Effect of highly active antiretroviral therapy (HAART) on the natural history of ocular manifestations in HIV-infected children

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Abstract

Purpose To determine the effect of highly active antiretroviral therapy (HAART) on the natural history of ocular manifestations in HIV-infected children.

Methods All of the HIV-infected children attending the Institute of Pediatrics, University of Milan, Milan, Italy, between 1982 and 2004 were studied. Every 3 months, they were physically examined and underwent indirect funduscopy conducted by an experienced ophthalmologist; if diagnosed as having eye disease, they were evaluated by the ophthalmologist every week while on specific therapy and monthly thereafter. The clinical and laboratory findings before and after the introduction of HAART were compared.

Results The cohort consisted of 117 HIV-infected children (61 males), with a follow-up ranging from 0.09 to 22.31 years (median, 16.33 years). A total of nine cases of ocular involvement (7.7%) were diagnosed between 1983 and 1994, before the introduction of HAART. All nine children died 4–24 months (median, 15 months) after the diagnosis of ocular involvement. No case of ocular involvement was observed after the introduction of HAART ($P = 0.011$ vs before HAART).

Conclusion The introduction of HAART has had a significant impact on the natural history of ocular manifestations in HIV-infected children, thus suggesting that a reduction in the frequency of ophthalmologic follow-up should be considered for HAART-treated HIV-infected children with

immune reconstitution and no visual symptom.

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Introduction

Until recently, ocular abnormalities were common in HIV-infected patients and often due to opportunistic infections.^{1–4} However, the introduction of highly active antiretroviral therapy (HAART) has led to a considerable decline in opportunistic infections and a reduction in HIV-related deaths.^{5,6} All of the available reports concerning ocular involvement in HIV-infected patients in the HAART era relate to adults;^{7–10} no childhood data are available. The aim of this study was to determine the effect of HAART on the natural history of ocular manifestations in HIV-infected children.

Materials and methods

We studied all of the HIV-infected children attending the Institute of Pediatrics, University of Milan, Milan, Italy, between 1982 and 2004. Every 3 months, they were physically examined and underwent indirect funduscopy conducted by an experienced ophthalmologist; if diagnosed as having eye disease, they were evaluated by the ophthalmologist every week

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Table 1 Characteristics at diagnosis of ocular manifestations and clinical outcome in HIV-infected children with ocular involvement

Case	Year of birth	Ocular manifestation	Age at diagnosis (months)	CD4 cell count (cells/ μ l)	CD4 cell percentage (%)	Antiretroviral therapy	Specific therapy	Ocular outcome at 1 month	Clinical outcome after ocular manifestation
1	1983	CMV retinitis	132	44	3	ZDV	Ganciclovir i.v. for 21 days	Smoldering	Died after 22 months
2	1986	CMV retinitis	21	2414	25	ZDV	Ganciclovir i.v. for 21 days	No disease	Died after 24 months
3	1987	CMV retinitis	96	7	7	None	Ganciclovir i.v. for 21 days	Smoldering	Died after 15 months
4	1987	CMV retinitis	15	1215	16	None	Ganciclovir i.v. for 21 days	Smoldering	Died after 21 months
5	1988	CMV retinitis	9	44	8	ZDV	Ganciclovir i.v. for 21 days	Smoldering	Died after 20 months
6	1990	CMV retinitis	17	16	1	ZDV	Ganciclovir i.v. for 21 days	Active	Died after 4 months
7	1991	CMV retinitis	16	26	2	ZDV	Ganciclovir i.v. for 28 days	Active	Died after 5 months
8	1992	CMV retinitis	20	48	2	ZDV	Ganciclovir i.v. for 28 days	Active	Died after 6 months
9	1994	Toxoplasmic retinochoroiditis	6	326	4	None	Pyrimethamine + sulfadiazine p.o. for 4 months	Active	Died after 5 months

CMV = cytomegalovirus; ZDV = zidovudine.

while on specific therapy and monthly thereafter. On the basis of previously published criteria,⁸ ocular involvement was graded as: 0 = no disease, 1 = stable, 2 = smoldering, and 3 = active.

The study was approved by the Ethics Committee of the University of Milan, Milan, Italy, and written informed consent was obtained from the parents or legal guardians of the children.

The patients' case notes, the hospital's HIV database, and laboratory records were monthly reviewed and recorded. The clinical and laboratory findings before and after the introduction of HAART were compared. HAART was defined as any combination antiretroviral therapy containing a protease inhibitor. The date of the introduction of HAART was defined as 1 January 1998, this being the date that protease inhibitors were first used at our centre.

All of the data were analysed using SAS Windows v.12. A *P*-value of <0.05 was considered statistically significant.

Results

The cohort consisted of 117 HIV-infected children (61 males), with a follow-up ranging from 0.09 to 22.31 years (median, 16.33 years). A total of nine cases of ocular involvement (7.7%) were diagnosed between 1983 and 1994, before the introduction of HAART (Table 1). The ocular manifestations were diagnosed in all cases during routine ophthalmologic screening in the absence of visual symptoms. Five of the patients with CMV retinitis showed granular retinitis with intraretinal haemorrhages, and three perivascular retinitis; in all eight children, CMV viremia was detected by polymerase chain reaction. The diagnosis of toxoplasmic retinochoroiditis was based on the presence of severe anterior chamber and vitreous inflammation, together with delicate white-greyish spots and haemorrhages on the ocular fundus, and the positive determination of anti-*Toxoplasma gondii* antibodies in blood.

Despite ganciclovir therapy and, in the case of toxoplasmosis, pyrimethamine and sulfadiazine, the ocular manifestations resolved only in the child without CD4 cell depletion; however, all nine children died 4–24 months (median, 15 months) after the diagnosis of ophthalmic disease.

No case of ocular involvement was observed after the introduction of HAART (*P* = 0.011 *vs* before HAART).

Discussion

This study demonstrates for the first time that the introduction of HAART has had a significant impact on

the natural history of ocular manifestations in HIV-infected children, thus suggesting that a reduction in the frequency of ophthalmologic follow-up should be considered for HAART-treated HIV-infected children with immune reconstitution and no visual symptom.

The protective effect of HAART on ocular manifestations may be explained by the post-HAART reconstitution of T-lymphocyte responses against a variety of pathogens, including CMV and *T. gondii*.¹¹ At the same time, paradoxical inflammatory complications attributed to post-HAART immune reconstitution have been frequently described in adults.^{11,12} However, no cases have been reported in childhood probably because of the small number of patients with ocular opportunistic infections since the introduction of HAART in paediatric age.

Low CD4 cell counts and high HIV RNA levels have been associated with ocular involvement and disease progression in HIV-infected adults. We have no HIV RNA data relating to our patients with ocular manifestations because all of them were followed up when viral load was not routinely measured. However, as the majority were severely immunosuppressed, and the only child with a favourable ocular outcome showed no CD4 cell depletion, we can confirm the importance of CD4 cell counts in ocular involvement, as well as in the favourable remission of disease.

Finally, it is still unknown how long the beneficial effect of HAART on the development of ocular involvement and the risk of progression after previous disease may be sustained. It is probable that CMV disease and other opportunistic infections will continue to evolve, and so further monitoring is required to document these changes.

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