

# The effect of highly active antiretroviral therapy on the prevalence of oral manifestation in human immunodeficiency virus-infected patients in Karnataka, India

Neelkant Patil<sup>1</sup>, Vishwajit Rampratap Chaurasia<sup>2</sup>, Prashant Babaji<sup>3</sup>, Dnsv Ramesh<sup>4</sup>, Kshitij Jhamb<sup>5</sup>, Akanksha Manmohan Sharma<sup>6</sup>

<sup>1</sup>Department of Oral Medicine, Vyas Dental College, Jodhpur, Rajasthan, India,

<sup>2</sup>Department of Conservative Dentistry and Endodontics, KLE Dental College, Belgaum, Karnataka, India,

<sup>3</sup>Department of Pedodontics, Vyas Dental College, Jodhpur, Rajasthan, India,

<sup>4</sup>Department of Oral Medicine and Radiology, AME'S Dental College and Hospital, Raichur, Karnataka, India,

<sup>5</sup>Department of Oral and Maxillofacial Surgery, Indraprasthaal College, Haryana, India,

<sup>6</sup>BDS Student, KLE Dental College, Belgaum, Karnataka, India

**Correspondence:** Dr. Prashant Babaji  
Email: babajipedo@rediffmail.com

## ABSTRACT

**Objectives:** Acquired Immunodeficiency Syndrome (AIDS) is a highly lethal, progressively epidemic viral infection characterized by profound impairment of the immune system. Oral manifestations are common in Human Immunodeficiency Virus (HIV) infected AIDS patients, and are usually the first indicator of symptom and disease progression. The main objective of the current study was to compare the prevalence of oral manifestations in HIV patients on Highly Active Antiretroviral Therapy (HAART) with those, not on HAART therapies. **Materials and Methods:** A cross sectional study was conducted among 100 patients diagnosed as human immune virus sero-positive. These patients were divided equally into two groups (50 each); Group I patients on HAART and Group II patients who were not on HAART. Information regarding age, sex and cluster of differentiation 4 cell count was obtained from the medical records. Oral examination was done, and findings were recorded by using internationally accepted presumptive clinical criteria. Statistical analysis was performed using Chi-square statistical test. **Results:** The presence of oral manifestations was significantly decreased in subjects on HAART (32%) compared to those who are not on HAART (56%). The most common oral lesions detected in patients on HAART were increased oral hyper-pigmentation (14%), recurrent aphthous stomatitis (8%), non-specific ulcerations (4%), pseudo-membranous candidiasis (2%), periodontitis (2%) and xerostomia (2%), whereas in non HAART oral hyperpigmentation (10%), pseudo-membranous candidiasis (8%), angular cheilitis (4%), and erythematous candidiasis (4%) and Periodontitis (14%) were more prevalent. **Conclusion:** The number and severity of oral manifestation decreased, and even there was a change in the type of oral manifestations on HAART, which may be because of the improvement in immunity gained by the therapy.

**Key words:** Cluster of differentiation 4 cell, highly active antiretroviral therapy, immunodeficiency virus/acquired immunodeficiency syndrome, oral manifestations

**How to cite this article:** Patil N, Chaurasia VR, Babaji P, Ramesh D, Jhamb K, Sharma AM. The effect of highly active antiretroviral therapy on the prevalence of oral manifestation in human immunodeficiency virus-infected patients in Karnataka, India. *Eur J Dent* 2015;9:47-52.

Copyright © 2015 Dental Investigations Society.

DOI: 10.4103/1305-7456.149640

## INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is an infectious disease caused by Human Immunodeficiency Virus (HIV) and it is a highly lethal, progressively epidemic viral infection characterized by profound impairment of the immune system that leads to opportunistic infections and secondary neoplasm.<sup>[1]</sup> According to World Health Organization (WHO) 2008 report, around 33.8 million people are living with AIDS worldwide of which around 3.8 million are in India.<sup>[2]</sup> According to WHO, an estimated 36 million people have died since, the first cases were reported in 1981, and 1.6 million people died of HIV/AIDS in 2012. According to WHO, in 2012, an estimated 2.3 million individuals worldwide were newly infected with HIV.<sup>[3]</sup> India carries the third largest number of HIV infected patients in the world after South Africa and Nigeria.<sup>[4]</sup> Clinical features in HIV infection ranges from asymptomatic to severe clinical illness and immunodeficiency.<sup>[2]</sup>

Mouth is a mirror of systemic problems. The occurrence of oral manifestations is favored by immune deterioration.<sup>[4]</sup> Oral manifestations are seen in 30-80% of HIV patients. HIV infection presents oral problems like; oral candidiasis, hairy leukoplakia, ulcers, pigmentations, etc. Hence, early identification of oral findings is helpful in early diagnosis, and monitoring of patients with HIV infection. Oral manifestations suggest a decrease in cluster differentiated (CD) count with increased viral load.<sup>[2]</sup> According to the new classification given by Center for Disease Control and Prevention (CDC), clinical AIDS is defined by a CD4 count of <200 and/or a CD4 <14%.<sup>[5]</sup> HIV is a retro virus, which has a specific affinity for CD4 cells (T helper cells).<sup>[1]</sup> CD4 count helps in evaluating disease diagnosis, progression, prognosis and making decision for antiretroviral therapy (ART).<sup>[2,6]</sup> Oral manifestations may be used as an alternative to CD4 counts at field based settings for diagnosis of HIV infected individuals. Oral manifestations can be easily detected by a trained clinician, and it is an inexpensive for diagnostic technique.<sup>[1]</sup>

Effective HIV prevention interventions have been proven to reduce HIV transmission. New treatment regimen using ART and HAART have shown promising results in HIV patients.<sup>[7]</sup> Hence the present study was undertaken to assess the effectiveness of HAART medication on HIV infected individuals to reduce oral lesions, and to improve the quality of life.

The main objectives of the current study were;

- To determine the prevalence of oral manifestations in HIV patients on HAART, and to compare with the prevalence in patients not on HAART.

To assess the most common oral lesion in the study groups.

To investigate the relationship between the prevalence of oral diseases with systemic marker of HIV infection progression namely, CD4 cell count.

## MATERIALS AND METHODS

### Source of data

Totally 100 patients diagnosed with HIV disease were selected from out patient department of P. M. Nadagouda Memorial Dental College and Hospital Bagalkot, Karnataka, India; and patients from non-governmental organization (NGO) centers working for HIV/AIDS, Bagalkot, Karnataka, India.

### Method of collection of data

A cross-sectional study was conducted among 100 patients diagnosed as HIV sero-positive. The laboratory investigation and confirmation of patients with HIV was done by western blot and tridot test in NGO center Bagalkot, Karnataka, India after pre-test counseling of the individuals. Relevant information including CD4 cell count and age/sex was obtained from the medical records. Ethical clearance about the study was obtained from institutional review board and informed consent from patients. Most common route of transmission of HIV in these selected patients was heterosexual route. HIV infected patient who were on any anti-tubercular, antifungal or HAART medications were excluded from the study. Selected HIV infected patients were divided into two groups. Group I consisted of 50 patients who were taking ART (Drugs includes; abacavir, efavirenz and ritonavir) and Group II consisted of 50 subjects who were not taking ART. Monotherapy or dual therapy was not applied.

Detailed history and physical examination was done for each patient at first visit. Specific oral examination for both the groups was done as per universal precautions recommended by CDC and trained single investigator, i.e. dentist in NGO center of Bagalkot, Karnataka, India. Findings were recorded by using internationally accepted presumptive clinical criteria of erythematous candidiasis (EC)-clearing

house (European Community) on oral problems related to HIV infection and WHO collaborating center on oral manifestations of the immunodeficiency virus.<sup>[4]</sup> Chi-square test was used to identify the statistical difference between HAART status and prevalence of oral lesions and between oral lesion prevalence and CD4 count.

## RESULTS

Out of 100 HIV sero-positive patients, 50 patients, who were on highly active ART (HAART) in that 32 were males (64%) and 18 were females (36%) and in non-HAART, 24 were males (48%) and 26 females (52%). The mean age of patients in the group on HAART was 35.16 compared to the group not on HAART 29.72. The prevalence of oral manifestations was 32% (16 of 50) in patients on HAART compared with 56% (28 of 50) in the second group [Table 1]. This difference was statistically significant ( $P < 0.05$ ) when the Chi-square test was used.

The CD4 cell count was available for all the patients in both study groups. The mean CD4 cell count for patients on HAART was 303.68, and non-HAART was 258.82, which was statistically significant ( $P < 0.05$ ) [Table 3]. The most common oral lesions detected in patients in study (Group I) group were recurrent aphthous stomatitis (8%), non-specific ulcerations (4%), pseudo-membranous candidiasis (2%), where as

in patient not on HAART pseudo-membranous candidiasis (8%) [Figure 1], angular cheilitis (4%), and erythematous candidiasis (4%) were more prevalent [Table 2]. In patients on HAART, the CD4 cell count was more, and the prevalence of oral manifestation was less as compared to non-HAART suggesting an inverse relationship between CD4 cell count and the prevalence of oral manifestation. One of the most common oral findings in our study was increased oral hyper-pigmentation (14%) in patients on HAART group compared to those, not on HAART (10%) [Figure 2 and Table 2]. Another significant finding in our study was the increased prevalence of periodontal disease in patients not on HAART (14%) as compared to patients on HAART (2%). Xerostomia (2%) was observed in patients on HAART group.

## DISCUSSION

Human immunodeficiency virus infection results in AIDS, which is a major global pandemic infectious disease. Some specific, common oral manifestations in HIV infection were found in association with immune suppression.<sup>[1]</sup> The present study is unique since, it covers oral manifestations of HIV patients on HAART and non HAART group with CD4 count since such a study in India is sparse.

The target of HIV is on CD4 cell count. Progressive reduction in CD4 cell count results into



Figure 1: Oral candidiasis



Figure 2: Angular cheilitis and oral hyper-pigmentation

Table 1: Prevalence of oral manifestations in HAART and non-HAART cohort						
Oral manifestations	Non-HAART	Percentage	HAART	Percentage	Total	Percentage
Without	22	44.0	34	68.0	56	56.0
With	28	56.0	16	32.0	44	44.0
Total	50	100.0	50	100.0	100.0	100.0

$\chi^2=5.8440$ , Degrees of freedom=1,  $P<0.05$ . \*HAART: Highly active antiretroviral therapy

**Table 2: Prevalence of oral manifestations in HAART and non-HAART groups**

Oral manifestations	HAART group in %	Non-HAART group in %
Oral manifestations	32	56
Hyper pigmentations	14	10
Aphthous stomatitis	8	9
Nonspecific ulcer	4	7
Pseudomembranous candidiasis	2	8
Erythematous candidiasis	00	4
Periodontitis	2	14
Angular cheilitis	00	4
Xerostomia	2	00

**Table 3: Comparison between on HAART and non-HAART cohort with respect to CD4 count**

Group	Mean	SD	T	P	Significance
HAART	303.6800	96.0505	3.0451	<0.05	S
Non-HAART	258.8200	40.3215		0.0030	

\*HAART: Highly active antiretroviral therapy, SD: Standard deviation

immunosuppression and related disorders. The CD4 count is an important investigation in the diagnosis of HIV and its stages and also helps in clinical monitoring and making decision about initiating ART or chemoprophylaxis. CD4 counts alone should not be the basis for taking decision on initiating ART.<sup>[6]</sup> Throughout the course of the disease, the total T-cell levels remain fairly constant despite a fall in CD4 cell count due to the compensatory rise in CD8 cells.<sup>[4]</sup>

In the present study, the mean CD4 cell count for patients on HAART was 303.68 and non-HAART was 258.82, which is statistically significant ( $P < 0.05$ ) [Table 3], which showed that HAART treatment improves the health status of HIV patients and it is in agreement with studies by Umadevi *et al.* (2007) and Bodhade *et al.* (2011).<sup>[1,8]</sup> Bodhade *et al.* 2011 found that CD4 count significantly correlated with oral candidiasis.<sup>[1]</sup> In patients on HAART, the CD4 cell count was more, and the prevalence of oral manifestation was less as compared to non-HAART suggesting an inverse relationship between CD4 cell count and the prevalence of oral manifestation.<sup>[9]</sup>

We observed 44% of cases with oral manifestations (out of 100 patients in both HAART and non-HAART groups) [Table 1] whereas 80.6% of oral manifestations was observed by Sharma *et al.* (2011), 80% by Annapurna *et al.* (2012), 61.9% by Adebola *et al.* (2012), 45.2% by Eweka *et al.* (2012), 76% by Shrimali *et al.* (2010) and 86% by Kroidl *et al.* (2005).<sup>[2,4,10-13]</sup> Adebola *et al.* (2012) found at least

one oral lesion in 21.0% cases and 43.8% with multiple oral lesions.<sup>[11]</sup> Present study showed that prevalence of oral manifestations was more in non-HAART group (56%) as compared to HAART group (32%) which is statically significant ( $P < 0.05$ ) [Table 1], similar response was observed by Sharma *et al.* (78% with ART and 82% without ART group).<sup>[4]</sup> Reduction in oral lesion following HAART therapy was observed by Hodgson *et al.* (10-50% in 2006), Tappuni *et al.* (2001), and Hamza *et al.* (2006).<sup>[9,14,15]</sup> Tappuni *et al.* (2001) observed decrease in oral lesions with dual therapy or triple therapy.<sup>[9]</sup> Eweka *et al.* (2012) observed 84% reduction in oral lesions following 3 months HAART therapy.<sup>[12]</sup> Tiawa *et al.* (2010) concluded that, HAART has different clinical effects on HIV depends on size and duration of treatment.<sup>[16]</sup> The most common oral lesions detected in patients in study (Group-I) group were recurrent aphthous stomatitis (8%), non-specific ulcerations (4%), pseudo-membranous candidiasis (2%), where as in patient not on HAART pseudo-membranous candidiasis (8%), angular cheilitis (4%), and erythematous candidiasis (2%) were more prevalent [Table 2].

One of the common oral findings in our study was increased oral hyper-pigmentation (14%) [Table 2] in patients on HAART compared to those not on HAART (10%), increased hyper pigmentation could be due to HAART medication. This is similar to studies by Umadevi *et al.* (2007) with 43.8% in the HAART group and 14.8% in the non-HAART group, Sharma *et al.* with 40.5% in ART, 23%, 6.1% and 32.8% by Ranganathan *et al.* in 2008 and 2010 respectively, 66.7% and 10.8% by Eweka (2012) *et al.*, 46% and 28% by Nittayananta (2009), 6.2% and 3.9% by Hamza *et al.* in HAART and no HAART groups respectively, and 33.5% by Sharma *et al.*, 28% by Annapurna *et al.*, 8.5% by Tiawo *et al.* and 19.5% by Bodhade *et al.*<sup>[1,4,8,9,12,15-20]</sup>

The relationship between the presence of oral lesions such as oral candidiasis and the depleted immune system has been documented and accepted. In our study, there was 8% pseudomembranous candidiasis (PC), 4% EC, in non-HAART group and only 2% PC in HAART group. Sharma *et al.* (2006) observed 44% erythematous candidiasis, and 10.5% PC.<sup>[17]</sup> Umadevi *et al.* in 2007 observed 4% and 18% PC in HAART and non-HAART groups respectively and oral candidiasis was 5.6% in the HAART group and 39.1% in the non-HAART groups.<sup>[8]</sup> Similarly, Sharma *et al.* observed 35.7% EC, 7.1% PC in ART and 41% EC, 9.8% PC in non-ART group.<sup>[4]</sup> Nittayanantha *et al.*, Hamza *et al.* and Eweka

*et al.* observed reduction in oral lesions and oral candidiasis following HAART therapy for long term duration.<sup>[12,15,20]</sup> 23.5% oral candidiasis observed by Hamza *et al.* (2006), 22.4% by Tiawo *et al.* (2010) and 47.7% by Eweka *et al.* (2012).<sup>[12,15,16]</sup> Adebola *et al.* observed candidiasis as most common oral lesion (79.1%) with reduced oral lesion (61.9%) using HAART therapy.<sup>[11]</sup> Ranganathan *et al.* in 2008 observed 33% PC as most common oral lesion and 14% EC.<sup>[18]</sup> Similarly oral candidiasis was noted by Ranganathan *et al.* (in 2010 with 56%), Annapurna *et al.* (54%), Shrimali (72%), Shobhana *et al.* (36%), Eyeson *et al.* (4.9%) and Bodhade *et al.* (39%).<sup>[1,2,10,19,21,22]</sup>

We found 16% and 12% ulcerative lesions (aphthous, nonspecific ulcers) in non-HAART and HAART groups respectively. In the present study, ulcerative lesions are more prevalent that was not observed in earlier studies. Oral ulcerative lesions were observed by, Ranganathan *et al.* (3%), Ranganathan *et al.* (in 2012 with 4.2%).<sup>[18,19]</sup> We recorded 4% and 2% angular chelosis in non-HAART and HAART groups respectively. Angular chelosis was also recorded by Shobhana *et al.* (1%), Sharma *et al.* (4.8%, and 6.6% in ART and non-ART group respectively).<sup>[4,21]</sup> Nittayanantha *et al.* (3-1%) and Hamza *et al.* (1.54-0.4%) found reduction in aphthous ulcers following HAART treatment.<sup>[15,20]</sup>

The prevalence of periodontal disease was (14%) more in non-HAART compared to HAART group (2%). Similarly, periodontal findings were recorded by Shrimali (2% necrotic periodontitis), Shobhana *et al.* (1% periodontal abscess), 5.3% by Bodhade, 9% by Ranganathan (2008), 9.9% by Eyeson *et al.* (2002), 30.2% by Kroidl *et al.* (2005).<sup>[1,2,13,18,21,22]</sup> Xerostomia (2%) was observed in patients on HAART group in our study due medication. Tiawa *et al.* observed 3.5% of xerostomia case in their study.<sup>[16]</sup>

Other oral problems such as gingivitis, oral hairy leukoplakia, herpes zoster, herpes simplex, squamous carcinoma, oral kopasi sarcoma, enlarged parotid gland, hodkin's lymphoma, xerostomia can be found in HIV patients in different degree, depends on severity and staging.<sup>[1,2,10,11,12,15,19,21,22]</sup> Nittayananta *et al.* (2009) observed greater risk of having orofacial pain, oral dryness in non-HAART group and significantly decreased unstimulated and stimulated saliva in HAART group as compared to non-HAART group.<sup>[20]</sup>

The present study demonstrated that in south India, generic HAART was safe effective and relatively

well tolerated on adult patients. Individuals, who were on HAART therapy had a significant rise in CD% and CD4 cell count with decrease oral lesions. Highly active antiretroviral treatment has decreased morbidity and mortality of people living with HIV/AIDS in Australia, Europe and Northern America. However, the vast majority of the people living with HIV/AIDS in developing countries do not have access to comprehensive HIV/AIDS care and to antiretroviral treatment in particular.<sup>[23]</sup>

### Limitations in the study

The study group was restricted to Bagalkot district not entire state or country. Only adult group was included not adolescent or children. The small sample size was not valuable enough to reiterate the important role of oral lesions, as diagnostic and disease progression markers and a tool in monitoring the efficacy of treatment for HIV.

## CONCLUSION

Acquired immunodeficiency syndrome is an infectious disease characterized by profound immunosuppressant leading to opportunistic infections. Oral manifestations are common in HIV infected patients, and are usually first indicator symptom and disease progression. Our results showed that the number of oral manifestation decreased with HAART. Further large cross-sectional and longitudinal observational studies are required to evaluate the prevalence of oral lesions need to be done, including less common manifestations.

## REFERENCES

1. Bodhade AS, Ganvir SM, Hazarey VK. Oral manifestations of HIV infection and their correlation with CD4 count. *J Oral Sci* 2011;53:203-11.
2. Shrimali L. A study of oral manifestation of HIV/AIDS. *Int J Oral Maxillofac Path* 2010;1:8-12.
3. AIDS. Available from: <http://www.aids.gov/federal-resources/around-the-world/global-aids-overview>. [Last assessed on 2014 May 14].
4. Gaurav S, Keerthilatha PM, Archana N. Prevalence of oral manifestations and their association with CD4/CD8 ratio and HIV viral load in South India. *Int J Dent* 2011;2011:964278.
5. Castro KG, Ward JW, Slutsker L, Buehler JW, Jaffe HW, Berkelman R, *et al.* 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Clin Infect Dis* 1993;17:802-10.
6. Ghate MV, Mehendale SM, Mahajan BA, Yadav R, Brahme RG, Divekar AD, *et al.* Relationship between clinical conditions and CD4 counts in HIV-infected persons in Pune, Maharashtra, India. *Natl Med J India* 2000;13:183-7.
7. Hoffmann C, Kamps BS. *HIV Medicine* 2003. Paris: Flying Publisher; 2003. p. 15-8.
8. Umadevi KM, Ranganathan K, Pavithra S, Hemalatha R, Saraswathi TR, Kumarasamy N, *et al.* Oral lesions among persons with HIV disease with and without highly active antiretroviral therapy in southern India. *J Oral Pathol Med* 2007;36:136-41.
9. Tappuni AR, Fleming GJ. The effect of antiretroviral therapy on the

- prevalence of oral manifestations in HIV-infected patients: A UK study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;92:623-8.
10. Annapurna CS, Prince CN, Sivaraj S, Ali IM. Oral manifestations of HIV patients in South Indian population. *J Pharm Bioallied Sci* 2012;4:S364-8.
  11. Adebola AR, Adeleke SI, Mukhtar M, Osunde OD, Akhiwu BI, Ladeinde A. Oral manifestation of HIV/AIDS infections in paediatric Nigerian patients. *Niger Med J* 2012;53:150-4.
  12. Eweka OM, Agbelusi GA, Odukoya O. Prevalence of oral lesions and the effects of HAART in adult HIV patients attending a tertiary hospital in Lagos, Nigeria. *Open J Stomatol* 2012;2:200-5.
  13. Kroidl A, Schaeben A, Oette M, Wettstein M, Herfordt A, Häussinger D. Prevalence of oral lesions and periodontal diseases in HIV-infected patients on antiretroviral therapy. *Eur J Med Res* 2005;10:448-53.
  14. Hodgson TA, Greenspan D, Greenspan JS. Oral lesions of HIV disease and HAART in industrialized countries. *Adv Dent Res* 2006;19:57-62.
  15. Hamza OJ, Matee MI, Simon EN, Kikwilu E, Moshi MJ, Mugusi F, *et al.* Oral manifestations of HIV infection in children and adults receiving highly active anti-retroviral therapy [HAART] in Dar es Salaam, Tanzania. *BMC Oral Health* 2006;6:12.
  16. Taiwo OO, Hassan Z. The impact of highly active antiretroviral therapy (HAART) on the clinical features of HIV-related oral lesions in Nigeria. *AIDS Res Ther* 2010;7:19.
  17. Sharma G, Pai KM, Suhas S, Ramapuram JT, Doshi D, Anup N. Oral manifestations in HIV/AIDS infected patients from India. *Oral Dis* 2006;12:537-42.
  18. Ranganathan K, Reddy BV, Kumarasamy N, Solomon S, Viswanathan R, Johnson NW. Oral lesions and conditions associated with human immunodeficiency virus infection in 300 south Indian patients. *Oral Dis* 2000;6:152-7.
  19. Ranganathan K, Geethalakshmi E, Krishna Mohan Rao U, Vidya KM, Kumarasamy N, Solomon S. Orofacial and systemic manifestations in 212 paediatric HIV patients from Chennai, South India. *Int J Paediatr Dent* 2010;20:276-82.
  20. Nittayananta W, Talungchit S, Jaruratanasirikul S, Silpapojakul K, Chayakul P, Nilmanat A, *et al.* Effects of long-term use of HAART on oral health status of HIV-infected subjects. *J Oral Pathol Med* 2010;39:397-406.
  21. Shobhana A, Guha SK, Neogi DK. Mucocutaneous manifestations of HIV infection. *Indian J Dermatol Venereol Leprol* 2004;70:82-6.
  22. Eyeson JD, Tenant-Flowers M, Cooper DJ, Johnson NW, Warnakulasuriya KA. Oral manifestations of an HIV positive cohort in the era of highly active anti-retroviral therapy (HAART) in South London. *J Oral Pathol Med* 2002;31:169-74.
  23. Nawaz T, Narain JP. *Emanuele pontal. The Use of Antiretroviral Therapy: A Simplified Approach for Resource-Constrained Countries.* Sea-AIDS. New Delhi, India: WHO-Searo; 2002. p. 133.

Access this article online	
<p><b>Quick Response Code:</b></p> 	<p><b>Website:</b> www.eurjdent.com</p>
<p><b>Source of Support:</b> Nill. <b>Conflict of Interest:</b> None declared</p>	