Terapia antirretroviral I: Casos especiales

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There are a number of circumstances in which antiretroviral combination therapy may be administered. Treatment to prevent vertical transmission between an HIV- infected woman and her infant is one such situation, which has already been addressed by Dr. Luque. The others also involve the earliest stage of infection - first as post-exposure prophylaxis to prevent transmission after accidental exposure to blood or body fluids in the health care setting, and, following sexual exposure and then for the patient with acute HIV infection.

Acute or primary HIV infection, defined by a constellation of symptoms and a laboratory profile in which HIV-1 RNA or DNA can be detected but antibodies are not yet present, has received considerable attention. Theoretically, intervention may prevent infection from initiating its inexorable course of destruction. Explicit in these efforts to identify the acutely infected person is the premise that early treatment may prevent establishment of HIV in "sanctuary sites" and eradicate the infection.

The initial clinical descriptions of primary HIV infection were of an illness similar to acute Epstein-Barr virus infection: fever, malaise, lymphadenopathy, and sore throat. It is estimated that up to 70% of newly infected persons will experience symptoms. These vary widely. The most frequent complaint or sign is fever, followed by malaise, lymphadenopathy, rash, oral ulcers, diarrhea, abdominal pain, oral candidiasis, etc. Leukopenia is usually present, and many patients have mild abnormalities of the liver enzymes. Occasionally the presenting manifestations are that of aseptic meningitis. There is prognostic significance to the manifestations of acute HIV infection. Symptoms predict a more rapid course, and the more severe or prolonged the symptoms the worse the prognosis.

The diagnosis may be established by documenting seroconversion (although this may take several weeks to months), by demonstrating P-24 antigenemia, HIV-1 DNA by qualitative PCR assay, or HIV-1 RNA by qualitative or quantitative assay. The P-24 antigen is less sensitive than the PCR assays, although most symptomatic persons will be positive. The quantitative HIV RNA PCR (the viral load assay used for monitoring therapy and prognosis) is comparable to the qualitative PCR assays, but more expensive.

The amplitude of the early rise in HIV RNA copies in the blood does not correlate with prognosis, but after approximately 4 months most patient reach an equilibrium, the "viral set point" which is of prognostic significance.

The initial immune response to acute HIV infection is cellular with activated cytotoxic lymphocytes leading the defense. Only somewhat later do antibodies develop. Neutralizing antibodies do not seem to play a critical role, certainly not sufficient to control the infection.

Early therapy is advocated in the hopes that control of the infection will allow the CD4 directed cellular immune response to fully develop so the unending cycle of activated CD4 cell infection-virus production-cellular death-CD4 cell infection does not develop. Early therapy can suppress replication in blood and lymphnodes for more than two years with maintenance of a normal immune system. Unfortunately, the hopes based on the model of Drs. Perlson, Ho and colleagues which suggests that eradication might be achieved with 3 to 4 years of therapy have been dashed by reports of viable HIV isolated from cells of some patients free of detectable virus in blood or lymphnode by ultrasensitive methods for more than two years. While this finding does not completely disprove the possibility of eradication, it does mean that the time to do so will be longer than initially thought.

Therapy in the earliest stage of HIV-1 infection is advocated on the grounds that even though eradication may not be achievable, suppression of virus is possible with prevention of immune dysfunction and clinical disease. At the present time, maximal therapy - i.e., combination therapy - is the only one that seems appropriate. Whether or not the drugs can be later stopped or the regimen simplified will be learned as we gain experience from patients now on therapy.

Once the infection is established, the decision to treat or not should be based on the viral load, the CD4 count and the patient's desire and ability to adhere to the rigorous and expensive therapy such treatment will entail. For patients with a low or non-detectable viral load there may be no progression for many years and observation with monitoring of viral load every six months is appropriate. A high viral load or a rise in a previously low/non-detectable load suggests an ominous course and therapy would be advised by many experts.

Postexposure prophylaxis has been advocated almost since zidovudine became available on a compassionate basis in late 1986. Because experimental data with animals inoculated with retroviruses was conflicting and because of several well publicized prophylaxis failures in health care workers (and because of the potential treatment toxicity), there was not much faith in prophylaxis until the dramatic results from ACTG Trial 076 demonstrated that zidovudine can prevent vertical transmission to the newborn child of an infected mother. The report that an international study of factors associated with transmission following percutaneous exposure found that post exposure zidovudine decreased transmission by approximately 70% laid the foundation for current recommendations. These recommendations represent extrapolations from the observations of: the international study (in which only zidovudine was given), recognition that combination therapy is highly active, the increasing prevalence of resistant HIV and the potential for adverse reactions to the antiretroviral drugs.

Because initmate sexual intercourse with an HIV-infected partner clearly represents a risk for exposure, prophylaxis in this situation has also received attention. Although the risk is

less, it is not neglible and if post-exposure prophylaxis prevents transmission through percutaneous exposure it theoretically should protect in the former circumstance also.

References

Cardo D.M., Culver D.H., Ciesielski C.A., *et al.* A Case-Control Study of HIV Seroconversion in Health Care Workers after Percutaneous Exposure. N Engl J Med. 1997; 337:1485-1490.

Carne C.A., Smith A., Elkington S.G., *et al.* Acute encephalopathy coincident with seroconversion for anti-HTLV-III. Lancet 1985;2:1206.

Cates W. Jr., Cohen M.S. Early treatment of HIV infection. N Engl J Med. 1995;333:1783.

Clark S.J., Shaw G.M. The acute retroviral syndrome and the pathogenesis of HIV-1 infection. Seminars in Immunol 1993;5:149-55.

Cooper D.A., Maclean P., Finlayson R. *et al.* Acute AIDS retrovirus infection. Lancet 1985;1:537.

Case-control study of HIV seroconversion in health-care workers after percutaneous exposure to HIV infected blood--France, United Kingdom and United States. January 1988-August 1994. MMWR. 1995;44:929-933.

Connner E.M., Sperling R.S., Gelber R., *et al.* Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331:1173-1180.

Denning D.W., Anderson J., Rudge P., *et al.* Acute myelopathy associated with primary infection with human immunodeficiency virus. Br Med J. 1987;294:143-4.

Dorrucci M., Rezza G., Vlahov D., *et al.* Clinical characteristics and prognostic value of acute retroviral syndrome among injecting drug users. Italian Seroconversion Study. AIDS. 1995;9:597-604.

Fox R., Eldred L.J., Fuchs E.J. *et al.* Clinical manifestations of acute infection with human immunodeficiency virus in a cohort of gay men. AIDS. 1987;1:35.

Gaines H., von Sydow M., Pehrson P.O., Lundbergh P. Clinical picture of primary HIV infection presenting as a glandular-fever-like illness. Br Med J 1988;297:1363.

Grant I., Atkinson J.H., Hessellink J.R. *et al.* Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. Ann Intern Med 1987;107:828.

Havlir D.V., Richman D.D. Viral dynamics of HIV: implications for drug development and therapeutic strategies. Ann Intern Med. 1996;124:984-994.

Henderson D.K., Postexposure Treatment of HIV - Taking some risks for Safety's Sake. N Engl J Med. 1997; 337:1542-1543.

Ho D.D. Time to hit HIV, early and hard [editorial]. N Engl J Med 1995;333:450-1.

Ho D.D., Sarngadharan M.G., Resnick L., Dimarzoveronese F., Rota T.R., Hirsch M.S. Primary human T-lymphotropic virus type III infection. Ann Intern Med 1985;103:880-3.

Imrie A., Carr A., Duncombe. C., *et al.* Primary infection with zidovudine-resistant human immunodeficiency virus type 1 does not adversely affect outcome at 1 year. J I D. 1996;174:195-8.

Katz M.H., Gerberding J.L. Postexposure treatment of people exposed to the human immunodeficiency virus through sexual contact or injection-drug use. N Engl J Med 1997:336:1097-1099.

Kinloch-de Loes S., Hirschel B.J., Hoen B., *et al.* A controlled trial of zidovudine in primary human immunodeficiency virus infection. N Engl J Med 1995;333:408-13.

Markowitz M., Cao Y., Hurley A., *et al.* Triple therapy with AZT, 3TC and ritonavir in 12 subjects newly infected with HIV-1. Presented at the XI International conference on AIDS; July 7-12, 1996; Vancouver, British Columbia, Canada. Abstract Th.B.933.

Markowitz M., Cao Y., Vesanen M., *et al.* Recent HIV infection treated with AZT, 3TC, and a potent protease inhibitor. Presented at 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract LB8.

Mellors J.W., Kingsley L.A., Rinaldo C.R. Jr, *et al.* Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Intern Med 1995;122:573-9.

Mellors J.W., Rinaldo C.R. Jr., Gupta P., White R.M., Todd J.A., Kingsley L.A. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996;272:1167-70.

Musey L., Hughes J., Schacker T., *et al.* Cytotoxic-T-Cell Responses, Viral Load, and Disease Progression in early HIV-1 Infection. N Engl J Med. 1997; 337:1267-1274.

Niu M.T., Stein D.S., Schnittman S.M. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in human and animal retrovirus infections. J Infect Dis 1993; 168:1490-501.

Oldstone M.B.A. HIV versus cytotoxic T Lymphocytes - The War being Lost. N Engl J Med. 1997; 337:1306-1308.

Perrin L. Rakik A., Yerly S., *et al.* Combined therapy with zidovudine and L-697, 661 in primary HIV infection. AIDS. 1996;10:1233-1237.

Rustin M.H.A., Ridely C.M., Smith M.D., *et al.* The acute exanthem associated with seroconversion to human T-cell lymphotropic virus III in a homosexual man J Infect Dis. 1986;12:161-3.

Schacker T. Collier A.C., Hughes J., *et al.* Clinical and epidemiologic features of primary HIV infection. Ann Intern Med. 1996;125:257-264.

Tindall B., Barker S., Donovan B., Sydney AIDS Study Group. Characterization of the acute clinical illness associated with human immunodeficiency virus infection. Arch Intern Med. 1988;148:945.

Tindall B., Cooper D.A., Donovan B. *et al.* Primary human immunodeficiency virus infection: Clinical and serologic aspects. Infect Dis Clin North Am 1988;2:329

Vanhems P., Allard R., Cooper D.A., *et al.* Acute human immunodeficiency virus type 1 disease as a mononucleosis-like illness: is the diagnosis too restrictive? Clin Infect Dis 1997;24:965-70.

Vanhems P., Lambert J., Cooper D.A., *et al.* Severity and Prognosis of Acute Human Immunodeficiency Virus Type 1 Illness: A dose-Response Relationship. Clin Infect Dis 1998;26:323-9.

Wallace M.R., Harrison W.O. HIV seroconversion with progressive disease in health care worker after needle stick injury. Lancet 1988;1:1454.

Zaunders J., Carr A., McNally L., Penny R., Cooper D.A. Effects of primary HIV-1 infection on subsets of CD4+ and CD8+ T lymphocytes. AIDS 1995;9:561-6.