Medical management of human immunodeficiency virus infection

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The human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) pandemic has pervasive effects on culture, economics, policy, and human development. All organs can be affected by complications of HIV/AIDS, including the eye. When sufficient resources are available and widespread antiretroviral resistance does not exist, the four available classes of antiretroviral agents - nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors - can be combined to provide highly active antiretroviral therapy (HAART). For many (not all) patients, HAART converts an inexorably fatal disease into a chronic disease with a fairly good prognosis. Use of HAART often induces partial immune recovery, which has predominantly beneficial effects on ocular complications of AIDS. However, HAART-induced immune recovery sometimes results in immune recovery inflammatory syndromes, such as immune recovery uveitis. Use of HAART is the single most useful intervention for most patients with ocular complications of AIDS. However, specific ocular therapy is also critical to avoid blindness in the early months before immune recovery can occur, or if HAART is unavailable.

Increasing availability of HAART worldwide shows great promise to alleviate one of the world’s greatest plagues. However, predictable secular trends in the AIDS epidemic make it likely that the number of cases of ocular complications of AIDS will increase substantially before they decrease. Ophthalmologists worldwide should be familiar with the diagnosis and management of cytomegalovirus retinitis - the most common ocular complication of AIDS - and should establish partnerships with physicians who are able to provide HAART. Research is needed to determine the optimal approach for managing cytomegalovirus retinitis in resource-constrained settings.

Key words: Acquired immune deficiency syndrome, antiretroviral therapy, cytomegalovirus retinitis, highly active antiretroviral therapy, human immunodeficiency virus, immune recovery

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The acquired immune deficiency syndrome (AIDS) pandemic was first recognized in 1981 in Los Angeles, California. Unfortunately, human immunodeficiency virus (HIV) infection was widespread throughout the world by the time these sentinel events were recognized. The HIV/AIDS pandemic has quickly advanced to become one of the great plagues of all time, now affecting between 30.6 and 36.1 million persons worldwide, including approximately 2.5 million Indians [Figure 1]. More than 2.08 million persons die of HIV/AIDS per year, worldwide. The pandemic has had pervasive effects on culture, economics, and policy, and has led to “the single greatest reversal in human development” in recent times. The aim of the present article is to provide a review of the medical management of HIV infection.

Four treatment strategies have been shown to prolong survival of patients with HIV/AIDS: antiretroviral therapy, prophylaxis for Pneumocystis carinii, prophylaxis for Mycobacterium avium and care by a physician experienced in the management of HIV/AIDS. Of these, only combination antiretroviral therapy, commonly called highly active antiretroviral therapy (HAART), frequently succeeds at reversing the otherwise inexorable progression of immunodeficiency, whereas P. carinii and M. avium prophylaxis prolong survival in a state of advanced immunodeficiency, during which time patients unfortunately are at increasing risk of advanced opportunistic complications of AIDS such as cytomegalovirus (CMV) retinitis. The current plan for widespread introduction of inexpensive co-trimoxazole prophylaxis will be of great value in improving survival, but the risk of CMV retinitis is likely to increase substantially as a result, in regions where HAART does not become widely used.

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Highly active antiretroviral therapy is defined as “an antiretroviral regimen that can reasonably be expected to reduce the viral load <50 copies/mL in treatment-naïve patients”. Highly active antiretroviral therapy (HAART) was the recognition that combination antiretroviral therapy would be needed to prevent the development of viral resistance to antiretroviral agents. The HIV, an RNA virus, mutates approximately once per replication, as a result of the poor fidelity of its reverse transcriptase. This property enables HIV to rapidly develop resistance to antiretroviral treatments, unless the treatment succeeds at arresting replication nearly completely. Simultaneous use of multiple agents, usually three or more, attacking different aspects of HIV replication is successful because HIV would have to develop mutations simultaneously to all agents in use in order to escape control, an improbable event. However, scrupulous adherence to such therapy is extremely important for patients with HIV disease, because intermittent use of antiretroviral agents leads to the development of resistance. Less than 95% adherence is associated with a 3.5-fold higher risk of treatment failure.

The four classes of antiretroviral agents currently available are listed in Table 1. At present, available antiretroviral drugs have their effect by interfering with one of two HIV-encoded enzymes required for reproduction of the virus (reverse transcriptase, which transcribes HIV’s RNA genome; or HIV protease, which is involved in the assembly and release of daughter viral particles) or by inhibiting fusion of the viral particle with the target cell.

Inhibitors of reverse transcriptase are divided into two classes: nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs), which competitively inhibit the enzyme;
and non-nucleoside reverse transcriptase inhibitors (NNRTIs),
which covalently inactivate the reverse transcriptase, exerting
a highly potent effect. Nucleoside inhibitors were the first
effective antiretroviral drugs to be developed, beginning with
zidovudine (AZT) in 1987. When given as monotherapy, most
of these drugs reduce the HIV load in peripheral blood on the
order of 0.5 to 1.0 log₁₀ units, followed by the rapid development
of drug resistance. The six agents in this class [Table 1] are quite
useful as a component of antiretroviral combination therapies,
and are widely used. Being older medications, some of them
are less expensive than newer antiretroviral agents. Tenofovir
is a nucleotide, rather than a nucleoside reverse transcriptase
inhibitor, which circumvents a common mechanism of NRTI
resistance, but otherwise works in a similar fashion to its
cousins.

Non-nucleoside reverse transcriptase inhibitors are more
potent than nucleoside reverse transcriptase inhibitors because
they covalently inactivate reverse transcriptase. Their side-
effect profile has made the three agents in this class among
the most popular agents for management of HIV infection,
although costs tend to limit their use worldwide. Nevertheless,
they are prone to extremely rapid development of resistance
if not used in appropriate combinations with a high degree of
adherence to the medication schedule.

Protease inhibitors make up a third class of antiretroviral
agents, the first class of “highly potent” drugs to become
available, suppressing HIV load by 1.0 to 2.0 log₁₀ units when
given as monotherapy. The HIV protease cleaves polyproteins
generated by HIV-encoded mRNA; its blockade renders several
essential viral enzymes inactive, resulting in production of
defective HIV virions that are rapidly cleared. Nine such
agents currently exist [Table 1]. Ideally, most are given in
conjunction with ritonavir, for its “boosting” effect, which
improves the pharmacokinetic profile of other protease
inhibitors without incurring the extent of side-effects associated
with full-dose ritonavir. Combination therapy with protease
inhibitors and thymidine analog NRTIs, a highly effective
antiretroviral combination, unfortunately is associated with
metabolic disturbances and peripheral lipoatrophy, which
appear to be less common when protease inhibitors are
combined with abacavir or tenofovir. The latter agents are
more expensive than older NRTIs.

Enfuvirtide - the first agent in a fourth class of agents,
fusion inhibitors, is a 36 amino acid peptide which inhibits
the function of gp41, potently inhibiting the HIV-cellular
membrane fusion sequence. Enfuvirtide is primarily used in
wealthy countries as a salvage therapy, due to its great expense
and the requirement that it be given by injection.

The arrival of HAART has led to one of the most spectacular
reversals in modern medicine, converting what is otherwise
an inexorably progressive, fatal disease into a chronic disease
with a fairly good prognosis for those who receive HAART
and benefit from it. Use of HAART results in a much reduced
risk of mortality, reduced opportunistic infection risk, and
improved quality of life, often with recovery to near-normal
health. Epidemiologically, widespread use of HAART tends to
result in increased prevalence of HIV/AIDS, because survival
improves to a greater extent than decline in transmission of
HIV infection.

Ocular complications of AIDS and their association with
a patient’s current immune status, as given by the CD4 + T
cell count, are summarized in Table 2. The risk of developing
CMV retinitis has declined substantially among patients
receiving HAART. Among patients already afflicted by
CMV retinitis, use of HAART is associated with an 81% lower
risk of mortality, a 46% lower risk of developing retinitis in
previously unaffected second eyes, a 60% reduction in the
risk of retinal detachment and an approximate 75% reduction
in the risk of loss of visual acuity. Most patients who develop
immune reconstitution characterized by a rise in the CD4+ T
cell count to a level greater than 100 to 150 cells/µL for four to

| CD4+ T cell count | Vascular | Infection | Tumor | Neuroophthalmological |
|-------------------|----------|-----------|-------|----------------------|
| Any (or uncertain) | Large vessel vaso-occlusion | Acute retinal necrosis | Squamous cell carcinoma of the conjunctiva | Direct complications of HIV Infection |
| ≤500 cells/µL | Herpes zoster ophthalmicus | Disseminated molluscum contagiosum | Kaposi’s sarcoma Lymphoma | Progressive multifocal leukoencephalopathy-related complications |
| ≤200 cells/µL | Pneumocystis chorioidopathy | Ocular tuberculosis | Microsporidial keratoconjunctivitis | |
| ≤100 cells/µL | HIV retinopathy | CMV retinitis | Progressive outer retinal necrosis | Complications of cryptococcal meningitis |
| | Conjunctival vasculopathy | Toxoplasmic retinitis | MAC chorioidopathy | |
| | | Progressive outer retinal necrosis | Cryptococcal chorioidopathy | |

*HIV - human immunodeficiency virus, CMV - cytomegalovirus; MAC - Mycobacterium avium complex; Modified from: Kempen JH, Jabs DA. Ocular Complications of Human Immunodeficiency Virus Infection. In: Johnson GJ, Minassian DC, Weale R, West SK, editors. The Epidemiology of Eye Diseases. London: Arnold, 2003: 318-340. (With permission)
six months can safely stop anti-CMV therapy, with only rare exceptions. Some patients also develop immune recovery uveitis (the first immune recovery inflammatory syndrome described) in which recovery of anti-CMV immunity leads to intraocular inflammation - often a vitritis - sometimes causing vision loss.

Because the overall effects of immune recovery are overwhelmingly beneficial, use of HAART is the single most important intervention for patients with ocular complications of AIDS. In fact, even if substantial immune recovery never occurs, outcomes of CMV retinitis are substantially improved in patients receiving HAART with respect to those who never take HAART. However, specific ocular therapy also is critical, in order to avoid blindness in the early months before immune recovery is complete, or if antiretroviral treatment fails to restore immunity.

Unfortunately, most persons with HIV/AIDS worldwide have limited access to HAART, as a result of both economic and health infrastructure limitations. In recent years, international efforts and cost reductions, largely because of generic drugs available from Indian pharmaceutical firms, have begun improving access to HAART. Still, only 1-1.5% of patients in India receive HAART presently, and the present goal is to expand to 6-7%. While it is encouraging to observe increasing use of combination antiretroviral therapy worldwide, it likely will be many years until treatment is available to the majority.

In the pre-HAART era, CMV retinitis was more than 20-fold more common than any other vision-threatening ocular complication of AIDS in the United States and affected approximately 30% of all patients with AIDS at some point in their lifetime. Case series from India and most parts of the world suggest that CMV retinitis is the preeminent ocular complication of AIDS everywhere, except possibly in sub-Saharan Africa, where patients until recently have died at a stage of AIDS earlier than when CMV retinitis would be expected to occur, a situation which is likely to change with improved AIDS care and infrastructure. Even if the risk of CMV retinitis is one-fourth as common worldwide as it used to be in the United States, millions of persons would be affected.

Treatment of ocular complications of AIDS is a complex topic, which I have addressed in more detail elsewhere. In general, because most ocular opportunistic pathogens cannot be eradicated, their management, including the management of CMV retinitis, requires lifelong suppressive therapy except in those fortunate few in whom HAART induces sufficient recovery of endogenous immunity to control the pathogen. Management of CMV retinitis, the most common pathogen, is particularly difficult. Even with ongoing suppressive systemic anti-CMV therapy, recurrences of active retinitis occur approximately every three months, due to limitations in drug delivery after restoration of the blood-retinal barrier with healing of retinitis and/or the development of drug resistance, which occurs in about 27.5% by nine months. The alternative of local therapy is effective, but also has its problems, with increased risk of second eye retinitis, systemic CMV disease and possibly mortality hence the overarching need in these patients to control the underlying HIV disease and restore endogenous immunity.

In countries with substantial treatment resources, valganciclovir is the most popular treatment for CMV retinitis, using a dose of 900 mg twice daily for initial control of active retinitis (‘induction’), followed by 900 mg daily as suppressive (‘maintenance’) therapy. Valganciclovir is the only oral treatment for CMV with high bioavailability, avoiding the need for a long-term central venous catheter, with its attendant high risk of life-threatening catheter complications and quality of life problems. Valganciclovir, the valine ester of ganciclovir, achieves blood ganciclovir levels similar to those with intravenous ganciclovir and therefore can serve as a replacement for intravenous ganciclovir in most situations. Oral ganciclovir is inferior to valganciclovir because of poor oral bioavailability, and is no longer marketed in the west. Intravenous foscarnet is an alternative therapy for CMV disease, but requires several hours per day to administer, has significant side-effects, and is comparably expensive, making it a second-line therapy. Intravenous cidofovir is similarly effective, has become unpopular due to a high risk of substantial renal injury and uveitis/hyponatremia. Local therapy with ganciclovir implants is the most effective anti-CMV treatment option in terms of time-to-retinitis relapse, and is still used in wealthy countries for immediately vision-threatening disease, generally in combination with valganciclovir to prevent systemic complications (see above). However, because of the need to treat with valganciclovir anyway, most use valganciclovir monotherapy to treat lesions that are not immediately vision-threatening, particularly if there is hope for immune recovery. Intravitreal injections of fomivirsen are no longer marketed because demand for the product was poor.

As the cost of all of these regimens is exceptionally high, on an order substantially higher than first-line HAART, none of them are commonly used except in wealthy countries. The most common approach to treating CMV retinitis in a large part of the world is to use intravitreal injections of ganciclovir (2.0 to −5.0 mg/0.1 cc twice weekly for three weeks, then weekly) or occasionally foscarnet (2.4 mg/0.1 cc twice weekly for three weeks, then weekly). This approach, although it has not been subjected to randomized trials, seems effective based on case series and clinical experience, but may be associated with a higher risk of second eye and systemic disease sequelae of CMV disease than a systemic treatment would be. Valganciclovir, which will not be available in generic form until 2014, may represent an improvement, particularly vis-à-vis systemic and second eye disease outcomes, but its cost-effectiveness as a generic drug vis-à-vis intravitreal injections remains to be seen.

With the anticipated widespread uptake of co-trimoxazole prophylaxis and absent full-scale implementation of HAART in most parts of the world, the number of cases of CMV retinitis, which may be already in the millions, is likely to nearly double. This substantial and increasing burden of disease calls for a more effective yet practical management strategy for CMV retinitis that can be implemented in resource-constrained settings. Ophthalmologists worldwide should be familiar with the diagnosis and management of CMV retinitis, and should establish partnerships with infectious diseases’ physicians able to provide appropriate treatment for patients with ocular complications of HIV/AIDS, because antiretroviral therapy is ultimately the most effective long-term treatment for CMV disease.
retinitis and for other ocular complications of AIDS. Research is needed to determine the optimal way of managing CMV retinitis in resource-constrained settings, particularly in the window before HAART-induced immune recovery occurs, during which the risk of vision loss and other complications is substantial.

References

1. Centers for Disease Control. Pneumocystis pneumonia-Los Angeles. MMWR Morb Mortal Wkly Rep 1981;30:250-2.
2. Cohen J. HIV-AIDS. India slashes estimate of HIV-infected people. Science 2007;317:179-81.
3. UNAIDS Annual Report 2007: Know Your Epidemic. UNAIDS, Geneva, Switzerland. Available at: http://data.unaids.org/pub/Report/2008/jc1535_annual_report07_en.pdf (accessed July 17, 2008).
4. United Nations Development Programme. Human Development Report 2005. 2005.
5. Fischl MA, Dickinson GM, La Voie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for Pneumocystis carinii pneumonia in AIDS. JAMA 1988;259:1185-9.
6. Pierce M, Crampton S, Henry D, Heifets L, LaMarca A, 17. Flexner C. HIV-protease inhibitors. N Engl J Med 1998;338:
16. Deeks SG, Smith M, Holodniy M, Kahn JO. HIV-1 protease inhibitors: A review for clinicians. JAMA 1997;277:145-53.
18. Moyle CJ, Sabin CA, Cartledge J, Johnson M, Wilkins E, Churchill D, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipodystrophy. AIDS 2006;20:2043-50.
19. Jamjian MC, McNicholl IR. Enfuvirtide: First fusion inhibitor for treatment of HIV infection. Am J Health Syst Pharm 2004;61:
20. Kreutz HB, Kliwer G, Gill MJ. Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. HIV Med 2005;6:99-106.
21. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Furhler J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.
22. Nieuwkirk PT, Reijers MH, Weigel HM, Lange JM, Sprangers MA. Quality of life in maintenance vs prolonged induction therapy for HIV. JAMA 2000;284:178-9.
23. Jabs DA, Bartlett JG. AIDS and ophthalmology: A period of transition. Am J Ophthalmol 1997;124:227-33.
24. Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK, Tonascia J. Mortality risk for patients with cytomegalovirus retinitis and acquired immune deficiency syndrome. Clin Infect Dis 2003;37:1365-73.
25. Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK. Incidence of cytomegalovirus (CMV) retinitis in second eyes of patients with the acquired immune deficiency syndrome and unilateral CMV retinitis. Am J Ophthalmol 2005;139:1028-34.
26. Kempen JH, Jabs DA, Dunn JP, West SK, Tonascia J. Retinal detachment risk in cytomegalovirus retinitis related to the acquired immunodeficiency syndrome. Arch Ophthalmol 2001;119:33-40.
27. Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK, Tonascia JA. Risk of vision loss in patients with cytomegalovirus retinitis and the acquired immunodeficiency syndrome. Arch Ophthalmol 2003;121:466-76.
28. Masur H, Kaplan JE, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons-2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. Ann Intern Med 2002;137:435-78.
29. Jabs DA, Van Natta ML, Kempen JH, Reed Pavan P, Lim JI, Murphy RL, et al. Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Am J Ophthalmol 2002;133:48-61.
30. Kempen JH, Min YL, Freeman WR, Holland GN, Friedberg DN, Dieterich DT, et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. Ophthalmology 2006;113:684-94.
31. Steinbrook R. HIV in India-the challenges ahead. N Engl J Med 2007;356:1197-201.
32. Jabs DA. Ocular manifestations of HIV infection. Trans Am Ophthalmol Soc 1995;93:623-83.
33. Kempen JH, Min YL, Freeman WR, Holland GN, Friedberg DN, Dieterich DT, et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. Ophthalmology 1996;114:821-7.
34. Kumarasamy N, Vallabhaneni S, Flanigan TP, Mayer KH, Solomon S. Clinical profile of HIV in India. Indian J Med Res 2005;121:377-94.
35. Biswas J, Madhavan NN, George AE, Kumarasamy N, Solomon S. Ocular lesions associated with HIV infection in India: A series of 100 consecutive patients evaluated at a referral center. Am J Ophthalmol 2000;129:9-15.
36. Jabs DA. Ocular manifestations of AIDS. 1998. p. 123-36.
37. Lim SA, Heng WJ, Lim TH, Leo YS, Wong SY. Ophthalmic manifestations in human immunodeficiency virus infection in
38. Mesaric B, Begovac J, Ugrinovic N, Babic K, Liscic M. Cytomegalovirus retinitis in patients with human immunodeficiency virus infection. Lijec Vjesn 1998;120:106-10.

39. Muccioli C, Belfort R Jr, Lottenberg C, Lima J, Santos P, Kim M, et al. Ophthalmological manifestations in AIDS: Evaluation of 445 patients in one year. Rev Assoc Med Bras 1994;40:135-8.

40. Nagata Y, Fujino Y, Matsumoto S, Nishi M, Ono A, Mochizuki M, et al. Ocular manifestations in Japanese patients with human immunodeficiency virus infection. Jpn J Ophthalmol 1993;37:275-81.

41. Tanterdtam J, Suwannagool S, Namatra C, Singalavanija A. A study of ocular manifestations in HIV patients. Thai J Ophthalmol 2002;10:11-20.

42. Wong KH, Lee SS, Lo YC, Li PC, Ho HF, Sitt WH, et al. Profile of opportunistic infections among HIV-1 infected people in Hong Kong. Zhonghua Yi Xue Za Zhi (Taipei) 1995;55:127-36.

43. Kestelyn P. The epidemiology of CMV retinitis in Africa. Ocul Immunol Inflamm 1999;7:173-7.

44. Kempen JH, Jabs DA. Ocular complications of HIV infection, 2nd ed. 2003. p. 318-40.

45. Arevalo JF, Gonzalez C, Capparelli EV, Kirsch LS, Garcia RF, et al. Cytomegalovirus retinitis in patients with human immunodeficiency virus infection. Ophthalmology 1998;105:1404-10.

46. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant: The Ganciclovir Implant Study Group. N Engl J Med 1999;340:1063-70.

47. Skiest DJ, Chiller T, Chiller K, Park A, Keiser P. Use of the ganciclovir implant for the treatment of cytomegalovirus retinitis in patients with AIDS. J Infect Dis 1993;168:557-63.

48. Muccioli C, Belfort R Jr, Lottenberg C, Lima J, Santos P, Kim M, et al. Ophthalmological manifestations in AIDS: Evaluation of 445 patients in one year. Rev Assoc Med Bras 1994;40:135-8.

49. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. N Engl J Med 2002;346:1119-26.

50. Skiest DJ, Chiller T, Chiller K, Park A, Keiser P. Protease inhibitor therapy is associated with markedly prolonged time to relapse and improved survival in AIDS patients with cytomegalovirus retinitis. Int J STD AIDS 2001;12:659-64.

51. Martin DF, Sierra-Madero J, Walmsley S, Wolitz RA, Macey K, Georgiou P, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. N Engl J Med 2002;346:1119-26.

52. Thorne JE, Jabs DA, Vitale S, Miller T, Dunn JP, Sembda RD. Catheter complications in AIDS patients treated for cytomegalovirus retinitis. AIDS 1998;12:2321-7.

53. Collaborative DHPG Treatment Study Group. Treatment of serious cytomegalovirus infections with 9-(1,3-dihydroxy-2-propoxymethyl)guanine in patients with AIDS and other immunodeficiencies. N Engl J Med 1986;314:801-5.

54. Spector SA, Weingeist T, Pollard RB, Dieterich DT, Samo T, Benson CA, et al. A randomized, controlled study of intravenous ganciclovir therapy for cytomegalovirus peripheral retinitis in patients with AIDS. J Infect Dis 1993;168:557-63.

55. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. Foscarnet-Cytomegalovirus Retinitis Trial: Final results of a randomized, controlled trial. Arch Ophthalmol 1994;112:1531-9.

56. Benson CA, Beber A, De S, Baird BF, Falloon J, Kovacs JA, et al. A randomized, controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS. Ann Intern Med 1991;115:665-73.

57. Laluzari JP, Stagg RJ, Kuppermann BD, Holland GN, Kramer F, Ives DV, et al. Intravenous cidofovir for peripheral cytomegalovirus retinitis in patients with AIDS: A randomized, controlled trial. Ann Intern Med 1997;126:267-74.

58. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. Parenteral cidofovir for cytomegalovirus retinitis in patients with AIDS: The HFMPC peripheral cytomegalovirus retinitis trial: A randomized, controlled trial. Arch Ophthalmol 1994;112:1531-9.

59. Martin DF, Dunn JP, Davis JL, Duker JS, Engstrom RE Jr, Friedberg DN, et al. Use of the ganciclovir implant for the treatment of cytomegalovirus retinitis in the era of potent antiretroviral therapy: Recommendations of the International AIDS Society-USA panel. Am J Ophthalmol 1999;127:329-39.

60. Martin DF, Dunn JP, Davis JL, Duker JS, Engstrom RE Jr, Friedberg DN, et al. Intravitreal fomivirsen for treatment of newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS. Am J Ophthalmol 2002;133:467-74.

61. Martin DF, Dunn JP, Davis JL, Duker JS, Engstrom RE Jr, Friedberg DN, et al. Intravitreal fomivirsen for treatment of newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS. Am J Ophthalmol 2002;133:467-74.

62. Vitravene Study Group. A randomized controlled clinical trial of intravitreous fomivirsen for treatment of newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS. Am J Ophthalmol 2002;133:467-74.

63. Vitravene Study Group. Randomized dose-comparison studies of intravitreous fomivirsen for treatment of cytomegalovirus retinitis that has reactivated or is persistently active despite other therapies in patients with AIDS. Am J Ophthalmol 2002;133:475-83.

64. Baudouin C, Chassain C, Caujolle C, Gastaud P. Treatment of cytomegalovirus retinitis in AIDS patients using intravitreal injections of highly concentrated ganciclovir. Ophthalmologica 1996;210:329-35.

65. Cochereau-Massin I, LeHoang P, Lautier-Frau M, Zazoun L, Marcel P, Robinet M, et al. Efficacy and tolerance of intravitreal ganciclovir in cytomegalovirus retinitis in acquired immune deficiency syndrome. Ophthalmology 1991;98:1348-53.

66. Young S, Morlet N, Besen G, Wiley CA, Jones P, Gold J, et al. High-dose (2000-microgram) intravitreal ganciclovir in the treatment of cytomegalovirus retinitis. Ophthalmology 1998;105:1404-10.

67. Diaz-Llopis M, Esparza E, Munoz G, Navea A, Chipont E, Cano J, et al. High dose intravitreal foscarnet in the treatment of cytomegalovirus retinitis in AIDS. Br J Ophthalmol 1994;78:120-4.

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