Oral lesions and immune reconstitution syndrome in HIV+/AIDS patients receiving highly active antiretroviral therapy. Epidemiological evidence

Luis A. Gaitan Cepeda [1], Alejandro Ceballos Salobreña [2], Karem López Ortega [3], Nancy Arzate Mora [1], Yolanda Jiménez Soriano [4]

(1) Laboratory of Clinical and Experimental Pathology, Division of Postgraduate Studies and Research, Dental School, Mexico National autonomous University, Mexico
(2) Chairman of Oral Medicine, Dental School, University of Granada, Spain
(3) Dental School, University of Sao Paulo, Brazil
(4) Doctor of Stomatology, Valencia, Spain

Correspondence:
Dr. Alejandro Ceballos-Salobreña
Emperatriz Eugenia 19-6D
18003 - Granada. Spain
E-mail: ceballos@ugr.es

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Summary

Objective: To determine whether opportunistic oral infections associated to HIV infection (OOI-HIV) are found in HIV+/AIDS patients with immune reconstitution related to highly active antiretroviral therapy (HAART).

Methods. From among 1100 HIV+/AIDS patients (Service of Internal Medicine, Carlos Haya Hospital, Malaga, Spain) subjected to review of the oral cavity between January 1996 and May 2007, we identified those examined in 1996 and which were again examined between 1997 and 2007, and were moreover receiving HAART. The following data were collected: age, gender, form of contagion, antiretroviral therapy at the time of review, number of CD4+ lymphocytes/ml, and viral load (from 1997 onwards). We identified those subjects with an increase in CD4+ lymphocytes/ml associated to HAART, and classified them as subjects with quantitative evidence of immune reconstitution (QEIR). Among these individuals with QEIR we moreover identified those with undetectable viral loads (QEIR+VL), and differentiated those patients with an increase in CD4+ lymphocytes >500/ml (QEIRm+VL). In each group we determined the prevalence of OOI-HIV, following the diagnostic recommendations of the EC-Clearinghouse (CDC-Atlanta, USA - WHO). In addition, we analyzed the prevalence of OOI-HIV in the different groups in relation to the duration of HAART.

Results. A total of 86 subjects were included (44 females and 42 males; 19 heterosexuals, 34 male homosexuals, and 33 intravenous drug abusers). Forty-two patients showed QEIR: 21 belonged to the QEIR+VL group, and 17 conformed the QEIRm+VL group. The prevalence of OOI-HIV per group was as follows: QEIR = 54.8%; QEIR+VL = 33%; QEIRm+VL = 35%. The most prevalent lesion in all groups was erythematous candidiasis. OOI-HIV increased with the duration of HAART ($p = 0.008$), and were seen to be dependent upon late appearance of the mycotic lesions (after 24 months under HAART).

Conclusions: It is suggested that opportunistic oral infections associated to HIV infection form part of the clinical picture of immune reconstitution inflammatory syndrome, though such infections are of late onset.

Key words: *HIV, AIDS, oral lesions, immune reconstitution inflammatory syndrome.*

Introduction

Human immunodeficiency virus (HIV) infection is characterized by a gradual reduction in the counts of CD4+ lymphocytes, among other cells, to the point of complete depletion (1-3). This reduction in turn leads to opportunistic infections and specific neoplastic processes. The introduction of highly active antiretroviral therapy (HAART) in the mid-nineties led to a decrease in the morbidity and mortality associated to HIV infection. However, it was seen that some patients under HAART who showed improvements in their immune system (immune reconstitution) paradoxically also developed clinical outbreaks of infectious diseases (4,5). This phenomenon was referred to as "immune reconstitution inflammatory syndrome" (IRIS), or immune reconstitution syndrome (IRS), immune restitution syndrome, immune reconstruction disease, immune restoration disease, among other terms. Thus, IRIS can be defined as the situation in which pre-existing subclinical or moderately symptomatic infections or inflammatory conditions paradoxically undergo worsening with a substantial increase in inflammation during the initial months of host immune reconstitution as a result of HAART (6). Although the pathogenesis of IRIS is still far from clear, the proposed mechanisms comprise a normal but vigorous pathogen-specific immune response; an immunopathogenic response; or a hyperinflammatory response to some pathogen (either intact or involving particles of the pathogen, or its residual antigens) already present at the time of rapid immune reconstitution (5,7) - thus suggesting restoration of host antigen-specific immunity.

Among the opportunistic infections strongly associated to HIV infection, mention must be made of the opportunistic oral infections (OOI-HIV). Certain OOI-HIV, specifically oral candidiasis (OC) and hairy leukoplakia (HL), have been attributed strong diagnostic and prognostic value (8,9). Moreover, they recently have been proposed as clinical markers of antiretroviral therapy failure (10). Despite the presence of elements warranting the inclusion of oral lesions as part of IRIS, and the presence of concrete pathogens prior to immune reconstitution (1), the behavior of opportunistic oral infections in subjects with immune reconstitution has not been investigated to date. The principal objective of the present study is to determine whether opportunistic oral infections associated to HIV infection are able to form part of the clinical picture of immune reconstitution in HIV+/AIDS subjects receiving HAART.

Material and Methods

A database comprising 1100 HIV+/AIDS patients from the Service of Internal Medicine (Carlos Haya Hospital, Malaga, Spain) was used in the present study. All patients were subjected to exhaustive review of the oral cavity by the same explorer, during the period between January 1996 and May 2007. The following data were obtained from the medical records: age at the time of review, gender, form of contagion, antiretroviral therapy at the time of review, number of CD4+ lymphocytes/ml, and the number of copies of HIV-1 RNA/ml of peripheral blood (viral load, VL). This latter parameter was determined on a routine basis starting in 1997; as a result, the reviews before this period do not contemplate this information. Starting in 1997, this center specialized in HIV infection adopted as first-choice antiretroviral treatment the combination of two nucleoside analog reverse transcriptase inhibitors (NRTIs) plus an HIV-1 protease inhibitor (PI) - conforming highly active antiretroviral therapy (HAART).

We thus selected those patients subjected to oral review before HAART (pre-HAART era) and which posteriorly again underwent oral review subjected to a minimum of 6 months of HAART (with full adherence to therapy).

The selected subjects were classified according to their CD4+ lymphocyte counts as follows: mild immune depression (CD4+ lymphocyte count > 500/ml), moderate immune depression (CD4+ lymphocytes > 200 - <500/ml), and severe immune depression (CD4+ lymphocytes < 200/ml). According to viral load, the selected subjects were grouped as follows: undetectable VL; VL <10,000 copies/ml, and VL >10,000 copies/ml.

For investigational purposes only, the subjects were distributed into a series of study groups based on IRIS risk defined as CD4+ lymphocytes <50/ml at the start of HAART, and high viral loads at the start of HAART - immune reconstitution in turn being defined as the increase in CD4+ lymphocytes associated with the introduction of HAART:

- *Subjects with quantitative evidence of immune reconstitution (QEIR).* These were patients with a rise in CD4+ lymphocyte counts associated to HAART, i.e., those who in the pre-HAART era presented CD4+ lymphocyte counts of <200/ml, followed by a rise in the HAART era to >200 - <500/ml, or >500/ml. Alternatively, these were patients with CD4+ lymphocyte counts of >200 - <500/ml in the pre-HAART era, followed by a rise in the HAART era to >500 CD4+ lymphocytes/ml.
- *Subjects with quantitative evidence of immune reconstitution and with viremia control (QEIR+VL).* These were patients with a rise in CD4+ lymphocyte counts associated to HAART, i.e., those who in the pre-HAART era presented CD4+ lymphocyte counts of <200/ml, followed by a rise in the HAART era to >200 - <500/ml, or >500/ml. Alternatively, these were patients with CD4+ lymphocyte counts of >200 - <500/ml in the pre-HAART era, followed by a rise in the HAART era to >500 CD4+ lymphocytes/ml. In addition to these lymphocyte counts, these patients showed an undetectable viral load.
- *Subjects with quantitative evidence of maximum immune reconstitution and with viremia control (QEIRm+VL).* These were patients showing an immune response, reaching CD4+ lymphocyte counts of >500/ml, with undetectable viral loads.

In each of the different study groups we determined the prevalence of oral lesions associated to HIV infection (OL-HIV). The diagnosis of the different OL-HIV was based on the recommendations of the CDC-Atlanta (USA - WHO) applicable in each period. The diagnosis of oral candidiasis was based on the clinical evidence and on standardized microbiological methods (culture as well as morphology). In addition, with the purpose of determining whether the duration of HAART influences the type and number of oral lesions, an analysis was made of the presence of oral lesions in the different study groups according to the duration of HAART.

The statistical methodology was based on the chi-square test (EPI-INFO, CDC-Atlanta, USA) for the bivariate analysis ($p<0.05$, 95%CI), while linear logistic regression was used (time determination of the curve)(SPSS® version 13.0 statistical package)($p<0.05$) for analyzing the behavior over time of OOI-HIV in relation to the duration of HAART.

Results

- *Demographic data*

Eighty-six long-time survivors (44 females and 42 males) were seen to meet the study inclusion criteria. As regards the form of contagion, 19 were heterosexuals, 34 were male homosexuals, and 33 were intravenous drug abusers.

At the start of the study period (pre-HAART era), the mean age of the 86 patients was 34.4 ± 8.8 years, with a range of 21-64 years. In this period, and according to immune status, the subjects were grouped as follows: 22 had CD4+ lymphocyte counts of >500/ml; 22 had counts of >200 - <500/ml, and 42 (48.8%) showed severe immune deficiency (CD4+ lymphocyte counts of <200/ml). The copies of HIV-1 RNA/ml (viral load, VL) were not used to monitor virological status on a routine basis until 1997; as a result, these values are not reported for the pre-HAART era.

Regarding immune status in the HAART era, the patients were distributed as follows: 30 (34.8%) presented mild immune deficiency, 28 (32.5%) moderate immune deficiency, and 28 (32.5%) severe immune deficiency. As to virological status, the individuals corresponding to the HAART era showed undetectable viral loads in 39 cases (45.3%), while 25 (29%) presented viral loads of <10,000 copies rna-HIV-1/ml, and 22 subjects presented viral loads of >10,000 copies of rna-HIV-1/ml.

- *Response to highly active antiretroviral therapy*

A decrease was seen in the number of subjects with severe immune deficiency in the HAART era, compared with the situation in the pre-HAART era (from 48.8% to 32.5%; $p = 0.02$). Regarding the patients with QEIR, a total of 42 subjects (representing 48% of the total patient series) increased their CD4+ lymphocyte counts while receiving HAART.

In relation to the viral loads, the absence of this parameter in the pre-HAART era does not allow us to establish comparisons. However, the data corresponding to the HAART era show a 45.3% success rate with antiretroviral therapy, defined by the presence of undetectable viral loads.

On relating the two paraclinical markers (CD4+ lymphocyte count and VL) in each of the subjects in the HAART era, 21 (24.4%) of the 86 patients with increases in their CD4+ lymphocyte counts moreover also showed undetectable viral loads (QEIR+VL group). Since it has been suggested that immune reconstitution syndrome is more likely in subjects with greater reconstitution of the immune system, we identified those patients who in the pre-HAART era had CD4+ lymphocyte counts of <200/ml and who under HAART reached counts of >500/ml together with viremia control as reflected by the presence of undetectable viral loads (QEIRm+VL group). A total of 17 of the 86 patients in the present analysis met these criteria. The distribution of the different study groups and subgroups is reported in Table 1.

Prevalence of opportunistic oral infections related to HIV

- *Pre-HAART era*

The prevalence of OOI-HIV in this pre-HAART era was found to be 66.3%, since 57 subjects presented OOI-HIV of some kind. The most common lesion was erythematous candidiasis, with 27 cases (31.4%), followed by angular cheilitis with 20 cases (23.3%), hairy leukoplakia (HL) with 18 cases (20.9%), and pseudomembranous candidiasis with a prevalence of 12.8%. Six cases of hyperplastic candidiasis were diagnosed (7%), as well as 7 cases of lip herpes (8.1%) and 4 cases of Kaposi sarcoma (4.7%).

- *HAART era*

The prevalence of opportunistic infections in the HAART era was 46.5% (40 cases). The most frequent lesion was erythematous candidiasis with 25 cases (29.1%), followed by hairy leukoplakia with 20 cases (prevalence 23.3%). Eight patients presented angular cheilitis (9.4%), and 4 were diagnosed with pseudomembranous candidiasis (4.7%). One case of lip herpes was registered (1.2%). This group of long-term survivors receiving HAART showed no cases of hyperplastic candidiasis or Kaposi sarcoma. Thus, a decrease was seen in morbidity attributable to opportunistic oral infections in the HAART era - though statistically significant differences ($p<0.05$) were only recorded in relation to angular cheilitis and lip herpes. The total oral lesions and their respective prevalences in both eras are reported in Table 2.

Opportunistic oral infections in the study groups

In concordance with the principal objective of the study, we identified those subjects with opportunistic oral infections in the different study groups. In this sense, of the 42 subjects with QEIR, 23 (54.8%) presented at least one opportunistic oral infection associated to HIV disease. The OOI-HIV diagnosed in this group were the following: erythematous candidiasis in 12 cases; HL in

Table 1. Demographic data of the 86 HIV+/AIDS patients studied.

STUDY GROUP			N
TOTAL			86
GENDER	FEMALE		44
	MALE		42
FORM OF CONTAGION		HETEROSEXUAL	19
		MALE HOMOSEXUAL	34
		INTRAVENOUS DRUG ABUSE	33
IMMUNE STATUS	PRE-HAART ERA	MILD IMMUNE SUPPRESSION	22
		MODERATE IMMUNE SUPPRESSION	22
		SEVERE IMMUNE SUPPRESSION	42
	HAART ERA	MILD IMMUNE SUPPRESSION	30
		MODERATE IMMUNE SUPPRESSION	28
		SEVERE IMMUNE SUPPRESSION	28
VIROLOGICAL STATUS	HAART ERA	UNDETECTABLE VIRAL LOAD	39
		<10,000 COPIES	25
		>10,000 COPIES	22
RESPONSE TO HAART	QEIR		42
	QEIR+VL		21
	QEIRm+VL		17
TIME UNDER HAART (in years)	1		24
	2		15
	4		28
	9		19

HAART = HIGHLY ACTIVE ANTIRETROVIRAL THERAPY; PRE-HAART = 1996; HAART ERA = ≥1997; QEIR = QUANTITATIVE EVIDENCE OF IMMUNE RECONSTITUTION; QEIR+VL = QUANTITATIVE EVIDENCE OF IMMUNE RECONSTITUTION PLUS UNDETECTABLE VIRAL LOADS; QEIRm+VL = MAXIMUM QUANTITATIVE EVIDENCE OF IMMUNE RECONSTITUTION PLUS UNDETECTABLE VIRAL LOADS (CD4+ COUNTS OF >500/ml)

Table 2. Prevalences of opportunistic oral infections among the 86 HIV+/AIDS patients analyzed in the different treatment eras.

ERA	OOI-HIV	EC	PC	HC	AC	LH	HL	KS
PRE-HAART	57 (66.3%)	27 (31.4%)	11 (12.8%	6 (7%)	20 (23.3%)	7 (8.1%)	18 (20.9%)	4 (4.7%)
HAART	40 (46.5%)	25 (29.1%)	4 (4.7%)	0	8 (9.4%)	1 (1.2%)	20 (23.3%)	0

HAART = HIGHLY ACTIVE ANTIRETROVIRAL THERAPY; PRE-HAART = 1996; HAART ERA = ≥1997; OOI-HIV = OPPORTUNISTIC ORAL INFECTIONS RELATED TO HIV INFECTION; EC = ERYTHEMATOUS CANDIDIASIS; PC = PSEUDOMEMBRANOUS CANDIDIASIS; HC = HYPERPLASTIC CANDIDIASIS; AC = ANGULAR CHEILITIS; LH = LIP HERPES; HL = HAIRY LEUKOPLAKIA; KS = KAPOSI SARCOMA.

Table 3. Prevalence of opportunistic oral infections in relation to the different study groups.

GROUP	OOI-HIV	EC	PC	AC	LH	HL
QEIR (42)	23 (54.8%)	12 (28.6%)	1 (2.4%)	4 (9.5%)	1 (2.4%)	10 (23.8%)
QEIR+VL (21)	7 (33.8%)	5 (23.8%)	1 (4.8%)	2 (9.5%)	0	4 (19%)
QEIRm+VL (17)	6 (35.3%)	4 (23.5%)	4 (23.5%)	2 (11.8%)	0	4 (23.5%)

QEIR = QUANTITATIVE EVIDENCE OF IMMUNE RECONSTITUTION; QEIR+VL = QUANTITATIVE EVIDENCE OF IMMUNE RECONSTITUTION PLUS UNDETECTABLE VIRAL LOADS; QEIRm+VL = MAXIMUM QUANTITATIVE EVIDENCE OF IMMUNE RECONSTITUTION PLUS UNDETECTABLE VIRAL LOADS (CD4+ COUNTS OF >500/ml); HAART = HIGHLY ACTIVE ANTIRETROVIRAL THERAPY; OOI-HIV = OPPORTUNISTIC ORAL INFECTIONS RELATED TO HIV INFECTION; EC = ERYTHEMATOUS CANDIDIASIS; PC = PSEUDOMEMBRANOUS CANDIDIASIS; AC = ANGULAR CHEILITIS; LH = LIP HERPES; HL = HAIRY LEUKOPLAKIA.

Table 4. Prevalence of oral lesions in relation to the duration of highly active antiretroviral therapy in each of the study groups.

		YEARS UNDER HAART			
STUDY GROUP		1	2	4	9
IMMUNE RESPONSE	OOI-HIV	3/11 (27.3%)	2/5 (40%)	6/12 (50%	8/14 (57.1%)
	MYCOTIC		3/5 (60%)	6/12 (50%)	8/14 (57.1%)
	VIRAL	3/11 (27.3%)	2/5 (40%)	3/12 (25%)	3/14 (21.4%)
EVIDENCE OF IMMUNE RECONSTITUTION	OOI-HIV	1/5 (20%)	1/4 (25%)	2/4 (50%)	3/8 (37.5%)
	MYCOTIC		2/4 (50%)	3/4 (75%)	3/8 (37.5%)
	VIRAL	1/5 (20%)	1/4 (25%)	1/4 (25%)	1/8 (12.5%)
TOTAL SUCCESS	OOI-HIV	1/4 (25%)	1/4 (25%)	2/4 (50%)	2/5 (60%)
	MYCOTIC		2/4 (50%	3/4 (75%)	2/5 (40%)
	VIRAL	1/4 (25%)	1/4 (25%	1/4 (25%)	1/5 (20%)

OOI-HIV = OPPORTUNISTIC ORAL INFECTIONS RELATED TO HIV INFECTION; HAART = HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

10 cases, and angular cheilitis in 4 cases. One case of lip herpes and one case of pseudomembranous candidiasis were also diagnosed.

In the case of the patients with QEIR+VL, and of the 21 individuals that met the selection criteria, 7 presented at least one OOI-HIV. In this group we identified 4 cases of HL, 5 cases of erythematous candidiasis, two cases of angular cheilitis, and one case of pseudomembranous candidiasis.

Of the 17 subjects with QEIRm+VL (CD4+ lymphocyte count >500/ml and undetectable viral load), 6 presented some type of OOI-HIV. Specifically, we diagnosed 4 cases of HL, 4 cases of erythematous candidiasis, two cases of angular cheilitis and one case of pseudomembranous candidiasis. The total opportunistic infections diagnosed in each group are shown in Table 3.

In relation to the duration of HAART, and as can be seen in Table 4, the subjects with QEIR showed an increased prevalence of OOI-HIV with the prolongation of HAART ($p = 0.008$). However, when analyzed according to the underlying etiology, we found that the lesions of viral origin, HL and herpes simplex, showed no association to the time elapsed. In contrast, the lesions of mycotic origin appeared later in time, after 24 months of HAART.

On examining the QEIR+VL population, the oral lesions of viral origin were seen to remain constant, while the total lesions and infections of mycotic origin showed no apparent trends. In the case of the patients with maximum immune reconstitution (QEIRm+VL), we likewise recorded an increase in the prevalence of OOI-HIV over time, together with the constant presence of viral lesions.

Discussion

The present study reflects the possibility that opportunistic oral infections associated to HIV infection may manifest as a consequence of immune reconstitution in certain HIV+/AIDS patients subjected to HAART. An important finding in our series is that HIV+/AIDS patients subjected to HAART who present CD4+ lymphocyte counts of >500/ml and undetectable viral loads can suffer OOI-HIV. Practically all studies on oral morbidity in HIV+/AIDS patients receiving HAART, and in which the prevalence of oral lesions is associated to immune and virological status, report that some patients with CD4+ lymphocyte counts of >500/ml and undetectable viral loads have oral lesions (11-17). In other words, none of the published series of HIV+/AIDS patients subjected to HAART have been able to demonstrate the absence of oral lesions among the global patients receiving successful antiretroviral therapy. An important observation is the fact that despite reaching quantitatively optimum CD4+ lymphocyte counts and viremia control to undetectable levels, clinically manifest oral lesions can appear. The hypothesis that some of these lesions in such patients may be the result of a reconstitutive immune response is attractive.

The chain of events leading to immune reconstitution inflammatory syndrome (IRIS) is not clear. A short-term effect of antiretroviral treatment is that it preserves pre-therapy immune system competence - thereby slowing disease progression and improving patient survival. On the other hand, if antiretroviral therapy controls viremia, T-cell clone expansion may occur, thereby allowing improved immune function (18). The reason why not all patients with immune reconstitution develop IRIS, and the characteristics and parameters that differentiate the two population groups, have not been established.

The pathogenesis of IRIS is multifactorial, and depends on the amount of pre-existing microorganisms, their virulence, and the characteristics of particular immune response (5,6). During the first four weeks after the start of HAART, an increase is seen in the circulating CD4+ cells, more associated with a redistribution of memory cell entrapped within the lymphoid tissue than with a new production of naïve cells (7). In the months following the start of HAART, viremia is brought under control, and this leads to restoration of thymus gland function - with a second increase in circulating CD4+ lymphocytes, this time related to the production of naïve CD4+ cells (7).

Approximately 20-30% of all patients subjected to HAART develop IRIS (7). Our results generally coincide with the data published in the literature, since the sample of patients with quantitative evidence of immune competence and controlled viremia showed a prevalence of OOI-HIV of 33.8% (versus 35% on reaching maximum immune competence). Different clinical conditions have been associated with IRIS, including herpes zoster, Kaposi sarcoma, Graves' disease, progressive multifocal leukoencephalopathy, as well as infections due to cytomegalovirus, Pneumocystis carinii, hepatitis B and C viruses, Mycobacterium avium complex, Mycobacterium tuberculosis, or Cryptococcus neoformans (19,20). However, few studies have addressed the oral lesions associated with IRIS. The facial lesions reported as part of IRIS are fundamentally attributable to herpes zoster (7), and molluscum contagiosum (21). Intraorally, there have been three reports of Kaposi sarcoma associated to IRIS (22). All three are OOI-HIV of viral origin. None of these lesions were identified in our series of patients. The fact that only viral oral lesions have associated with IRIS may be due to the fact that none of these studies conducted long-term follow-up. In this context, our results suggest that opportunistic mycotic infections re-emerge after more than 12 months. The most frequent OOI-HIV was found to be oral candidiasis (OC). Of note is the fact that there are no studies on the presence of OC associated to IRIS. Our results indicated a prevalence of OC of close to 30%, including one case of pseudomembranous candidiasis. In contrast, other clinical studies report that the initial systemic opportunistic infections in IRIS are caused by fungal species (Cryptococcus spp.) or mycobacteria (Mycobac-

terium tuberculosis, Mycobacterium avium complex)(7), and that viral infections appear at a later point in time. The time-analysis of our cases indicates that mycotic lesions are identified in later stages.

In the present series, the lesions most commonly identified in the population with immune reconstitution were HL and OC. Erythematous candidiasis showed very constant values in the four study groups, with a slight improvement in the patients with QEIR+VL. The prevalence of OC (excluding angular cheilitis) in our subjects with QEIR was found to be 30%, i.e., clearly greater than the 9% prevalence reported by Umadevi et al. (16) in subjects receiving HAART and with CD4+ lymphocyte counts of over 200/ml (16). If our finding is confirmed, and considering that both types of lesions - particularly OC (10,23) - have been reported to be of great prognostic value (their presence moreover being considered suggestive of antiretroviral therapy failure)(10,24), then it would become necessary to establish the differential diagnostic parameters between lesions associated to IRIS and oral lesions associated to immune deficiency. To date, no parameters for the differential diagnosis of lesions due to persistence, reinfection or a vigorous host immune response have been identified. Such is the case of pseudomembranous candidiasis. The presence of this clinical variety of candidiasis has been proposed as an immune suppression marker (25). However, in our series we recorded a case of pseudomembranous candidiasis in a QEIRm+VL patient. This finding raises new questions, and the importance of differentiating the origin of such lesions (secondary to immune competence or to immune deficiency), with a view to management and antiretroviral treatment decisions, is obvious. In fact, it is always recommended to distinguish between clinical failure of antiretroviral therapy and immune reconstitution inflammatory syndrome. At present, it has been proposed that the diagnosis of lesions associated to IRIS should be made on an exclusion basis (7). There are no differences in paraclinical marker values associated to IRIS. Our results agree with this suggestion, since the study groups showed no statistical association between the CD4+ lymphocyte counts or viral loads and oral lesions. The lack of scientific information regarding the behavior of OOI-HIV in subjects with immune reconstitution prevents us from specifying whether this condition is pertinent in the case of oral lesions.

In the present study, the viral lesions diagnosed in subjects with immune reconstitution corresponded to the family Herpes viridae. A case of lip herpes and 10 cases of HL were identified. Of note is the behavior of HL in our series. The constant presence of hairy leukoplakia in all the groups, regardless of the response (success or failure) to antiretroviral therapy (HAART) or the duration of such treatment, suggests that HL does not form part of the clinical picture of IRIS. In effect, HL remained practically constant in all the study groups, regardless of the time under HAART. This can be explained by the demonstration of both a high prevalence of Epstein-Barr virus carriers and of high viral loads corresponding to this same virus in HIV+ subjects under to HAART (26). The fact that cases of HL were recorded in subjects with immune reconstitution and with undetectable viral loads again reflects the importance of incorporating this possibility in the prognostic role of these viral lesions. Although HL has been associated to CD4+ lymphocyte counts of <200/ml (25), it also has been suggested that susceptibility to HL is not necessarily associated to impaired mucosal immune function (27). Our results support this latter possibility.

A point that should be stressed is that among the four study groups, the group with the highest prevalence of OOI-HIV corresponded to the patients with maximum immune competence and undetectable viral loads (56.3%), while the group with the lowest prevalence was that considering only an increase in CD4+ lymphocyte counts under HAART. On adjusting the sample in relation to undetectable viral load, the prevalence of such lesions increased. This suggests that a risk factor additional to an increase in the number of CD4+ lymphocytes is viremia control. This suggestion has been published elsewhere. It has been reported that lesions of infectious origin associated to IRIS are mainly found in subjects who before the introduction of HAART suffered severe immune depression and/or viral loads of >10,000 copies/ml, and who under HAART reached CD4+ lymphocyte counts of >500/ml (28). Our results indicate that the subjects with greatest immune reconstitution (i.e., the QEIRm+VL group) exhibit a slightly greater presence of oral lesions than the patients who fail to reach such levels of immune competence.

It has been proposed that the lesions associated to IRIS manifest between 4-8 weeks after the start of HAART. However, there have been reports of cases manifesting even 80 weeks after the start of HAART (7). In our patients with immune reconstitution, the fewest diagnoses of OOI-HIV corresponded to subjects with one year or less of HAART. In this context, a gradual and statistically significant increase in lesions was seen over time under HAART. This suggests that successful HAART secures immediate control of OOI-HIV, as evidenced by the very low prevalence of such lesions recorded in the period immediately after the introduction of protease inhibitors to antiretroviral therapy, and that as the time under HAART increases, another immune competent factor is needed (in addition to the quantitative boost in immune function) in order to ensure an optimum oral mucosal immune response. This hypothetical factor presumably would require more time for reconstitution than the CD4+ lymphocyte count. It has been suggested that viewing HIV infection simply as a decrease in CD4+ lymphocyte count is too simplistic, in view of the extreme complexity of the host immune response (18). Another possible explanation

for the above finding could be that the Candida strains that colonize the oral mucosa in HIV+ patients receiving HAART acquire resistance to the HIV-1 protease inhibitors, which have been considered to possess anti-Candida effects (29). However, it is also possible that these cases of OC may be due to qualitative exhaustion of the immune system. On the other hand, if time is the most important factor for differentiating IRIS from a delay in acquiring a competent immune capacity, then it could be speculated that our results - particularly those relating to 24 months of HAART - could be associated to IRIS, while posterior lesions could be the result of a delay in immune improvement or of immune function exhaustion or failure. The clarification of these aspects falls outside the scope of the present study, and specific investigational protocols should be defined to explore them. Furthermore, it recently has been demonstrated that oral lesion morbidity associated to HIV disease is present in the HIV+ population under to HAART in the present era (30,31).

The confirmation of whether OOI-HIV can form part of the clinical picture of IRIS is necessary. At present we are unable to rule out the possibility that these lesions are the consequence of a qualitative failure of immune cell response; of the incomplete acquisition of mucosal immune response following HAART; or simply examples of de novo infection.

The present study shows the human immunodeficiency syndrome to be a dynamic disorder characterized by an intense inter-relationship with therapy (and the consequences this has for the patient); as a result, it is very difficult to establish a prognosis once treatment has been started.

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