EDITORIAL

AIDS and Ophthalmology: A Period of Transition

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SINCE ITS INITIAL DESCRIPTION IN 1981, ACQUIRED immunodeficiency syndrome (AIDS) has become a major health problem. From 1981 through 1996, more than 574,000 persons with AIDS were reported to the Centers for Disease Control and Prevention (CDC).[1] The number of persons currently infected with human immunodeficiency virus (HIV) in the United States is estimated at 700,000 to 1 million. Human immunodeficiency virus disease remains the leading cause of death among persons aged 25 to 44 years.[1] The AIDS epidemic has had a major impact upon ophthalmology. Cytomegalovirus retinitis has also been transformed from a rare disease into one of the most common intraocular infections encountered in the United States.[2]

See also pp. 141–157, 158–167, 168–180, 181–189, 190–198, 199–205, and 234–239.

Since its beginning, the AIDS epidemic has been evolving. Over the years, the demographics have shifted, with a declining proportion of cases attributed to men having sex with men and an increasing number and proportion of cases among women and resulting from heterosexual transmission.[3] The use of primary and secondary prophylaxis for opportunistic infections has changed the clinical picture of AIDS. One of the most dramatic effects of HIV infection is the impairment of the immune system and an increased susceptibility to a precisely defined group of opportunistic pathogens.[4,5] Prophylaxis is advocated for routine use to prevent *Pneumocystis carinii* pneumonia when the $CD4^+$ T-lymphocyte count is below 200 cells per μl and *Mycobacterium avium* complex infections when the $CD4^+$ T-lymphocyte count is below 50 cells per μl.[6] With the widespread use of primary prophylaxis for *P carinii* pneumonia, its incidence decreased, but one consequence of this progress was an increase in the frequency of cytomegalovirus retinitis and other forms of cytomegalovirus disease, from an estimated 25% to 45% of patients with AIDS.[7] This increase in cytomegalovirus disease presumably reflected a larger proportion of patients living longer with lower $CD4^+$ T-lymphocyte counts. Secondary consequences of the use of trimethoprim-sulfamethoxazole as primary prophylaxis for *P carinii* pneumonia have been reduced rates of sinusitis, bacterial pneumonia, and toxoplasmosis.[6,8] The effectiveness of trimethoprim-sulfamethoxazole in decreasing the incidence of toxoplasmosis has resulted in an apparent decline in the incidence of ocular toxoplasmosis at our institution.

During the past 2 years, two developments have begun to alter the nature of the AIDS epidemic even more radically. The first is an improved understanding of the pathogenesis of HIV infection. Early in the AIDS epidemic, it was known that acute HIV infection was associated with a burst of viral replication followed by immune response and a decline in HIV culturable from the blood. Human immunodeficiency virus–infected individuals then entered a period of clinical latency, associated with a slow decline in $CD4^+$ T-lymphocyte counts. Once $CD4^+$ T-lymphocyte counts became sufficiently low, culturable virus began to rise, and clinical symptoms occurred. Once $CD4^+$ T lymphocytes fell below 200 cells per μl, opportunistic infections were encountered that led to

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a clinical diagnosis of AIDS.[9] Recently, technology has become available to asses the amount of HIV present in the blood (virus load) by either a plasma polymerase chain reaction assay or a branched-chain DNA assay. Data have shown that even during clinical latency, there is no virologic latency but rather a tremendous ongoing production of HIV (approximately 10 billion virions per day[10]) and an ongoing, substantial turnover in $CD4^+$ T lymphocytes. Studies have demonstrated that HIV load predicts mortality, independent of $CD4^+$ T-lymphocyte count,[11] and that suppression of HIV load is associated with improved survival.[12] Physicians now follow a patient's HIV load and alter antiretroviral therapy to suppress virus load.

The second development that has begun to alter the nature of the AIDS epidemic is the increased number of antiretroviral drugs, with the development of highly active antiretroviral therapy. The genetic material of HIV is encoded in RNA. Upon entry into the cell, the viral enzyme reverse transcriptase converts the viral RNA to DNA, and the cellular machinery is used to produce multiple copies of HIV. A viral-encoded protease clips viral proteins to appropriate sizes for assembly of intact virions. Zidovudine (formerly known as azidothymidine or AZT) was the first antiretroviral drug approved by the United States Food and Drug Administration for the treatment of HIV.[13] Zidovudine, approved in 1987, is a nucleoside analog that inhibits reverse transcriptase. Between 1987 and 1996, the only additional antiretroviral drugs approved by the FDA were the reverse transcriptase inhibitors didanosine (dideoxyinosine, or ddI), in 1990, and zalcitabine (dideoxycytidine, or ddC), in 1991. Monotherapy with zidovudine reduced the incidence of opportunistic infections and improved survival,[14] but its effect was modest and short-lived.[15] A major problem of prolonged treatment with monotherapy for HIV was the emergence of resistant HIV. In 1996, two new nucleoside reverse transcriptase inhibitors were approved by the FDA: stavudine (d4T) and lamivudine (3TC). The first non-nucleoside reverse transcriptase inhibitor, nevirapine, was approved in 1996, and an entirely new class of highly potent drugs, protease inhibitors, was introduced in late 1995 through early 1997. Four new protease inhibitors have been approved by the FDA: saquinavir, ritonavir, indinavir, and nelfinavir. Protease inhibitors are substantially more potent than reverse transcriptase inhibitors. Furthermore, combination therapy using two reverse transcriptase inhibitors and a protease inhibitor is highly effective in suppressing virus load. These combinations have led to dramatic increases in $CD4^+$ T lymphocytes. More importantly, this "triple therapy" had resulted in decreasing virus burden to undetectable levels (<400 copies per ml) in some patients for periods exceeding 68 weeks. Coincident with the introduction of combination antiretroviral therapy and protease inhibitors has been a leveling of the number of opportunistic infections and a leveling or, in some areas, a decline in the number of AIDS deaths (reference 1 and Chiasson MA, Berenson L, Li W, Schwartz S, Mojica B, Hamburg M, unpublished data, "Declining AIDS mortality in New York City," presented at the IV Conference on Retroviruses and Opportunistic Infections, Washington, DC, 1997). These efforts have led to new hope in the treatment of HIV infection and the promise of prolonged survival and improved quality of life. Nevertheless, several caveats remain. Protease inhibitors have substantial side effects; there are important drug interactions; and commonly used regimens generally require 15 to 20 pills daily in extraordinarily complex dosing schedules. The great concern is durability of the response with the risk of incomplete viral suppression, mutation, and viral resistance.[16]

Included in the revised therapeutic strategies are the new guidelines for management of occupational exposures by healthcare workers.[17] They reflect the results of a retrospective case-control study that showed that zidovudine prophylaxis was associated with a fivefold reduction in the risk of HIV transmission.[18] The new recommendations are reviewed in this issue of THE JOURNAL.[19]

The changes in the AIDS epidemic are having substantial effects in the field of ophthalmology. The most evident is a declining incidence of cytomegalovirus retinitis. At the Johns Hopkins medical institutions, we have seen a 55% decrease in the incidence of cytomegalovirus retinitis during the past 3 years (Figure). Informal surveys of other centers that are following large numbers of HIV-infected patients have reported similar declines. The most likely explanation is a decrease in the cohort of patients who are at high risk for cytomegalovirus retinitis (that is, those

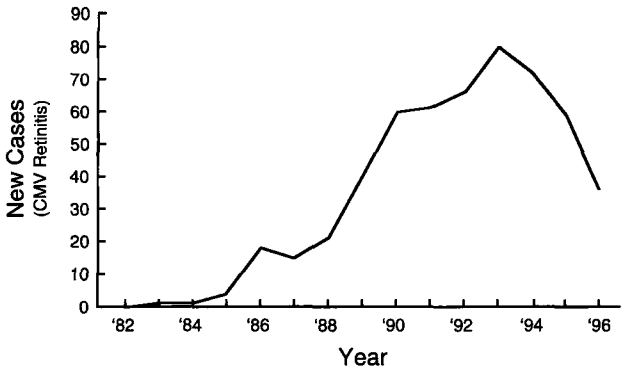

FIGURE. Annual number of new cases of cytomegalovirus retinitis at the Johns Hopkins Medical Institutions.

who have CD4+ T-lymphocyte counts of less than 50 cells per μl)[20-22] as a consequence of improved immune function in patients on highly active antiretroviral therapy. The decline in the incidence of cytomegalovirus retinitis predated the commercial availability of protease inhibitors, but they had been available in clinical trials before FDA approval. A similar dip in the incidence of cytomegalovirus retinitis was seen when zidovudine was introduced (Figure), but that decline was short-lived and modest, consistent with the limited effect of zidovudine on HIV. The current decline in the incidence of cytomegalovirus retinitis is not associated with the use of primary prophylaxis for cytomegalovirus because it is hardly ever used in our area.

Another potential contributor to the decline is the changing epidemiology of the AIDS epidemic. Some studies have suggested that men having sex with men are at a greater risk for cytomegalovirus retinitis than are other risk groups for HIV.[2] If true, then as the proportion of cases with AIDS caused by other risk factors increases, the incidence of cytomegalovirus might decline. How low the nadir of the incidence of cytomegalovirus retinitis will be and how long it will last remain to be determined. As the number of patients who fail antiretroviral therapy increases, because of either an inability to tolerate the regimen or the development of resistance, the incidence of cytomegalovirus retinitis may begin to increase again. Indeed, the number of cases seen at our institution during the first quarter of 1997 suggests that the nadir already may have been reached in our area.

This period of transition has raised several issues that remain unresolved. With suppression of circulating HIV to undetectable levels for sustained periods, the average CD4+ T-lymphocyte count increase is 100 to 150 cells per μl, thus indicating incomplete immune restitution for most patients. Furthermore, most of the reconstituted CD4+ T-lymphocyte population is composed of memory cells rather than naive cells. The functional capacity of these cells is not clear, so the protection they afford against opportunistic infections is unknown. Hence, even if CD4+ T-lymphocytes rise with highly active antiretroviral therapy, it is not clear that the patient is protected against cytomegalovirus.

Before the availability of current antiretroviral agents, some studies suggested that 13% to 15% of patients with CD4+ T-lymphocyte counts below 50 cells per μl who have not undergone regular ophthalmologic examination could harbor unsuspected cytomegalovirus retinitis[22,23]; therefore, some clinicians advocated the routine evaluation of patients at high risk for cytomegalovirus retinitis for early detection of disease. Although this approach was never validated in a long-term outcome study, and although not all experts agree with this recommendation, it is widely practiced in some areas. A typical approach is to see patients with CD4+ T-lymphocyte counts below 50 cells per μl three or four times per year, those with CD4+ T-lymphocyte counts between 50 and 100 cells per μl twice annually, and those with CD4+ T-lymphocyte counts above 100 cells per μl (who are at low risk for cytomegalovirus retinitis) annually.

For patients whose CD4+ T-lymphocyte counts previously have put them in a high-risk group but who now have CD4+ T-lymphocyte counts that potentially put them in a low-risk group, what should be the frequency of "screening"? No data currently indicate what the magnitude of the risk may be. Three separate groups at Fourth Conference on Retroviruses and Opportunistic Infections in January 1997 reported case series of patients who had low CD4+ T-lymphocyte counts, were treated with highly active antiretroviral therapy, and responded with high CD4+ T-lymphocyte counts, but then were found to have cytomegalovirus retinitis (Jacobson MA, Kramer F, Pavan PR, Owens S, Pollard R, and NIAID ACTG Protocol 266 Team, unpublished data, "Failure of highly active antiretroviral therapy [HAART] to prevent CMV retinitis despite marked CD4 count

increase"; Michelet C, Arvieux C, Aubert V, Andre P, Riou A, Cartier F, unpublished data, "Viral ocular and involvement after initiation of antiprotease inhibitor therapy"; and Gilquin J, Piketty C, Thomas V, Gonzales-Canali G, Kazatchkine MD, unpublished data, "Acute CMV infection in AIDS patients receiving combination therapy including protease inhibitors," all presented at the IV Conference on Retroviruses and Opportunistic Infections, Washington, DC, 1997). Jacobson and associates also reported that, before highly active antiretroviral therapy, only 4% of their patients with cytomegalovirus retinitis had $CD4^+$ T-lymphocyte counts above 50 cells per μl but that, subsequent to the widespread use of current regimens, 29% had $CD4^+$ T-lymphocyte counts above 50 cells per μl, and 14% had $CD4^+$ T-lymphocyte counts above 100 cells per μl. These reports suggest that specific immunity may not be restored by current drugs in all cases and that one cannot completely relax one's vigilance.

A thornier issue is that of secondary prophylaxis. Although primary prophylaxis for cytomegalovirus is not widely used, secondary prophylaxis (maintenance therapy) is generally required because of the prompt occurrence of relapse on discontinuation of therapy. The article in this issue of THE JOURNAL by Reed and associates[24] suggests that in some patients, restoration of immune function with highly active antiretroviral therapy may result in control of cytomegalovirus retinitis without the need for specific anticytomegalovirus therapy. When zidovudine was first introduced, there were case reports[25-27] of patients with cytomegalovirus retinitis who had been started on zidovudine and whose retinitis went into remission (at least temporarily). The case reports were few, and the phenomenon was not widespread. The reports by Jacobson and associates, Michelet and associates, and Gilquin and associates suggest that the control of retinitis by highly active antiretroviral therapy alone will not occur in all patients. Knowledge regarding the proportion of patients that will experience control of retinitis from improved immune function only, and knowledge regarding those patients for whom it might be safe to stop secondary prophylaxis, await the results of future studies.

With the availability of the ganciclovir intraocular device for the treatment of cytomegalovirus retinitis, the issue may be even more complex. The ganciclovir intraocular device is highly effective for the control of cytomegalovirus retinitis,[28] but it does not prevent the development of contralateral ocular or visceral disease. In patients treated with the implant only, the rates of contralateral ocular and visceral disease are, respectively, 50% and 31% at 6 months.[28] One approach often used in practice is a combination of the ganciclovir intraocular device and oral ganciclovir; the oral ganciclovir is given to prevent the development of contralateral ocular and visceral disease. A study comparing the efficacy and risks of this approach to the use of the implant alone and to intravenous ganciclovir is under way, but data are unavailable. The implant requires scheduled replacement every 6 to 7 months, when the reservoir of ganciclovir is exhausted. If a patient is on highly active antiretroviral therapy and has a marked improvement in $CD4^+$ T-lymphocyte count, should the ganciclovir implant be replaced or should the patient be observed? The answer is unknown. Does a patient who has a marked increase in $CD4^+$ T-lymphocyte count because of highly active antiretroviral therapy after the diagnosis of cytomegalovirus retinitis still require systemic treatment to prevent dissemination to the fellow eye or the viscera, or is the improved immune system adequate to prevent these events? The same technology that was applied to the development of assays for HIV load is now being used to develop assays for cytomegalovirus load. Although these assays are not commercially available, their use in the future may provide data to help resolve the latter issue in patients whose immune systems have improved.

To understand how new treatments for AIDS have affected the ocular manifestations of AIDS, it is important to understand these manifestations before the availability of new treatments. The article in this issue of THE JOURNAL by The Studies of Ocular Complications of AIDS Research Group[29] carefully documents the clinical features of cytomegalovirus retinitis at diagnosis in a large number of patients. This article provides an important resource to compare with future studies of cytomegalovirus as to how new treatments for HIV may have affected the disease. As the life span of patients with AIDS increases and the incidence of cytomegalovirus retinitis decreases, other causes of vision loss will assume increasing importance. The article by Mueller and

associates[30] continues this group's work on visual dysfunction in HIV-positive patients without retinitis. They suggest that HIV-infected patients, even those with good visual acuity, will have subtle abnormalities on a variety of visual tests. The pathogenesis of this problem is unknown, although a cumulative insult from HIV retinopathy or a direct HIV toxicity on visual structures have both been suggested. An evaluation of patients with subtle visual defects who have been started on highly active antiretroviral therapy, and the response of their visual defects, may help elucidate the impact of new agents on these changes.

Although the incidence of cytomegalovirus retinitis has decreased, it continues to occur, and it is a major cause of morbidity in patients with AIDS. In one large study of patients with cytomegalovirus retinitis treated with intravenous ganciclovir or foscarnet,[2] the median time to a visual acuity of 20/200 or worse in either eye with cytomegalovirus retinitis was 13.4 months, and to a bilateral visual acuity of 20/200 or worse was 21.1 months. With the possibility of prolonged life spans for patients with cytomegalovirus retinitis, improved treatment approaches are needed. Laycock and associates[31] document a new model of cytomegalovirus infection that may be useful for the evaluation of potential anticytomegalovirus agents. In addition to the need for more effective anticytomegalovirus therapy, therapies with fewer side effects are needed. Treatments requiring daily intravenous infusions require the placement of a central venous catheter. In patients with AIDS, central venous catheter complications occur at a rate of 1.3 to 1.5 complications per person per year,[32] and newer treatments are aimed at eliminating the central venous catheter. These treatments include the ganciclovir intraocular device,[28] oral ganciclovir,[33,34] and intravenous cidofovir.[35,36] Cidofovir has a prolonged duration of effect, can be given by intermittent intravenous administration (once weekly as induction and once every 2 weeks as maintenance therapy), and therefore does not require placement of a central venous catheter. Repetitive intravitreous injections of cidofovir given every 5 to 6 weeks also have been used investigationally to treat cytomegalovirus retinitis.[37] The article in this issue of THE JOURNAL by Banker and associates[38] reports on the characteristics and potential cause of hypotony, a serious complication that has occurred in such investigations. The occurrence of hypotony also has been reported in patients receiving intravenous cidofovir.[36] Although intravitreous cidofovir is only an investigational treatment and is not being used clinically, this paper[38] provides insight into the mechanisms of this ocular complication that may be applicable to intravenous therapy. Furthermore, the authors suggest that ophthalmologists will have to monitor patients receiving systemic cidofovir for ocular complications, as well.

Finally, the article by Magone and associates[39] not only documents the breakdown in the blood-ocular barrier caused by cytomegalovirus retinitis but also reports an increasing breakdown in the blood-ocular barrier over time in patients with AIDS even without cytomegalovirus retinitis. The reasons for this change over time are unclear, but they could be a cumulative insult from the HIV-associated microangiopathy in the eye.[2] This paper also notes that the breakdown in the blood-ocular barrier in a small number of patients with cytomegalovirus retinitis–associated retinal detachments is substantially greater than in patients with cytomegalovirus retinitis but without detachments. Because most of the data on the intraocular penetration of systemically administered anticytomegalovirus drugs comes from series of patients undergoing retinal detachment surgery,[40-42] the available data on the intraocular drug levels may overestimate these levels in an eye without a retinal detachment.

In conclusion, this era is one of transition in the treatment of patients with HIV infection and, in particular, of patients with AIDS. These changes have already affected and will continue to affect the field of ophthalmology for the next several years. Multiple issues have been raised, many of which do not yet have answers, and studies will be needed to help resolve them.

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