treated proposed in this study makes the ILA an excellent tool for the evaluation of such patients, enhancing the diagnosis' accuracy, sometimes more realistic than the patient's photographic follow-up.

By correlating the ILA with the staging at different grades of severity, it is possible to have a better notion of the facial lipoatrophy involvement grade. This can be an excellent tool for future epidemiological studies of facial lipoatrophy incidence, not only in already affected individuals but also in the total population treated

for HIV infection. It can also corroborate future studies with different classes of ARV medications, enabling to demonstrate whether any ARV class can or cannot cause greater facial lipoatrophy, and even compare which ARV of a same class causes more lipoatrophy.

As the ILA provides a numeric value for the lipoatrophy, it can not only evaluate the facial lipoatrophy grade and help in the evaluation of the treatment's efficacy, but also work as a tool that helps to identify the possible failures or technical difficulties in the treatment of the different areas. As example of this, a group of patients of a same centre not improving their indexes in the temporal area, may demonstrate the practitioners' difficulties to treat such anatomical area in that specific centre. The National STD/Aids Program should thus be advised regarding the need of new professional training for the practitioners of that centre, improving the treatment.

The ILA can provide data regarding lipodystrophy progression in HIV/Aids patients using HAART. In these patients using ILA for the follow-up may permit the observation of previously untreated areas not affected by atrophy, demonstrate an increase in lipoatrophy and, in some patients, the speed of the lipoatrophy progression. In such cases, therapy may need a new filler injection and/or reassessment of the ARV therapy.

The ILA, in future, may also be applied in comparative studies with other materials for facial lipoatrophy treatment, supporting the identification of parameters for the evaluation of the real cost/benefit of the different treatments, as well as their long-term efficacy.

This study will help the future validation of ILA, which already determines the main anatomical sites to be observed in each area and their different levels of severity, increasing the homogenization of the clinical examination and offering a better evaluation of the patient's facial atrophy.

This index is being used during National STD/Aids Program PMMA facial filler courses, as it is one of the inclusion criteria for facial lipoatrophy treatment. Such changes, suggested in this study, should now be applied in large scale to provide an idea of the real frequency and severity of facial lipoatrophy in HIV/Aids patients, which currently is a high stress situation for such patients. Nowadays, it is the manifestation that mainly affects their self-esteem and quality of life.

Being a pilot study based on small group of patients, it was not possible to apply statistic tests for a stratified and more detailed analysis that would allow correlating the grade of atrophy with the grade of improvement, or quantity of the used materials by the different groups. It was also not possible to compare ILA numbers obtained by different researchers in the current study, to evaluate the percentage of agreement between them, in a way that could validate ILA's applicability by different health professionals. However, it does not invalidate its applicability as a tool for diagnosis and evaluation for lipoatrophy and facial filling. In our study, the index was always calculated by the same researcher, different from the one who applied the PMMA. This minimizes evaluation discrepancies and thus improves the procedure's efficiency. Besides, the standardization of the anatomical criteria for the ILA calculation resulting from this work might facilitate future validation studies.

Facial filling with PMMA turned out to be an excellent treatment method for facial atrophy, with an approximate 85% efficacy. No unexpected adverse effects occurred, but the final study data should allow a better assessment of such effects, although until now it has repeated findings from previous cases reported.[7,9] Long-term studies for the evaluation of late side effects and their real frequency would be very interesting.

This is one of the first studies correlating the average quantity of PMMA used by patients. Despite the small number of patients, this data is being used and has been helping in the implementation of public health policies in States and Municipalities that need to set up facial filler centres for HIV/Aids patients.

Conclusion

The ILA is a simple and highly useful tool for assessment of the patient's facial lipoatrophy grade, helping diagnosis and evaluation of the therapy response. Although still subjective, as dependent on the applicant's perception, when correlated to the main anatomic sites of each area to be treated, it is possible to enhance its sensitivity, by enhancing the degree of perception of the anatomical changes and thus making it more objective and uniform.

Polymethylmethacrylate has demonstrated to be an efficient and safe facial filler and its most common adverse effect was oedema. There was no unexpected adverse reaction. It was not possible to correlate the quantity of used materials according to the grade of atrophy due to the small number of patients, but the average volume of PMMA applied per patient was 13ml and the average response was 86%, demonstrating a great therapeutic result.

This is one of the first studies correlating the average quantity of PMMA used by patients. Despite the small group evaluated, this data will certainly help the implementation of public health policies in the States and Municipalities that need to organize the application of facial filler in centres for HIV/Aids patient.

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