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HIV Disease/Oral Medicine

Effect of PI-HAART on the prevalence of oral lesions in HIV-1 infected patients. A Greek study

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OBJECTIVE: To investigate the association between the prevalence of oral lesions and highly active antiretroviral therapy (HAART) including a protease inhibitor (PI).
DESIGN: Prospective study.
PATIENTS AND METHODS: Ninety-five consecutive patients, attending an AIDS Unit, in Greece entered the study. Fourty-four patients were receiving PI- HAART, 14 patients were on double antiretroviral therapy, and 37 patients were not receiving antiretroviral therapy at the time of oral examination. Oral lesions were diagnosed by established presumptive clinical criteria.
MAIN OUTCOME MEASURES: Oral lesions were scored. CD4 counts and viral load were determined and related to the prevalence of oral lesions.
RESULTS: Oral lesions, and specifically oral candidiasis, were significantly reduced ($P < 0.001$) in patients receiving PI-HAART. Oral lesions were significantly increased in patients with CD4 counts <200 cells μl^{-1} and viral load >20 000 copies ml^{-1} ($P < 0.001$). The percentage of patients, with lesions on PI-HAART, and with CD4 < 200 and viral load >20 000 was 1.5 times lower (37.5% *vs* 58.8%, $P < 0.001$) than that of patients not receiving antiretroviral therapy, but with similar immune and viremic status.
CONCLUSIONS: Oral lesions were significantly reduced in patients on PI-HAART. A direct anticandidal effect of PI was suggestive and seemed to have accounted, beyond the HAART-related immune reconstitution, for the reduction of candidiasis and all other oral lesions.
Oral Diseases (2004) **10**, 145–150

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Introduction

In the era of highly active antiretroviral therapy (HAART), a marked decrease in the recurrence of thrush (Gripshover *et al*, 1998; Revankar *et al*, 1998) and in the incidence of oral candidiasis (OC) was reported (Hood *et al*, 1998; Cauda *et al*, 1999; Diz Dios *et al*, 1999). Discontinuation of prophylactic antifungal treatment was suggested in most patients receiving HAART.

A marked decrease in the overall incidence of oral lesions (van der Waal, Schulten and Pindborg, 1991; Nicolatou *et al*, 1999; Porter *et al*, 1999; Ranganathan *et al*, 2000), was further reported in patients receiving HAART (Aguirre *et al*, 1999; Ceballos-Salobrena *et al*, 2000; Patton *et al*, 2000; Schmidt-Westhausen *et al*, 2000; Greenspan *et al*, 2001; Tappuni and Fleming, 2001; Eyeson *et al*, 2002). With the overall decrease of oral lesions, the pattern of specific oral lesions changed.

Oral hairy leukoplakia (OHL) and necrotizing ulcerative gingivitis (NUG), both lesions strongly associated to HIV infection, were found significantly decreased (Aguirre *et al*, 1999; Patton *et al*, 2000; Schmidt-Westhausen *et al*, 2000; Tappuni and Fleming, 2001) or remained unchanged (Ceballos-Salobrena *et al*, 2000). Oral warts and salivary gland disease were reported to increase (Schmidt-Westhausen *et al*, 2000; Greenspan *et al*, 2001), although a recently published study reported paucity of Sjogren-like syndrome in an unseleceted HIV-1 population (Panayiotakopoulos *et al*, 2003).

The reduction of OC seems to be the main contributor to the overall reduction of oral lesions.

The above marked decrease of OC and of all oral lesions following HAART was attributed to immune

reconstitution, as measured by the elevation of circulating CD4+ cells and by the at least partial recovery of T-cell activity, after the reduction of viral burden.

Furthermore, several clinical and laboratory studies evaluated a direct, early, immune reconstitution-independent effect of protease inhibitors (PIs) on the prevention of OC (Cauda *et al*, 1999; Cassone *et al*, 2002), which was attributed to the induction of secreted aspartyl proteinases (SAPs) by HIV envelope proteins (Gruber *et al*, 1998).

Hypothesis

Since HAART reduces the prevalence of oral lesions and of OC, in particular, and since PI further exerts a direct effect on *Candida* virulence, the prevalence of OC and of all oral lesions should be significantly reduced in patients on HAART, which includes a PI (PI-HAART).

An immune status-independent, PI-related decrease should be observed, in addition to the immune-dependent, HAART-related decrease.

Study endpoint

The aim of this prospective study was to determine the prevalence of HIV-related oral lesions among a group of patients, in Athens, Greece, receiving PI-HAART, which included two nucleoside reverse transcripase inhibitors (NRTI) and a PI, and to compare it with the prevalence of oral lesions observed in a group of patients who were not receiving antiretroviral therapy (ART).

The prevalence of oral disease was related to the counts of circulating CD4+ lymphocytes and the viral load (VL).

The prevalence of oral lesions was also determined in a group of patients receiving double therapy, which included two NRTIs, and was compared with that of the group without ART.

Patients and methods

Patients

Ninety-five consecutively examined patients, 10 females and 85 males, were prospectively evaluated in the present study, from December 1997 to December 1998, during the early era of HAART. All, but three, were Greeks (Caucasian). They were followed-up at the AIDS Unit, Department of Pathophysiology, Laikon General Hospital in Athens. The study was not a cross-sectional one.

All participants provided informed consent before enrollment and the study was approved by the Bioethics Committee of the Laikon General Hospital.

Patients were divided in three groups, according to the ART administered.

Group 1 consisted of 37 patients who did not receive ART; 13 of them were newly diagnosed HIV infections, at the time of oral examination.

Group 2 consisted of 14 patients who received double therapy, which included two NRTIs.

Group 3 consisted of 44 patients who received PI-HAART, which included two NRTIs and one PI.

Table 1 Patients' demographics

	Group 1 (no ART, n = 37)	*Group 2 (double ART, n = 14)*	*Group 3 (PI-HAART, n = 44)*
Age (years) [mean (s.d.)]	36.73 (9.82)	35.64 (10.08)	37.48 (9.59)
HIV risk behavior [*n* (%)]			
MSM	35 (94.60)	9 (64.30)	31 (70.47)
HS	2 (5.40)	2 (14.28)	10 (22.72)
IVDU		2 (14.28)	2 (4.54)
BT		1 (7.14)	1 (2.27)

MSM, male having sex with male; HS, heterosexual transmission; IVDU, intravenous drug user; BT, blood transfusion.

Table 1 shows patients' demographics in each group.

Methods

Patients were classified according to CDC (1993) classification criteria.

Oral lesions were recorded by using established presumptive clinical criteria for HIV-associated oral lesions (EC-Clearinghouse on oral problems, 1993).

Blood for CD4 counts, VL measurements and general laboratory evaluation were obtained on the same day that the oral examination was taking place. A branched-DNA (bDNA) signal amplification assay (Chiron Corp., Emeryville, CA, USA) was used for the determination of HIV-1 VL. The lower quantification limit for VL was 500 copies ml^{-1}.

The oral medicine specialist was blinded on the clinical, laboratory and ART of the patients at the time of oral examination. Sixty-seven of 95 patients (70.5%) were examined from two to 11 times, throughout the study period.

Mycology

Following the clinical evaluation of patients, laboratory diagnosis of OC was based on direct microscopic examination of Gram stained lesion scrapings and culture of the clinical material in 90 mm Petri dishes with CHROMagar Candida (CHROMagar, Paris, France), which was used for rapid presumptive differentiation of common *Candida* species. Plates were incubated at 35°C for 48 h. The identity of each isolate, including the *Candida* species that were concurrently isolated from a single specimen, was confirmed by the API (bioMerieux, Marcy l'Etoil, France). Susceptibility to amphotericin B, fluconazole, itraconazole and voriconazole was determined by using the National Committee for Clinical Laboratory Standards (NCCLS) microdilution method M 27A2 (NCCLS, 2002) and Etest (AB Biodisk, Solna, Sweden), as described previously (Kollia *et al*, 2003).

Data analysis

The data were coded to enable comparisons to be made with the SPS.S 11 computer package. Statistical level of significance was at $P < 0.001$. That level of significance was decided in order to be more strict with our analysis.

Oral lesions were evaluated per patient, and not per patient visit.

Pearson chi-square and logistic regression analysis were used.

The patients who were on antifungal prophylaxis were excluded from the statistical analysis for estimating the prevalence of OC.

Results

Group 1

Of the 37 patients in the group 22 lesions were observed, in 17 (45.95%) patients. Five patients presented with two oral lesions. Twelve of those 17 patients with lesions had CD4+ counts <200 cells μl^{-1} and 13 of 17 patients had VL $>$ 20 000 copies ml^{-1}. Ten of 17 patients (58.8%) with lesions had both CD4 $<$ 200 and VL $>$ 20 000.

Group 2

Nine oral lesions were observed in 7 (50%) in this group consisting of 14 patients. Two patients presented with two lesions. None of the seven patients with lesions had CD4+ counts <200 cells μl^{-1}, while one of seven had VL $>$ 20 000 copies ml^{-1}.

Group 3

Sixteen oral lesions were observed in 44 (36.36%) patients in this group.

Seven of those 16 patients with lesions had CD4+ counts below 200 cells μl^{-1} and six of 16 patients (37.5%) with lesions had both CD4 $<$ 200 and VL $>$ 20 000 copies ml^{-1}. As it can be observed, the percentage of patients on PI-HAART, with lesions, with CD4 $<$ 200 and with VL $>$ 20 000 was 1.5 times lower (37.5% *vs* 58.8%) than that of patients without ART, with lesions, and with similar immune and viremic status.

The low CD4 count and the high VL observed in several of the patients on PI-HAART was related to the short duration of HAART and not to HAART failure.

Table 2 Immune and viremic status of all 95 patients

	Group 1 (no ART, n = 37)		*Group 2 (double ART, n = 14)*		*Group 3 (PI-HAART, n = 44)*	
	n	*Mean**	*n*	*Mean**	*n*	*Mean**
CD4+ (cells μl^{-1})						
0–200	15	99.60	0		13	82.84
201–500	11	343.45	9	360.1	20	349.10
$>$500	11	725.81	5	658.60	11	720.09
Total	37	358.27	14	556.64	44	363.18
Viral load (copies ml^{-1})						
0–500	1	500	2	500	21	500
501–20 000	16	6298	11	9496	13	6239
$>$20 000	20	216 759	1	48 800	10	93 530
Total	37	119 904	14	10 018	44	23 298
AIDS cases, *n* (%)	18	48.65	4	28.57	29	65.91

*Standard deviation is not shown.

Table 3 Prevalence of oral lesions in the three groups of patients

Oral lesions	*Group 1 (no ART, n = 37)*	*Group 2 (double ART, n = 14)*	*Group 3 (PI-HAART, n = 44)*
POC	9 (24.32)	2 (14.28)	5[a] (11.90[c])
EOC	4 (10.81)	2 (14.28)	3[a] (7.14[c])
OHL	3 (8.1)	2 (14.28)	4 (9.09)
NUG	3 (8.1)		
SGD	2 (5.4)	2 (14.28)	3 (6.81)
IHSV	1 (2.7)		1 (2.27)
VZV		1 (7.14)	
Total[b]	17 (45.95)	7 (50)	16 (36.36[c])

Values are represented as *n* (%).
[a]Two patients with antimycotic prophylaxis were excluded from the evaluation of OC.
[b]Total number of patients with one or more lesions.
[c]Significant reduction of all oral lesions and both forms of OC (Pearson chi-square: 7.00, d.f.: 3, $P < 0.001$) in group 3.
POC, pseudomembranous oral candidiasis; EOC, erythematous oral candidiasis; OHL, oral hairy leukoplakia; NUG, necrotizing ulcerative gingivitis; SGD, salivary gland disease; IHSV, intraoral herpes simplex virus infection; VZV, varicella-zoster virus infection.

Table 2 shows the detailed immune and viremic status of the patients in each group and Table 3 shows the prevalence of oral lesions.

Oral lesions were significantly decreased in the group of patients on PI-HAART as compared with the group of patients without ART (36.36% *vs* 45.95%, $P < 0.001$).

Oral candidiasis, in both pseudomembranous (POC) and erythematous (EOC) forms (Figures 1–3), was the most common lesion in all groups.

The prevalence of OC, both forms, was found significantly decreased in the group of patients on PI-HAART, as compared with the group of patients without ART (19.04% *vs* 35.10%, $P < 0.001$).

Oral lesions were not decreased in group 2 (patients on double ART), as compared with the group 1 (patients without ART), while the reduction of the prevalence of OC observed in group 2, was not significant ($P > 0.001$) when compared with that in

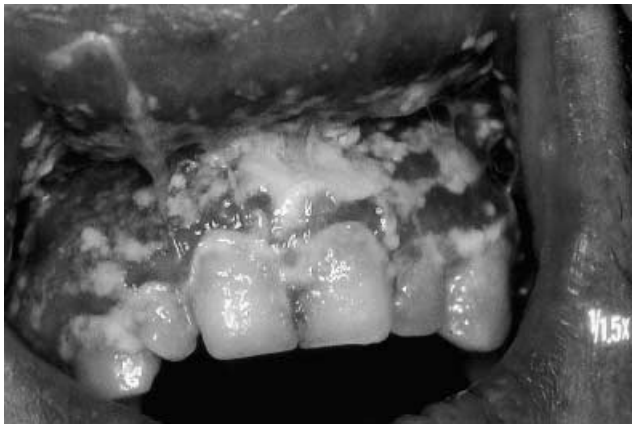

Figure 1 Oral pseudomembranous candidiasis covering all oral mucosa on an HIV infected male, 33 years old, without ART. CD4 = 67 cells μl^{-1}, VL = 10 200 copies ml^{-1}

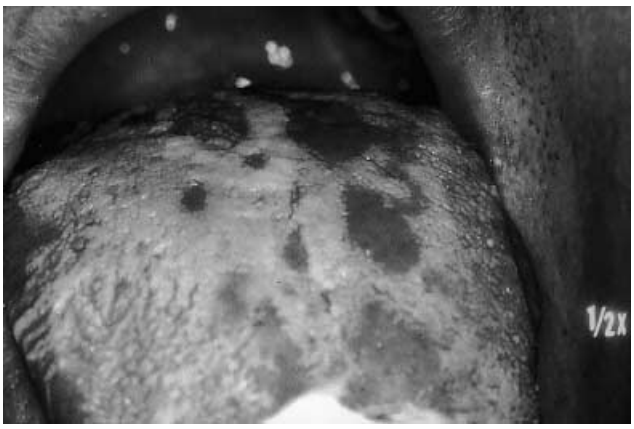

Figure 2 Erythematous candidiasis on the tongue of a newly diagnosed, due to a severe varicella zoster infection, HIV infected male, 37 years old. CD4 = 294 cells μl^{-1}, VL = 192 100 copies ml^{-1}. Concomitant bilateral oral hairy leukoplakia was observed on the tongue

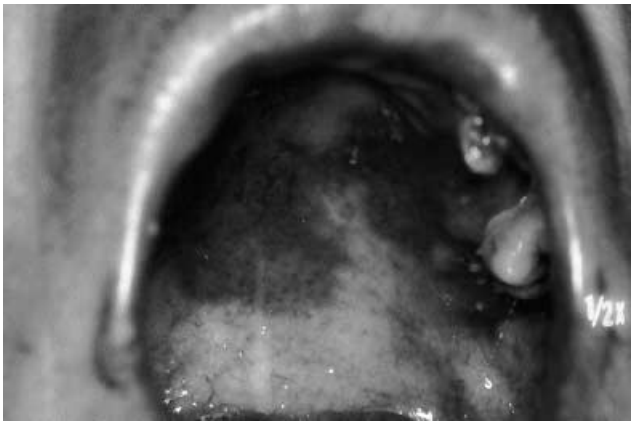

Figure 3 Erythematous oral candidiasis on the palate of a 27-year old HIV infected male, who was receiving PI-HAART. CD4 = 17 cells μl^{-1}, VL = 38 600 copies ml^{-1}. Erythematous candidiasis was also observed on the tongue. Angular cheilitis was seen on the commissures. Patient responded well to antifungal treatment. Interestingly, the patient had come complaining of spontaneous gingival bleeding, which also responded well to antifungal treatment

group 1. Interestingly, the immune and viremic status of the patients in group 2, as is shown in Table 2, is superior to that of patients in both groups 1 and 3.

Oral hairy leukoplakia and SGD did not show any significant change in the different study groups, while no case of NUG was detected in the groups on double therapy and PI-HAART.

Nineteen of all 40 patients with lesions had CD4 counts below 200 cells μl^{-1} and 20 of these 40 patients had VL > 20 000 copies ml^{-1}.

Logistic regression analysis showed that the prevalence of oral lesions was significantly increased in patients with CD4+ counts <200 cells μl^{-1} and VL > 20 000 copies ml^{-1} ($P < 0.001$). In addition, logistic regression analysis showed that the difference of the percentage of patients on PI-HAART, with lesions, and with CD4+ counts <200 cells μl^{-1} and VL > 20 000 copies ml^{-1} (6/16, 37.5%) when compared with the percentage of patients without ART, and with similar immune and viremic status (10/17, 58.8%) was significant ($P < 0.001$).

Mycology

Twenty-four specimens, obtained from all 24 of 25 clinically evaluated *Candida* lesions, were positive for *Candida albicans*. In one case *C. dubliniensis* was concurrently isolated with *C. albicans*, while *C. tropicalis* was a co-isolate in two cases.

No resistance was documented, whereas a low median voriconazole minimum inhibitory concentration of 0.125 $\mu g\ ml^{-1}$ was recorded in all occasions. Dose dependent sensitivity (MIC16 $\mu g\ ml^{-1}$) was recorded for the *C. dubliniensis* isolate and for one *C. albicans* strain. All 25 *Candida* lesions responded to antifungal chemotherapy.

Discussion

In the present study, the prevalence of all oral lesions and of OC, in particular, in patients receiving PI-HAART were significantly reduced when compared with those of patients without ART.

Oral hairy leukoplakia and SGD did not show any significant change, while no case of NUG, a lesion strongly related to poor immune status, was observed in patients on PI-HAART.

The short period of the administration of HAART in the present study and the relatively small number of the study patients may explain the lack of observation of oral warts, as they have been reported by others (Schmidt-Westhausen *et al*, 2000; Greenspan *et al*, 2001). It should be mentioned that PI-HAART was first introduced in Greece in August 1996 and most patients on HAART (80%), in the present study, were receiving it for less than a year.

The reduction of oral lesions, in our study, was mainly attributed to the reduction of OC, which was the dominant lesion in all groups.

Most earlier clinical studies showed a reduced prevalence of oral lesions in patients of HAART therapy (Gripshover *et al*, 1998; Hood *et al*, 1998; Revankar *et al*, 1998; Aguirre *et al*, 1999; Cauda *et al*, 1999; Diz Dios *et al*, 1999; Ceballos-Salobrena *et al*, 2000; Patton *et al*, 2000; Schmidt-Westhausen *et al*, 2000; Greenspan *et al*, 2001; Tappuni and Fleming, 2001; Eyeson *et al*, 2002). Despite large variations in the study design, the immune and viremic status of the study patients, the administration of antifungal prophylaxis in some or all of the study patients, and the type of HAART used, which may include or may not include a PI, agree with the above reduced prevalence of OC and of all oral lesions following the PI-HAART.

As it has been widely, thus far, accepted, that the significant reduction of oral lesions and of OC, can be attributed to the improved immune and viremic status of the patients on PI-HAART, when compared with that of patients without ART. Oral lesions were found significantly related to CD4+ counts <200 cells μl^{-1}

and VL > 20 000 copies ml^{-1}. This was also confirmed in the present study.

However, the lack of reduction of oral lesions and the insignificant reduction of OC observed in patients on double ART, despite their higher mean CD4+ count and the lower mean VL value, when compared with that of patients on PI-HAART, indicate that other factors, besides immune reconstitution, may affect OC prevention and overall oral lesions' reduction in patients on PI-HAART. In addition, the significantly lower percentage of patients on PI-HAART, with lesions, and with CD4+ counts <200 cells μl^{-1} and VL > 20 000 copies ml^{-1} when compared with that of patients without ART, with lesions, and with similar immune and viremic status (given, also, the significant association of oral lesions to CD4 < 200 and VL > 20 000), further denoted, although indirectly, that other factors, besides immune and viremic status, seem to affect the prevalence of oral lesions and OC, in particular.

The above findings indicate that PI-HAART has an *in vivo* limiting effect on oral lesions and OC, in particular, and points, though indirectly, to a beneficial effect of PI on OC control.

Despite recent evidence, from *in vitro* studies, on the absence of a direct effect of saquinavir, ritonavir, nelfinavir and indinavir against *Candida* species (Dostal *et al*, 2003), earlier studies are in agreement with the results of the present study and have shown that PIs exert a direct, early, immune reconstitution-independent effect on *Candida* virulence (Cauda *et al*, 1999; Cassone *et al*, 2002) in the oral cavities of HIV-infected individuals. This is credited to the induction of SAPs by HIV envelope proteins (Gruber *et al*, 1998). Furthermore, HIV virus PIs have been also shown to act *in vitro* against the aspartic proteinase secretor *Pneumocystis carinii*, an infection also controlled in patients under PI-HAART (Atzori *et al*, 2001).

The clinical findings of our patients, evaluated within 1997–1998, during the early period of PI-HAART administration, further support the direct anticandidal effect of PIs shown later by others (Cauda *et al*, 1999; Cassone *et al*, 2002). Both, literature data and the present findings indicate that OC control and the resulting reduction of all oral lesions, exerted by PI-HAART is multifactorial entailing host–*Candida* interactions and PI-HAART–*Candida* interactions. In that respect of PI-HAART–*Candida* interactions, PI-HAART regimen would appear advantageous when compared with PI-sparing HAART. Further studies comparing HIV infected patients receiving PI-HAART with patients receiving PI-sparing HAART would lead to useful observations on that subject.

Candida albicans was isolated from all cases of candidiasis in all three groups of patients. In addition, a 7.5% frequency of mixtures of *Candida* species was observed. This reflected the change from single to multiple *Candida* species isolates, which has been responsible for epidemiological shifts in OC (Odds, 1996). In carriage studies, the reported incidence of mixtures of *Candida* species among seropositive individuals ranges between 15% (Baumgartner, Freydiere and Gille, 1996) to 29% (Schoofs *et al*, 1998). The lower incidence observed in the present investigation could be attributed to the study design, where the clinical material was exclusively obtained from clinically evaluated oral candidal lesions and not from all patients to test for carriage.

In conclusion, oral lesions and candidiasis, in particular, were significantly reduced in patients on PI-HAART, in the present study.

A direct anticandidal effect seemed to have accounted for the reduction of candidiasis and the resulting significant reduction of all oral lesions, in addition to immune reconstitution after the reduction of viral burden.

Candidiasis, although not as extensive, continued to be the most common oral lesion in patients on PI-HAART, as in patients on double therapy and in patients without ART. *Candida albicans* was the dominant species isolated.

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