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 intimate 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 negligible and if post-exposure prophylaxis prevents transmission through percutaneous exposure it theoretically should protect in the former circumstance also.

References


