

Effectiveness of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy: a 5-year experience

Eficácia do ácido poli-L-láctico no tratamento da lipoatrofia facial associada ao HIV: uma experiência de cinco anos

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ABSTRACT

Introduction: HIV-associated facial lipoatrophy can impair social relationships, treatment adherence, and mental health, frequently leading to depression. Correction of facial lipoatrophy is associated with significant improvement in quality of life.

Objectives: To evaluate the efficacy of poly-L-lactic acid (PLLA) in correcting HIV-related facial lipoatrophy. **Methods:** Sixty-one patients with HIV-associated facial lipoatrophy received PLLA injections once a month until clinical improvement. The primary endpoint was the need for retreatment. Two independent dermatologists and the researcher classified lipoatrophy according to photographs. Malar skinfold thickness was measured with an adipometer.

Results: All patients showed improvement in facial lipoatrophy after receiving a mean of 7.9 vials of PLLA. Skinfold thickness improved by 105%. Maximum follow-up was 58 months, and the mean duration of the effect was 33.4 months. Patients who discontinued HAART or had higher CD4+ cell counts at baseline presented better responses. Lower responses were observed in patients with very severe lipoatrophy and thinner skin.

Conclusion: PLLA treatment is an effective and durable alternative for patients with moderate HIV-associated facial lipoatrophy, but of limited effectiveness for patients with thin skin and very severe lipoatrophy.

Keywords: HIV-Associated Lipodystrophy Syndrome; Poly(lactic Acid-Polyglycolic Acid Copolymer); Antiretroviral Therapy, Highly Active; Skinfold Thickness

RESUMO

Introdução: A lipoatrofia facial associada ao HIV prejudica as relações sociais, a adesão ao tratamento e a saúde mental, frequentemente levando à depressão. A correção da lipoatrofia facial está associada a uma melhora significativa na qualidade de vida.

Objetivos: Avaliar a eficácia do ácido poli-L-láctico (PLLA) na correção da lipoatrofia facial associada ao HIV.

Métodos: Sessenta e um pacientes com lipoatrofia facial associada ao HIV receberam injeções mensais de PLLA até obterem melhora clínica. O desfecho primário foi a necessidade de retratamento. Dois dermatologistas independentes e o pesquisador classificaram a lipoatrofia com base em fotografias. A espessura da prega cutânea malar foi medida com adipômetro.

Resultados: Todos os pacientes apresentaram melhora da lipoatrofia facial após recebem, em média, 7,9 frascos de PLLA. A espessura da prega cutânea melhorou 105%. O seguimento máximo foi de 58 meses e a duração média do efeito foi de 33,4 meses. Melhores respostas ocorreram em pacientes que suspenderam a HAART ou que apresentavam contagem inicial de CD4+ mais elevada. Respostas inferiores foram observadas em casos de lipoatrofia muito grave e pele fina.

Conclusão: O PLLA constitui uma alternativa eficaz e duradoura para a lipoatrofia facial moderada associada ao HIV, mas apresenta resultados limitados em pacientes com pele muito fina e lipoatrofia grave.

Palavras-chave: Copolímero de Ácido Poliláctico e Ácido Poliglicólico; Síndrome de Lipodistrofia Associada ao HIV; Espessura de Dobras Cutâneas; Terapia Antirretroviral de Alta Atividade

Original Article

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INTRODUCTION

Highly active antiretroviral therapy (HAART), a combination regimen comprising 2 or more classes of antiretroviral medications with different targets in the HIV replication cycle, was introduced in the mid-1990s for the treatment of HIV infection.¹ Lipodystrophy was first described in people living with HIV (PLHIV) in 1998.² Initially, it was believed that protease inhibitors were the main cause, but nucleoside analogues^{3,4} and HIV itself are also responsible.⁵

Lipodystrophy is an association of fat redistribution and metabolic disturbances, such as insulin resistance and hypertriglyceridemia. Fat redistribution is characterized by lipoatrophy of the legs, arms and face, and lipohypertrophy of the abdomen, breasts and neck, consequently developing a characteristic buffalo hump. Lipoatrophy is by far the most bothersome of these alterations, interfering with social relationships and adherence to treatment and causing depression.^{6,7} Treatment of facial lipoatrophy is, therefore, associated with improvement in quality of life.

There is no proven strategy for the effective treatment of facial lipoatrophy in PLHIV. Poly-L-lactic acid (PLLA) is a biocompatible and biodegradable polymer derived from the L-lactic and D-lactic isomers, and it has been used as a therapeutic approach to restore lost facial volume, improving patients' appearance and quality of life.

The use of PLLA is recommended for the treatment of HIV-associated facial lipoatrophy and has been approved in the United States since 2004.⁸ There are many studies⁸⁻¹⁸ regarding PLLA and PLHIV, mostly related to safety and efficacy, but most of them have follow-up periods of up to 2 years. There is a lack of standardization regarding the quantity of PLLA indicated for each patient and the assessment of outcomes. The lack of an easy-to-use objective method to measure regional fat is a major difficulty in the assessment of lipodystrophy in PLHIV.¹⁹ Improvement of cheek skinfold, measured by an adipometer, and improvement of the lipoatrophy severity score of the malar region, assessed with photographs, were used as evaluation methods to determine treatment response. The aim of this study was to evaluate measurement methods for lipoatrophy related to PLHIV receiving HAART, to establish factors related to better PLLA performance, and to identify clinical conditions related to PLLA injection durability.

METHODS

This study is a prospective, non-randomized clinical trial involving PLHIV with moderate to severe facial lipoatrophy.

Sixty-one PLHIV with moderate to very severe lipoatrophy without prior fillers, received cheek injections of PLLA. Treatment was administered between October 2002 and October 2004, with follow-up and data collection completed in February 2008. Key parameters analyzed included age, sex, HIV infection duration, CD4+ cell count, viral load, HAART regimen, and body mass index (BMI).

All patients were treated at the Reference Center on AIDS/STD, São Paulo, Brazil and gave written informed consent. The study was approved by the institutional review board (IRB #079/2001).

Assessment of lipoatrophy severity was based on digital photographs of the frontal and lateral aspects of the face, obtained using a Sony Cyber-shot DSC F707T digital camera. The evaluation focused exclusively on the cheek region. To minimize bias, 3 dermatologists analyzed the photographs—2 independent specialists and the author, who administered the PLLA injections, measured cheek skinfold thickness, and conducted follow-up consultations. Patients were given clinical scores from 0 to 20, according to the affected area and depth, classified as mild (0-5), moderate (5.1-10), severe (10.1-15), and very severe (15.1-20) lipoatrophy. Digital photographs taken immediately before the first treatment and 1 month after the final injection were considered the pre- and post-treatment assessments, respectively. In addition, the evaluation included cheek skinfold measurements at both time points.

A scientific adipometer (Cescorf) was positioned along a virtual line extending from the lower portion of the earlobe to the nostrils, with the measurement taken 1 centimeter lateral to the nostrils.

Each vial of PLLA (Sculptra, Sanofi-Aventis) was reconstituted with 3 mL of sterile water at least 4 hours before the procedure. Immediately before the procedure, 1 mL of 2% lidocaine was added to the vial, and it was thoroughly shaken. Each patient received one vial per cheek at each visit, except at the last one, when half a vial could be injected into each cheek, according to the judgment of the dermatologist. The injections were made at the junction of the deep dermis and the subcutaneous tissue, with a 25-gauge needle. The injection sites covered the entire affected region, with 1-cm intervals, 0.1 mL of suspension each time, in 4 directions.

Patients were treated at 4-week intervals. The number of PLLA vials was determined during the follow-up visits, and the decision to stop treatment was made jointly by the patient and the physician. After the injections, vigorous massage was performed in order to evenly distribute the PLLA. Patients were instructed to apply ice and massage the area twice a day, for 3 days, as well as to avoid excessive exposure to sunlight and heavy exercise.

Patients were evaluated every 2 months during the first year, and every 6 months until retreatment was indicated. The indication for retreatment, agreed upon by both the patient and the physician, was considered an endpoint.

Pearson correlation and the paired t-test were used for statistical analysis, and the level of significance was set at $p < 0.05$.

RESULTS

The mean age of the 61 patients was 44.6 (9.3) years (range, 30 to 71), and 86.9% were male. Twenty-four patients (39.3%) were classified as having moderate lipoatrophy, 22 (36.1%) as having severe lipoatrophy, and 15 (24.6%) as having very severe lipoatrophy. Fifty-eight patients completed the treatment, 3 were lost to follow-up because of cardiovascular disease, depression, and abandonment of HIV treatment (4.9%).

The mean duration since HIV infection diagnosis was 111.3 months, and patients had experienced signs of lipoatrophy for

30.6 months before the beginning of the study (median = 24 months).

The mean nadir CD4+ cell count was $176.3 \times 10^6/L$, and the median was $114 \times 10^6/L$ before HAART. On the other hand, the mean CD4+ cell count increased to $495.6 \times 10^6/L$, and only 5 patients presented with a CD4+ cell count of less than $200 \times 10^6/L$ when the study began. Viral load was below 400 copies/ mm^3 in 33 patients (54.1%), and the median detectable viral load was 8005 copies/ mm^3 . All but one patient was treated with stavudine for a mean of 44.4 months, and the remaining patient was treated with zidovudine for 61 months.

Fifteen patients discontinued HAART for periods ranging from 2 to 51 months, due to various reasons: drug toxicity, inadequate adherence, and structured treatment interruption. In some patients, HAART was introduced when the CD4+ cell count was above $350 \times 10^6/L$, when early treatment was recommended, despite the CD4+ cell count criteria.¹ In some of these patients, HAART was interrupted. We observed that patients who had their antiretroviral therapy suspended had a correlation between the time of suspension and the duration of results (Pearson correlation coefficient $r = 0.771$; $p < 0.001$).

Patients received a mean of 7.9 PLLA vials until clinical improvement. They were treated in 2 to 7 sessions, with a total of 4 to 13 vials of PLLA.

Before the procedure, the mean clinical evaluation score was 11.9, representing severe lipoatrophy (Figure 1a). After treatment, the mean score was 4.2, showing significant improvement ($p < 0.001$) (Figure 1b). The mean skinfold thickness was 6.09 mm before the treatment, increasing to 11.03 mm at the end (81%; $p < 0.001$, paired t-test). The maximum improvement in

skinfold thickness was 12.47 mm, obtained 15.9 months after the end of the treatment, corresponding to 105% improvement. We observed an inverse correlation between clinical scores and pre-treatment skinfold thickness ($r = -0.675$; $p < 0.001$) (Figure 2).

The quantity of PLLA used was related to the severity scores for lipoatrophy ($r = 0.609$; $p < 0.001$) as assessed by the photographs. The correlation was not significant when compared to skinfold thickness ($r = -0.359$; $p = 0.06$).

There was a negative correlation between pre-treatment skinfold thickness and the clinical assessment score from post-treatment photographs ($r = -0.589$; $p < 0.001$). There was also a good correlation between pre- and post-treatment clinical scores, showing that patients with worse pre-treatment scores also had the worse post-treatment scores ($r = 0.740$; $p < 0.001$).

Patients did not present papules or nodules as complications of the procedure, and immediate effects, such as ecchymosis, pain, and edema, were not considered.

Fifty-three patients completed follow-up until the indication for a new treatment. Five patients did not complete follow-up because of death from myocardial infarction, diagnosis of rectal cancer, renal failure, change of residence, and treatment with polymethylmethacrylate. The maximum follow-up period was 58 months, and the mean follow-up period was 31.7 months. The results were maintained for 25 to 48 months in most patients ($n = 44$). The mean duration of the effect was 33.4 months. In February 2008, when we stopped collecting data, 2 patients had not required retreatment yet.

There was a trend toward a weak correlation between age and durability of effect ($r = -0.275$; $p = 0.047$). There was no association between durability of the PLLA treatment and time of lipoatrophy,



FIGURE 1: Clinical aspects.
A - Pre-treatment (score = 16); skinfold measurement site;
B - Post-treatment (score = 5.0).

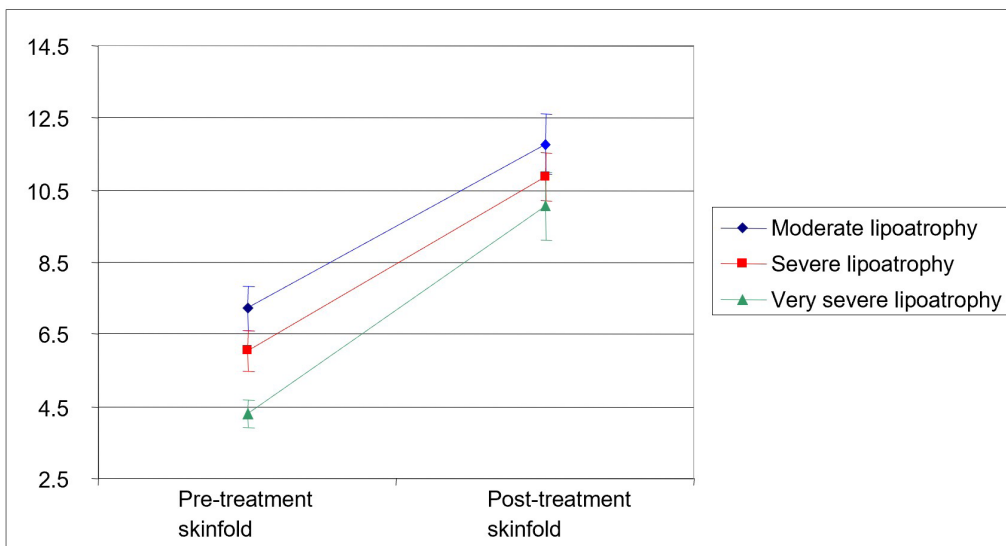


FIGURE 2: Comparison between lipoatrophy severity and pre- and post-treatment skinfold measurements (in mm).

time of diagnosis of HIV infection, CD4 nadir, viral load, or BMI. On the other hand, CD4+ cell count at the time of treatment with PLLA was weakly correlated with durability of results ($r = 0.342$; $p = 0.013$). The quantity of PLLA was weakly inversely correlated with duration of results ($r = -0.356$; $p = 0.009$). The clinical severity score before treatment was inversely correlated with the durability of PLLA injection ($r = -0.525$; $p < 0.001$).

DISCUSSION

The use of PLLA for HIV-associated lipoatrophy and cosmetic purposes has been widely reported in the literature, although the data regarding long-term follow-up is scarce.⁸⁻¹⁴

Our longest follow-up was almost 5 years, and during this period we did not observe any major adverse effects. The most frequently reported complication after PLLA injection in the literature⁸⁻¹³ is the development of palpable and/or visible papules and/or nodules. The risk of papule and nodule formation is directly linked to the physicochemical properties of the polymer, its degradation rate, reconstitution method, application site, and the patient's immunological response.¹⁶⁻¹⁸

We believe that these complications did not occur in this study because of prior dilution of PLLA to a compatible volume, correct placement of the product at the junction of the deep dermis and subcutaneous tissue, and avoidance of sites of thin skin, such as orbital and temporal areas. In addition, the host's immunological response may have played a role in preventing adverse reactions.¹⁶⁻¹⁸ Patients in this study had been diagnosed with HIV infection for a mean time of almost 10 years. Most had improved their immunological status after HAART, as the majority had an undetectable viral load when undergoing PLLA injections. The severity and duration of HIV infection and effective viral suppression have been described as risk factors for HIV-associated lipoatrophy,^{19,20} as we have seen in this study.

The use of nucleoside analogues can alter mitochondrial function in adipocytes and eventually cause apoptosis.²¹ Sta-

vudine has been implicated as the major nucleoside analogue responsible for mitochondrial toxicity,²² and consequently for the development of lipodystrophy. All patients, except one, had received stavudine for more than 3 years. It has been shown that prolonged use of HAART, especially stavudine, is associated with lipodystrophy.²³ There is no gold-standard method for assessing facial lipoatrophy. For this reason, many authors have suggested different approaches, such as sonography,¹⁵ magnetic resonance imaging (MRI),²⁴ computed tomography (CT),²⁵ and anthropometry.²⁵

Pre-treatment evaluation using an adipometer and digital photographs revealed an inverse correlation between clinical severity scores and cheek skinfold thickness, demonstrating that these methods are not only effective but also cost-efficient and easy to implement in clinical practice. Although radiologic imaging has been utilized for assessing facial lipoatrophy, each technique presents specific limitations.^{15,21-23} Moreover, these methods—including high-frequency ultrasound—are often too expensive for routine clinical application.

In their study, Mest and Humble¹¹ showed a 65.1% improvement in measured skinfold at the end of treatment and 73% at 12-month follow-up. These authors limited the maximum quantity of PLLA injected, and there were patients who would need to undergo more treatment sessions. To date, there is no standardization regarding the quantity of PLLA injection, dilution for the treatment of HIV-associated lipoatrophy, or number of sessions, making comparisons with other studies difficult. Levy et al. used a quantity of PLLA similar as that used in this study, and the results lasted more than 2 years.¹³ In this study, the number of applications was determined based on patient satisfaction, with their agreement as a key factor in the decision-making process. The extended follow-up period enabled a thorough assessment of PLLA injection longevity, which lasted nearly 3 years. We suggest that the optimal number of treatment sessions should be determined through a collaborative decision-making process,

balancing patient satisfaction with medical expertise.

The quantity of PLLA required to achieve the desired outcome was closely linked to lipoatrophy severity scores, as assessed through digital photographs. However, no significant correlation was observed between this requirement and pre-treatment skinfold measurements. This discrepancy may stem from individual variations in skin thickness,²⁶ as patients with comparable skinfold measurements can exhibit different degrees of lipoatrophy. Moreover, aging—both natural and accelerated by HIV infection—can weaken skin firmness, leading to sagging and compromising the accuracy of skinfold assessments. The progressive loss of structural support both affects measurement precision and diminishes skin responsiveness to PLLA treatment, ultimately reducing its bio-stimulatory effectiveness and volumetric enhancement. In some patients, even when we used a greater quantity of PLLA, despite increasing skin thickness, clinical improvement was not as evident. There was also a negative correlation between pre-treatment skinfold measurements and clinical assessment scores based on post-treatment photographs, suggesting that the thinner the skin, the worse the outcome of treatment with PLLA. For this reason, a complete evaluation of lipoatrophy, including the adipometer and clinical assessment, should be performed. Therefore, a multifactorial clinical evaluation is essential to determine the most appropriate treatment protocol for each patient.

After treatment, assessment of the photographs showed improvement in all patients ($p < 0.001$), the score changing from 11.9 to 4.2 on the severity scale. However, patients presenting with worse pre-treatment scores also improved less after treatment, even when a greater quantity of PLLA was used. It has been suggested that patients with severe fat loss do not achieve good results with PLLA and that better results are seen in patients who have had lipoatrophy for a shorter period of time.²⁷ We believe that there is a limit to clinical improvement for each individual and, once it is reached, the clinical aspect does not improve, regardless of how much PLLA is injected.

When analyzing factors that could interfere with durability, we observed that patients who had their antiretroviral therapy suspended had longer-lasting results, in proportion to the length of suspension. Clinical improvement lasted for more than 48 months in 3 patients, and all of them had had their HAART suspended for 21 to 51 months. We believe that the efficacy observed in these patients is associated both with the improvement of lipoatrophy and the potential partial recovery of fat.^{28,29} Studies on PLLA durability indicate that its clinical effects generally do not exceed 30 to 40 months.^{14,30} However, an alternative hypothesis suggests that PLLA may persist in the tissue longer than assumed, and that available studies should focus solely on clinical outcomes without considering the long-term presence of the biomaterial in the tissue.

As the PLLA mechanism of action is based on neocollagenesis,³¹ one could expect a worse response in older adults, given the impairment of collagen production and increased degradation.³² Inevitably, we have seen this tendency, but with a weak correlation.

The CD4+ cell count at the moment of treatment with

PLLA was weakly correlated with the durability of the treatment with PLLA, and the severity of lipoatrophy was inversely correlated with durability. Based on these findings, we can suggest that the better the patient's immunological status, the longer-lasting the response, and also that more severe lipoatrophy results in a less durable treatment effect.

Facial lipoatrophy lacks a standardized measurement method, and proposed approaches such as MRI, ultrasound, and CT have limitations and high costs. Our analysis revealed an inverse correlation between clinical scores and adipometer measurements, supporting digital photography and anthropometric evaluation as practical, cost-effective alternatives for clinical assessment.

We observed that patients who received more PLLA vials presented less durable treatment effects, contrary to expectations. It is possible that, once an optimal quantity of PLLA has been injected, intrinsic features of each person determine the outcome. The patients who received more PLLA were also those with the worst severity scores. In other words, patients with more severe lipoatrophy have worse results. Thus, the study confirms the efficacy of PLLA in treating moderate to severe facial lipoatrophy in HIV-positive patients; however, thin skin and severe lipoatrophy impose certain limitations, requiring complementary therapeutic approaches. In some cases, the effects of PLLA persisted for up to 48 months, underscoring its importance in the aesthetic and psychosocial management of these patients.

LIMITATIONS

Individual differences in skin thickness mean the assessment of skinfold measurements across different patients is inherently variable, limiting its precision as a comparative metric. Similarly, imaging modalities, despite their advanced capabilities, remain constrained by the absence of standardized measurement protocols and their high cost, restricting their feasibility for routine clinical application. Although the sample size in this study was relatively small, the long duration of the study provided a robust framework for evaluating the long-term effects of PLLA, partially offsetting this limitation. Additional constraints include the lack of a control group and the absence of standardized injection protocols, both of which could impact treatment reproducibility and the comparability of outcomes.

CONCLUSIONS

PLLA injections improve malar lipoatrophy in PLHIV receiving HAART. This study identified features associated with better responses, such as immunological status and suspension of HAART. On the other hand, skin thickness and lipoatrophy severity are associated with worse responses to PLLA. Severity of lipoatrophy is also related to the use of more PLLA vials and a shorter duration of results. Based on these findings, we can suggest that treatment with PLLA is a good option in patients presenting mild or moderate HIV-associated lipoatrophy, but good results will not be achieved in patients presenting severe lipoatrophy and thinner skin. ●

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