Early Versus Delayed Treatment of HIV Infection
Zidovudine Should be Given Before Symptoms Develop

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Summary

An understanding of the virology and pathogenesis of HIV infection provides a rationale for initiating early intervention with antiretroviral drugs. Even at the earliest stages of infection when HIV-infected patients are asymptomatic, viral replication is ongoing, particularly in lymphoid tissues. Initiation of antiretroviral therapy can reduce viral replication and delay disease progression. A possible objection to early intervention therapy with zidovudine is the risk of selecting out resistant isolates of HIV, which would be difficult to treat. In practice, zidovudine-resistant isolates occur significantly less frequently in patients with early-stage disease compared with those with late-stage HIV infection, thus supporting the early use of zidovudine; in addition, alternative therapies, active against zidovudine-resistant isolates, are available.

Clinical trials with zidovudine in asymptomatic patients have differed in terms of length of follow-up, patient inclusion criteria, dosages and end-points. However, a number of conclusions are possible based on the results obtained: early intervention delays the progression to AIDS, delays the onset of symptomatic disease, has a favourable effect on surrogate markers of HIV infection and is well tolerated; it does not, however, seem to produce any benefit in terms of survival. It is this last point that has given rise to much of the controversy regarding early intervention with zidovudine in asymptomatic patients.

Since the disease is progressive in nature with persistent and high levels of viral replication and as prolonging the period of relative health and quality of life when the patient is asymptomatic is desirable, the choice to treat before symptoms develop would appear to be the optimal therapeutic strategy.

Zidovudine has been the most widely studied antiretroviral agent in HIV-infected patients and, as such, has been evaluated at all stages of the disease. Initially, it was used in patients with AIDS or AIDS-related complex (ARC).¹² Indeed, in the first placebo-controlled trial (BW 002) involving 282 patients with advanced infection, the short term benefits of zidovudine at 1500 mg/day in terms of reducing opportunistic infections and mortality were very evident.¹¹ As a result of these encouraging findings, and in the face of few therapeutic alternatives, zidovudine was quickly approved and widely accepted as the treatment of choice for patients with AIDS or ARC.

Experience with the drug following these early trials has clarified our understanding of not only
its strengths but also its weaknesses in patients with advanced HIV infection. Certainly the high dosages initially employed (1200 to 1500 mg/day) were associated with significant haematological toxicity.\textsuperscript{[2-5]} The therapeutic benefits of zidovudine in terms of survival were more difficult to discern after 6 to 12 months’ continued therapy.\textsuperscript{[6-12]} Finally, resistant strains of the virus were observed in symptomatic patients on prolonged therapy.\textsuperscript{[13-15]}

In light of these limitations there has been controversy surrounding the appropriate use of antiretroviral drugs, of zidovudine in particular, in patients with early HIV infection and who remain asymptomatic. This is a very important and practical management issue because individuals with HIV infection are asymptomatic and have CD4+ cell counts > 200 cells/µl for the majority of the time.

In this overview we assess the merits of early intervention in patients with HIV infection and try to answer the following questions:

- What is the scientific rationale for treating HIV-infected patients during the asymptomatic period?
- What is the evidence for clinical benefit in asymptomatic patients?
- Based on evidence from the literature, which antiretroviral therapy regimen is most appropriate?

\textbf{1. Early Intervention with Chemotherapy: Principles and Supporting Evidence}

In other areas of medicine (e.g. in most neoplastic diseases, bacterial infections and other viral infections) the principle of initiating chemotherapy at an early stage is well accepted and constitutes standard practice. The reasons why early treatment has not been so well accepted in patients with HIV appear to be twofold: first, the available drugs (i.e. the approved nucleoside analogues) have limited efficacy; and second, the natural history of the disease is mostly symptom free, even when the infection has progressed and is associated with high levels of viral replication and extensive pathology.

In terms of natural progression of the disease it is now well established that almost all patients who are seropositive for HIV, even those with normal CD4+ counts (> 500 cells/µl), have detectable viral RNA, most probably in the form of replication-incompetent neutralised virus in plasma and in perifollicular regions of lymphoid tissue.\textsuperscript{[16-18]} With time viral RNA titres increase, together with increasing levels of HIV in plasma.\textsuperscript{[19-22]} This increased viral replication is associated with progressive destruction of normal lymphoid architecture, lymphocyte function and CD4+ counts.\textsuperscript{[16,17,23]} These changes occur in asymptomatic patients who may or may not be aware that they are infected.

A major objection to early intervention with zidovudine has been the possibility of selecting out highly resistant isolates of HIV, which would be far more difficult to treat.\textsuperscript{[24]} Fortunately, while still a real concern, it appears that the rate of emergence of resistant isolates is related to the patient’s stage of HIV disease.\textsuperscript{[15]} Resistant isolates evolve more quickly in those with late-stage disease, presumably because of higher viral burdens, and occur significantly less often in patients with early asymptomatic infection. This supports the early use of zidovudine rather than opposes it.\textsuperscript{[15,25]}

\textbf{2. Early Intervention with Zidovudine}

\textbf{2.1 Clinical Data}

A consistent finding in all placebo-controlled clinical trials with zidovudine has been the positive impact of monotherapy in delaying clinical HIV disease progression for some period of time (table I).\textsuperscript{[11,5-7,26]} It would seem likely that the mechanism involved in extending the disease-free interval during zidovudine monotherapy relates to suppression of viral replication, with a consequent increase in CD4+ counts;\textsuperscript{[27]} however, other factors may be involved.\textsuperscript{[28]}

In symptomatic HIV-infected patients, therapeutic trials have demonstrated that mortality is reduced with zidovudine administration. Measures of the patient’s quality of life are also improved by