Ocular Problems in Brazilian Patients With AIDS Before and in Highly Active Antiretroviral Therapy (HAART) Era

Marcia Lopes Rodrigues[1], Maria de Lourdes Veronese Rodrigues[2], José Fernando de Castro Figueiredo[3] and João Alberto Holanda de Freitas[4]

[1]Graduate Program of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery; [2]Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery; [3]Division of Infectious and Tropical Diseases/Department of Internal Medicine; School of Medicine of Ribeirão Preto, University of São Paulo; Ribeirão Preto, SP; [4]Sorocaba Hospital Complex/PUC-SP, Holanda de Freitas Clinic; Campinas, SP, Brazil

This study determined the total frequency of patients with AIDS and ophthalmologic problems before and after the introduction of combined highly active antiretroviral therapy (HAART), regardless of the use of this treatment; it also determined the frequency of external ocular diseases, intraocular infections and inflammations, and problems of the anterior portion of the optic nerve in these two groups of patients; and it determined the differences in the frequency of ophthalmologic problems in patients receiving HAART or not. This was a retrospective study of 207 patients examined using the same protocol, from June 1995 to February 1998 (n=58, pre-HAART era) and from March 1998 to May 2005 (n=149, HAART era). The frequency of ophthalmologic problems was significantly higher in the pre-HAART group, with a predominance of intraocular infections and inflammations. Comparison of patients receiving HAART or not revealed that ocular involvement tended to be reduced in the treated group and that treatment was effective in preventing infectious diseases; however, the prevalence of external ocular diseases was similar in the patients receiving HAART or not. As a consequence of HAART, we observed a reduction in the frequency of ocular problems, especially intraocular infections and inflammations. However, this benefic influence was less important in the ocular surface or in external ocular disease.

Key-Words: Ocular problems, AIDS, HAART.

Since the appearance of acquired immunodeficiency syndrome (AIDS), ophthalmologic problems and diseases associated with it have been reported, including alterations of the ocular surface, opportunistic infections, inflammations, and neurological problems [1-9].

With introduction of highly active antiretroviral therapy (HAART), changes in the frequency and type of ocular manifestations have occurred, with emphasis on the reduction of opportunistic infections [10-19] and on the onset of immune recovery uveitis [20-23].

In Brazil, investigators of the Federal University of São Paulo compared the profile of ophthalmologic problems of 200 patients attended at the uveitis/AIDS sector over a period of 1 year with the profile of patients studied in two previous investigations [6,8] and observed that during the post-HAART period there was a tendency to a reduction of the number of patients with cytomegalovirus retinitis and to an increase of patients with normal ophthalmologic examinations [13].

Since patients with AIDS, in addition to living with a serious and potentially fatal disease, have other types of suffering and limitations, including visual involvement, it is important to introduce appropriate preventive and curative measures in the different services. Then, it is important to determine the profile of ocular problems observed in ophthalmology services that provide care for patients with AIDS.

The objectives of the present study were: 1) to determine the total frequency of patients with AIDS and with ophthalmologic problems before and in HAART era, in Sorocaba region (geographical center located at 23.31S, 47.27W); 2) to determine the differences in the frequency of external ocular diseases, intraocular infections and inflammations, and problems of the anterior portion of the optic nerve in these two groups; 3) to determine the differences in the frequency of ophthalmologic problems in patients receiving HAART or not.

Materials and Methods

A retrospective study was conducted on patients with AIDS diagnosed according to current criteria [24].

The study was conducted at the Hospital Complex of Sorocaba/PUC-SP and at the Votorantim Specialties Center/SP. Patients of both genders aging 18 years or older with a laboratory confirmation of HIV infection by ELISA and Western blot were included. The authors analyzed the medical records of 207 patients examined according to the same protocol, which included ectoscopy and indirect binocular ophthalmoscopy performed by one of the authors. Only the first ophthalmologic exam of each participant was considered and the patients were divided into two groups.

Group 1 (Pre-HAART Era)

Fifty-eight patients examined from June 1995 to February 1998, 39 men and 19 women ranging in age from 19 to 46 years (median=30), 39 of them caucasoids, 10 mulattos and 9 blacks. Nine of these patients received HAART.

Received on 11 July 2006; revised 6 December 2007.

Address for correspondence: Dr. Maria de Lourdes Veronese Rodrigues. Hospital das Clínicas – Oftalmologia, 12 andar – Campus USP. Zip code: 14048-900 – Ribeirão Preto – SP. E-mail: mdlvrodr@fmrp.usp.br. Phone: 55-16-36022523. FAX – 55-15-36022860. Financial support: CAPES.

Group 2 (HAART Era)

One hundred and forty-nine patients examined from March 1998 to May 2005, 97 men and 52 women ranging in age from 18 to 51 years (median=30), 97 of them caucasoids, 26 mulattos, and 26 blacks. Seventy-seven of these patients received HAART.

The CD_4^+ cells count of the two groups were significantly different (Group 1: median 27.5, ranging from 6 to 581; Group 2: median 78, ranging from 8 to 880; $p < 0.05$).

For the analysis of the influence of to be using HAART on the profile of ocular problems, the patients were allocated to other two groups, one consisting of Group 1 and Group 2 patients who had not received HAART (n=121) and the other consisting of Group 1 and Group 2 patients who was receiving HAART (n=86).

For statistical analysis, the ophthalmologic alterations were divided into external ocular problems/diseases, intraocular infections/inflammations, and problems of the anterior segment of the optic nerve. Data were analyzed by the chi-square test with Yates correction and, when one of the numbers was less than 5, by the two-tailed exact Fisher test.

Results

Considering both Groups (I and II), 107 individuals presented ophthalmologic diseases. The distribution of ophthalmologic problems among these individuals [48 (82.75%) from Group 1 and 59 (39.59%) from Group 2] is presented in Table 1.

Table 2 shows the frequency of individuals with ocular involvement according to the groups of problems/diseases and to the group to which they belonged.

The distribution of ocular problems according to the use or not of HAART is presented in Table 3.

Table 4 shows the frequency of individuals with ocular involvement according to the grouping of problems/diseases and the use of HAART.

Discussion

The introduction of HAART changed the incidence profile of ocular diseases associated to AIDS, in consequence of its benefic effects in restoration of the immune function. In the population of the present study this profile also changed, with decreasing in the frequency of infections and inflammations of the internal layers of the eye.

Considering the total frequency of ocular problems and of cytomegalovirus retinitis in particular, our results were similar to the ones reported by Arruda, Muccioli and Belfort Jr., in São Paulo city [13]. However, the type and frequency of other ocular diseases were different. Despite the fact of these studies have been carried out in southeast region of Brazil, the epidemiological profiles of the patients with AIDS were different [25].

Cytomegalovirus retinitis was the most frequent ocular disease in the group of patients researched in the pre-HAART period. It was expected, considering the low CD_4^+ cells count (median 27,5) among the patients and the prevalence of cytomegalovirus in southeast of Brazil [26,27]. In the second position is toxoplasmosis retinitis. *Toxoplasma gondii* infection is also frequent in São Paulo State and the ocular manifestation is a consequence of the reactivation of an infection acquired before AIDS [26].

In HAART era, the number of infections/inflammations decreased and the most prevalent ocular problem was *keratoconjunctivitis sicca*, supporting the results of a study carried out in the same region [28].

Considering the groups pre and post HAART, as expected, the advent of HAART had a stronger preventive effect against

Table 1. Ocular problems/diseases in patients with AIDS before and in HAART era (Sorocaba, SP; June 1995-February 1998 / March 1998 – May 2005)

Problems/Diseases	Pre HAART (N=58)		HAART era (N=149)	
	N	%	N	%
External ocular problems				
Blepharitis	0	0	7	4.70
Keratoconjunctivitis sicca	3	5.17	23	15.35
Conjunctivitis	1	1.72	8	5.37
Episcleritis	0	0	3	2.01
Intraocular infections/inflammations				
Chorioretinitis due to toxoplasmosis	10	17.24	5	3.35
Iridocyclitis	6	10.34	1	0.67
Cytomegalovirus retinitis	20	34.48	11	7.38
Herpes virus retinitis	3	5.17	1	0.67
Anterior segment of the optic nerve				
Optic atrophy	2	3.44	0	0
Papilledema	3	5.17	0	0
Total with ocular problems/diseases	48	82.75	59	39.60
Total without ocular problems/diseases	10	17.25	90	60.40

Table 2. Frequency of ocular involvement according to the groups of problems/diseases before and in the HAART era (Sorocaba, SP; June 1995-February 1998 / March 1998 – May 2005)

Problems/Diseases	Pre HAART (N=58)		HAART era (N=149)		p
	N	%	N	%	
External ocular	4	6.89	41	27.51	0.002
Intraocular infections/inflammations	39	67.24	18	12.08	0.000
Anterior segment of the optic nerve	5	8.62	8	0	0.001
Total with ocular problems/diseases	48	82.75	59	39.60	0.000
Total without ocular problems/diseases	10	17.25	90	60.40	

Table 3. Frequency of ocular problems/diseases before the study according with the use, or not, of HAART (Sorocaba, SP; June 1995-February 1998 / March 1998 – May 2005)

Problems/Diseases	Not using HAART (N=121)		Using HAART (N=86)	
	N	%	N	%
External ocular problems				
Blepharitis	3	2.48	4	4.65
Keratoconjunctivitis sicca	13	10.74	13	15.12
Conjunctivitis	4	3.30	5	5.81
Episcleritis	1	0.83	2	2.33
Intraocular infections/inflammations				
Chorioretinitis due to toxoplasmosis	12	9.92	3	3.49
Iridocyclitis	7	5.78	0	0.00
Cytomegalovirus retinitis	21	17.35	10	11.63
Herpes virus retinitis	4	3.31	0	0
Anterior segment of the optic nerve				
Optic atrophy	2	1.65	0	0
Papilledema	3	2.48	0	0
Total with ocular problems/diseases	70	57.85	37	43.02
Total without ocular problems/diseases	51	42.15	49	56.98

Tabela 4. Frequency of ocular involvement according to the groups of problems/diseases and the use, or not, of HAART (Sorocaba, SP; June 1995-February 1998 / March 1998 – May 2005)

Problems/Diseases	Not using HAART (N=121)		Using HAART (N=86)		p
	N	%	N	%	
External ocular	21	17.35	24	27.91	0.10
Intraocular infections/inflammations	44	36.36	13	15.12	0.001
Anterior segment of the optic nerve	5	4.13	0	0.00	0.07
Total with ocular problems/diseases	70	57.85	37	43.02	0.05
Total without problems/diseases	51	42.15	49	56.98	

the development of opportunistic infections than against external ocular diseases. However, despite the tendency to a decrease, we are still observing ocular problems in patients using HAART. Many patients remain having the diagnosis in late stages of immunodeficiency and, as a consequence, late access to HAART. In this situation, the immune recovery is not immediate, being the patient susceptible to infectious complications during a long period of time, after the beginning of treatment. Other possible reason might be individual differences in susceptibility to specific infections, e.g. CMV retinitis [27,29,30,31].

It is also important to mention the occurrence of immune recovery uveitis during the follow-up in two of our patients using HAART. This fact was not reported in the results, because, for the present study, we only considered the first ophthalmic examination.

Conclusion

As a consequence of HAART, we observed a reduction in the frequency of ocular problems, especially intraocular infections and inflammations. However, this benefic influence was less important in the ocular surface or in external ocular disease.

References

1. Holland G.N., Gottlieb M.S., Yee R.D., et al. Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. Am J Ophthalmol **1982**;93:393-402.
2. Palestine A.G., Rodrigues M.M., Macher A. M., et al. Ophthalmic involvement in acquired immunodeficiency syndrome. Ophthalmology **1984**;91:1092-9.
3. Humphty R.C., Weber J.N., Marsh R.J. Ophthalmic findings in a group of ambulatory patients infected by human immunodeficiency virus (HIV): a prospective study. Br J Ophthalmol **1987**;71:565-9.
4. Jabs D.A., Green W.R., Foox R., et al. Ocular manifestation of acquired immune deficiency syndrome. Ophthalmology **1989**;96:1092-9.
5. Holland G.N. Acquired immunodeficiency syndrome and ophthalmology: the first decade. Am J Ophthalmol **1992**;114:86-95.
6. Muccioli C., Belfort R. Jr., Lottenberg C. Achados oftalmológicos em AIDS: avaliação de 445 casos atendidos em um ano. Rev Assoc Med Bras **1994**;40:155-8.
7. Belfort R. Jr., Muccioli C. Experience of HIV/AIDS and the eye in Brazil, South America. Community Eye Health **1995**;8:26-7.
8. Matos K.T.F., Santos M.C.M., Muccioli C. Manifestações oculares do paciente infectado pelo HIV atendido no Departamento de Oftalmologia da Universidade Federal de São Paulo. Rev Assoc Med Brasil **1999**;45:323-6.
9. DualibY.P.T., Suleiman J.M.A.H. Achados oculares em AIDS no Instituto de Infectologia "Emilio Ribas" antes da introdução das drogas inibidoras de protease. Revista Brasileira de Oftalmologia **1999**;58:383-7.
10. Verbraak F.D., Boom R., Wertheim-van Dillen P.M., et al. Influence of highly active antiretroviral therapy on the development of CMV disease in HIV positive patients at high risk for CMV disease. Br J Ophthalmol **1999**;83:1186-9.
11. Whitcup S.M. Cytomegalovirus retinitis in the era of highly active antiretroviral therapy. JAMA **2000**;283:643-7.
12. Jabs D.A. AIDS and ophthalmology in 2004. Arch Ophthalmol **2004**;122:1040-2.
13. Arruda R.F., Muccioli C., Belfort Jr. R. Achados oftalmológicos em infectados pelo HIV na era pós-HAART e comparação com série de pacientes avaliados no período pré-HAART. Rev Assoc Med Bras **2004**;50:148-52.
14. Jabs D.A, Van Natta M.L., Thorne J.E., et al. Course of cytomegalovirus retinitis in the era fo highly active antiretroviral therapy: 1. Retinitis progression. Ophthalmology **2004**;111:2224-31.
15. Jabs D.A, Van Natta M.L., Thorne J.E., et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. Ophthalmology **2004**;111:2232-9.
16. Ng W.T., Versace P. Ocular association of HIV infection in the era of highly active antiretroviral therapy and the global perspective. Clin Exp Ophthalmol **2005**:33:317-29.
17. Kaharaman G., Krepler K., Franz C., et al. Seven years of HAART impact on ophthalmic management of HIV-infected patients. Ocul Immunol Inflamm **2005**;13:213-8.
18. Goldberg D.E., Smithen L.M., Angelilli A., et al. HIV-associated retinopathy in the HART era. Retina **2005**;25:633-49.
19. Thorne J.E., Jabas D.A., Kempen J.H., et al. Studies of Ocular Complications of AIDS Research Group. Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Ophthalmology **2006**;113: (in press).
20. Karavellas M.P., Lowder C.Y., Macdonald C., et al. Immune recovery vitritis associated with inactive cytomegalovirus retinitis: a new syndrome. Arch Ophthalmol **1998**;116:169-75.
21. Silverstein B.E., Smith J.H., Sykes S.O., et al. Cystoid macular edema associated with cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol **1998**;125:411-15.
22. Karavellas M.P., Azen S.P., MacDonald J.C., et al. Immune recovery vitritis and uveitis in AIDS: clinical predictors, sequelae, and treatment outcomes. Retina **2001**;21:1-9.
23. Kempen J.H., Min YI. Freeman W.R., et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. Ophthalmology **2006**;113:684-94.
24. Centers for Disease Control and Prevention. 1993. Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. JAMA **1993**;269:729-30.
25. Marins J.R.P., Jamal L.F., Chen S., et al. Sobrevivência atual dos pacientes com aids no Brasil. Evidências dos resultados de um esforço nacional. Boletim epidemiológico – AIDS **2002**;15.
26. Figueiredo J.F.C., Rodrigues M.L.V., Souza N.V., et al. Aspectos da AIDS de interesse para o oftalmologista. Medicina, Ribeirão Preto **1998**;31:577-83.
27. Rodrigues M.L.V., Figueiredo J.F.C., Deghaide N.H.S., et al. Frequency of HLA class 1 and 2 alleles in Brazilian patients with AIDS and cytomegalovirus retinitis. Acta Ophthalmol Scand **2003**;81:514-6.
28. Rodrigues M.L., Rodrigues M.L.V., Freitas J.A.H. Estudo da síndrome da ceratoconjuntivite seca de pacientes soropositivos para o vírus da imunodeficiência adquirida humana tipo 1 e com síndrome da imunodeficiência adquirida, em uso ou não de terapia anti-retroviral combinada (HAART). Arq Bras Oftalmol **2004**;67:283-7.
29. Schrier R.D., Freeman W.R., Wiley C.A., et al. Immune predispositions for cytomegalovirus retinitis in AIDS. J Clin Invest **1995**;95:1741-6.
30. Price P., Keane N.M., Stone S.F., et al. MHC haplotypes affect the expression of opportunistic infections in HIV patients. Hum Immunol **2001**;62:157-64.
31. Fernandes A.P., Gonçalves M.A., Zavanella R.B., et al. HLA markers associated with progression to AIDS are also associated with susceptibility to cytomegalovirs retinits. AIDS **2003**;17:2133-6.