AIDS and the lung

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2—Antiretroviral treatment in human immunodeficiency virus disease

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Introduction

As our understanding of the aetiology, pathogenesis, natural history and clinical profile of the acquired immune deficiency syndrome (AIDS) and human immunodeficiency virus (HIV) infection have increased, the therapeutic approach has become increasingly focused. There are two broad categories of chronic HIV infection: asymptomatic infection, which includes disease with and without persistent generalised lymphadenopathy, and symptomatic infection, comprising the AIDS related complex, AIDS itself, and HIV encephalopathy. There are four discrete components of treatment: general and supportive management, treatment and prophylaxis for opportunist diseases, antiretroviral treatment, and immunorestorative approaches.¹ The management of individual patients requires attention to all four components as they are essentially complementary.

The first strategy is applicable to all stages of HIV infection and includes counselling and education about the nature of HIV and AIDS, health maintenance, avoidance of cofactors for progression,² and the provision of an open access and responsive model of integrated hospital and community care.¹³ The management of opportunist events is largely restricted to symptomatic disease and has for most of the epidemic been the central aspect of treatment.¹⁴⁻⁶ Although there is some interest in the use of antimicrobial prophylaxis in symptomless individuals, the optimal approach for most opportunist organisms has yet to be defined even in symptomatic patients⁶; the need for prophylaxis in early infection, the specific approach to be used, and the subsets of patients most likely to benefit have not been determined. Immuno-

restorative approaches are generally thought most appropriate in immunodeficient patients. Results so far have been disappointing when used alone,¹ but there is likely to be considerable interest in combining such strategies with the use of antiretroviral agents. In recent years the latter have been the main focus of attention and the present state of clinical practice in this area is reviewed in this article.

Zidovudine

Zidovudine (azidothymidine, AZT) is the only antiretroviral agent to have been shown unequivocally to influence HIV replication and to affect the clinical course of symptomatic HIV infection. It has been licensed for use in many countries. It is a nucleoside analogue that acts as a reverse transcriptase inhibitor and serves as a DNA chain terminator. Studies showing in vitro efficacy⁷ were soon followed by phase I studies in patients with severe HIV disease,⁸ and these provided evidence of in vivo activity. These were followed by a major phase II placebo controlled evaluation which showed lower mortality and a lower incidence and severity of opportunist events in addition to greater well being in the treated group than in those taking placebo.⁹ The benefits became apparent after some six to eight weeks of treatment. This study also showed that the drug had substantial bone marrow toxicity, notably affecting the erythroid and myeloid series.¹⁰ A brief report indicated a beneficial effect in HIV associated neurological disease.¹¹ Subsequent studies have shown that serum and cerebrospinal fluid HIV p24 antigen concentrations fall significantly with treatment, but rise again if the drug is discontinued.^{12,13} A characteristic observation in treated patients is a transient rise in CD4 lymphocytes one to two months after the start of treatment.⁹ Since these early studies zidovudine has been very widely

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used in the treatment of symptomatic HIV infection and this has allowed a fuller assessment of the benefits and adverse effects of the drug.¹⁴⁻¹⁹

Efficacy of zidovudine

The overall clinical effect of zidovudine on the immunodeficiency disease^{9,14-17,19} may be summarised as decreasing the rate at which it progresses. The disease process is spread therefore over a longer period, during which time the patient also has improved quality of life. This benefit is presumably due to the drug's slowing the pace of cell to cell infection within the host and reducing the production of potentially immunosuppressive HIV proteins. Patients' wellbeing is improved, as judged by Karnofsky scores, weight,⁹ or visual analogue scale assessment.¹⁵ It is clear that disease progression continues, albeit at a slower rate. Contrary to earlier hopes and expectations, there is negligible evidence of true immunological recovery. Intercurrent opportunist infections continue to occur, but, at least in the first year of treatment, their frequency is reduced and they also tend to be less severe. As a result there is a reduction in early mortality in patients with AIDS, and those with the AIDS related complex progress less rapidly to AIDS. Zidovudine does not, however, remove the rationale for prophylaxis of the more common opportunist infections. Even in patients able to continue zidovudine at full dose, the beneficial effects are less apparent after the first year.

Some observations have been made on the effects of zidovudine on specific manifestations of AIDS. Previously untreated patients with cryptosporidiosis given zidovudine may show resolution of this infection,¹⁷ though the results of this study have not been confirmed, and there is no doubt that patients may develop cryptosporidiosis while receiving zidovudine. Patients with Kaposi's sarcoma, who have usually been those with other features of AIDS or AIDS related complex, show variable tumour responses with zidovudine. Some have no change in tumour behaviour or tempo, but some show acceleration of tumour growth and a substantial proportion (30-50%) show reduction in tumour size to an extent rarely seen to occur spontaneously in any but the very mildest disease.^{15,17}

Although patients typically show a rise in circulating CD4 positive cells between the first and the second month of treatment, this is not sustained and values return to baseline within a few months.^{9,14,15} The dissociation between these changes and the timing of clinical benefit suggests that the alterations reflect a temporary change in lymphocyte traffic rather than any sustained reconstitution. Some restoration of delayed type hypersensitivity skin responses has been

apparent in some studies,^{17,19} but their biological significance is not clear. Functional studies on blood lymphocytes have shown increased mitogen responsiveness during treatment (Knox *et al*, unpublished observations). A reduction in polyclonal hypergammaglobulinaemia has been reported in children treated with zidovudine,²⁰ though such an effect is not apparent in adults.

After the initial fall in HIV p24 antigen seen in antigenaemic patients after treatment there is a slow rise in antigen levels in serum even when full dose treatment is maintained, though serum levels remain well below the pretreatment levels.^{12,14-17} The meaning of this finding is not clear. It may represent the cumulative effect of incomplete slowing of viral replication or possibly the emergence of relatively resistant strains.²¹ Antibodies to p24, which are typically absent in advanced disease, possibly as a result of forming complexes with HIV p24 antigen, do not return with treatment; but this may reflect incomplete reduction in replication of the virus. Results of virus culture have proved to be a much less adequate marker of the efficacy of treatment than p24 antigen levels, presumably because latent viral DNA is unaffected.

HIV encephalopathy shows a variable response, but many patients show substantial and often sustained improvement.^{15,18,22} This is most striking in patients with a recent onset of symptoms and in those who lack motor signs.¹⁵ Serious clinical impairment may resolve even though some deficit often remains; neuropsychological tests also show evidence of improvement.^{15,18,22} Children often show considerable neurological improvement, in addition to evidence of the kinds of benefit seen in adults.²⁰ These benefits suggest that at least a part of the encephalopathy is due to neuronal dysfunction, whether this is caused by HIV proteins or by host mediators released from infected macrophages, rather than neuronal loss. Early introduction of zidovudine might prevent the appearance of HIV encephalopathy, though this has not been formally demonstrated; the sustained improvement in neuropsychological tests seen in patients without overt clinical encephalopathy¹⁵ is encouraging in this regard. HIV associated myelopathy and peripheral neuropathy have shown little, if any, improvement and may progress after the introduction of zidovudine. This may signify that these disorders are due more to loss than to dysfunction of neurones.

A rise in previously low platelet counts has been seen after treatment with zidovudine^{9,15,16} and severe thrombocytopenic purpura has shown a good initial clinical response.²³ Zidovudine offers a valuable new approach to the management of this complication of HIV infection. Longer term follow up suggests that

myelotoxicity from zidovudine may affect platelet precursors at a later date, especially when other myelotoxic drugs are being used concurrently (see below).

Toxicity of zidovudine

In the first weeks of treatment patients may experience nausea, headache, rash, and general malaise; but these subside completely despite continuing drug treatment in virtually all cases. In the ensuing months symptomatic side effects are uncommon. Some patients having long term treatment may experience malaise, nausea, and headache at a later stage; these resolve when they discontinue the drug. The incidence of these later effects has not been defined.

The major medium to long term toxicity is due to bone marrow suppression. This is first seen as anaemia, which affects some 40% of patients.¹⁰⁻¹⁷ Many become transfusion dependent, requiring on average four units a month. In some cases red cell aplasia develops.¹⁶ Virtually all patients have an increased mean corpuscular volume¹⁰; this does not seem to be related to the development of anaemia and may not be seen in those developing red cell aplasia.¹⁶ The effect appears not to be due to low B₁₂ or folate concentration. Interestingly, two patients with thalassaemia whom we have treated have shown a rise in mean corpuscular volume from low values into the normal range (unpublished observations).

Neutropenia tends to develop later than anaemia and affects some 20–30% of patients.¹⁰⁻¹⁵ This may be severe (white cell counts may fall below $0.5 \times 10^6/l$) and it leads to additional susceptibility to staphylococcal and Gram negative infections, systemic candidal infection, and invasive aspergillosis (Pinching *et al*¹⁵ and unpublished observations). Neutropenia may be exacerbated by the use of some other drugs (see below). Reduction of the dose of zidovudine is often necessary to avert or ameliorate this effect and the drug may need to be discontinued. Recovery of neutrophils is slow, taking two to four weeks in most cases but several months in others.

Although platelet counts that are low initially may rise when zidovudine is started, counts then tend to fall in all patients. This is rarely severe unless other myelosuppressive drugs are being used concurrently (see below), but dose reductions may be required for severe thrombocytopenia; recovery is again relatively slow. An increased incidence of haemarthroses has been described in a haemophiliac patient taking zidovudine²⁴; the drug apparently exacerbated the effects of a non-steroidal anti-inflammatory drug on platelet function.

Factors affecting the development of marrow toxicity have been shown to include low CD4 cell counts,

prior haematological defects,¹⁰ and the concurrent use of some other drugs. Paracetamol appeared to have such an effect in the phase 2 study¹⁰ but other concurrent drugs were not permitted in the protocol. Subsequent experience¹⁵ suggests that the most important interactions are with dapsone and ganciclovir, which is itself myelosuppressive though rarely causing severe toxicity. Daily or alternate day dapsone, used for pneumocystis infections with trimethoprim and for toxoplasma infections with pyrimethamine, may show a profound interaction, and similar problems are seen with ganciclovir during either acute or maintenance treatment. Co-trimoxazole, Fansidar (pyrimethamine and sulfadoxine), antifungal agents, acyclovir, antituberculous drugs, and the chemotherapy combination bleomycin and vincristine do not seem to have such an effect.¹⁵

As other drugs are frequently indicated for patients with AIDS, these interactions are of considerable practical importance and may necessitate modification of therapeutic regimens. Some very hard clinical decisions may have to be made about which drug to stop or reduce. The immediate need for treatment or maintenance for cytomegalovirus retinitis or toxoplasma will usually take precedence over the longer term potential benefits of zidovudine. Alternative antimicrobial drugs may be substituted in some instances. There appears to be no basis, however, for the practice of automatically stopping zidovudine during treatment of all intercurrent infections, a practice that has emerged quite commonly, apparently in inappropriate emulation of the phase 2 study protocol.

In patients receiving long term zidovudine necrotising myopathy has emerged as an important and unexpected toxic effect.²⁵⁻²⁷ In our own experience this has affected some 18% of patients having more than 200 days of treatment.²⁷ It is characterised by the rapid onset of proximal muscle weakness, usually affecting the lower limbs predominantly, often associated with pain and tenderness. Raised creatine phosphokinase levels are seen and in prospective studies may precede the development of clinical symptoms and signs by some weeks (Peters and Pinching, unpublished observations). Symptoms, signs, and muscle enzyme changes resolve with cessation of zidovudine but not with dose reduction.²⁷ The histological features are predominantly of muscle necrosis with little or no inflammatory infiltrate. The disorder is distinct from the uncommon (1–2%) HIV associated myopathy, in which inflammatory change is seen without necrosis and in which raised creatinine phosphokinase is less of a feature. A prospective study of zidovudine in treated and untreated patients with AIDS shows no evidence of myopathy or sustained muscle enzyme changes in the untreated group (Peters and Pinching, unpublished observations). The pathogenesis of this toxicity is

obscure but it does not appear to be related to concurrent drug usage, as has been claimed. Preliminary observations imply a mitochondrial disorder.

A few cases of seizures apparently related temporally to zidovudine treatment have been described^{28 29} but they are uncommon and their relation to treatment remains somewhat uncertain.

If the dosage of zidovudine is abruptly reduced or stopped, some patients may develop an acute meningoencephalitic syndrome in the succeeding days or weeks.^{1 15 30} It is characterised by headache, fever, extreme fatigue, confusion, and impaired consciousness in severe cases. In most instances it is self limiting, lasting two to three weeks, but in some cases it has contributed to the patient's death. In the original report³⁰ other neurological opportunist disease was rigorously excluded; other clinicians have reported similar events likely to represent the same phenomenon. One report described an acute myelopathy that followed dose reduction³¹ and we have recently seen another such case. This "rebound" phenomenon is more frequent in patients with pre-existing HIV induced neurological disease, but it is not restricted to such patients. It may be prevented or ameliorated by more gradual changes in dosage, when this is practicable.

Practicalities of zidovudine treatment

Early pharmacokinetic studies suggested that four hourly doses of zidovudine were required and this was used in early studies. Most regimens have used 200 mg four hourly. It has emerged more recently that less frequent doses are equally effective in suppressing HIV p24 antigen, at least in the short term.³² Though many patients adjusted surprisingly well to the rigours of four hourly dosing (sometimes helped by the use of "bleeping pill boxes"), the night time doses were not popular. Many patients are now having four times daily regimens with 250 or 300 mg doses. The long term efficacy and toxicity of such regimens have not been evaluated. There are some early hints that toxicity may be somewhat reduced by adjusting dose to body weight, but formal recommendations are not yet available.

Commonly used current indications for zidovudine treatment in symptomatic HIV infection are:

- 1 AIDS with opportunist infection (with or without tumours);
- 2 AIDS related complex;
- 3 AIDS with tumours and features of AIDS related complex;
- 4 HIV encephalopathy;
- 5 HIV associated thrombocytopenia.

The value of zidovudine in patients with Kaposi's sarcoma but no features of AIDS related complex

remains unproved and practice varies. One study suggested that zidovudine could affect lymphocytic interstitial pneumonitis³³ but another failed to show such an effect.³⁴ There are also variations in the criteria used for diagnosing AIDS related complex. Our own practice is to use zidovudine when there are two or more clinical features of AIDS related complex or when there is one feature of AIDS related complex with Kaposi's sarcoma. Some centres use criteria based on laboratory tests, such as the finding of p24 antigen or a CD4 cell count below 200, to supplement clinical criteria in uncertain cases. A recent trial has apparently shown reduced progression to AIDS in HIV infected patients with minor symptoms and low CD4 counts, but details have not yet been published (discussed in ref 52).

Current evidence would favour the introduction of zidovudine early in the evolution of symptomatic HIV infection, it being more likely then to reduce morbidity and mortality in the medium term. The patient may wish to consider the pros and cons of this approach carefully, so we have found it advisable to allow some weeks for the patient to make this decision. This is especially valuable for the newly diagnosed patient with AIDS who has an opportunist infection. At diagnosis this issue is raised along with other guidance about the nature of the disease and its management with a view to instituting treatment, if the patient wishes, as an outpatient after successful treatment of the first infection. For patients with clinically overt HIV encephalopathy zidovudine should be introduced as early as possible to minimise permanent neuronal damage.

Patients should be warned about possible early symptoms and should be told that they will subside if the drug is continued, to avoid inappropriate early discontinuation. The patient must be carefully monitored for haematological toxicity, especially in the early months. Those with marrow suppression should have frequent blood counts. This enables transfusion to be planned to pre-empt symptoms of anaemia, which will start at different concentrations of haemoglobin, depending on the patient's level of activity and other factors. It will also allow early identification of a falling neutrophil count so that gradual dose reduction can be achieved, thus avoiding both severe neutropenia (below $0.5 \times 10^9/l$) and dose reduction encephalopathy. In general, there is no need to discontinue zidovudine during treatment of intercurrent infections or chemotherapy for tumours. Patients who require ganciclovir or dapsone, however, should be intensively monitored and the dose of zidovudine reduced as soon as there is a rapid fall in the neutrophil or platelet count. When values are low initially patients should have the zidovudine dose either reduced or stopped, or an alternative drug used

for cytomegalovirus, pneumocystis, or toxoplasma infection (for example, phosphonoformate, sulphonamide or pentamidine, sulphonamide or clindamycin).

Regular creatine phosphokinase estimations should be included in biochemical screening, especially in patients treated for more than 200 days; a sustained rise may provide early warning of zidovudine associated myopathy and will thus enable the drug to be discontinued at the earliest signs of clinical disease.

Zidovudine in asymptomatic HIV infection?

There is naturally much interest in whether zidovudine should be used in asymptomatic HIV infection to prevent damage to the immune or nervous system (or both). Though this would seem a logical approach on theoretical grounds, there are several equally compelling reasons for suggesting that such an approach may be ineffective or even hazardous. A high proportion of HIV positive individuals progress to AIDS (half of the total at 10 years, with others showing minor symptoms or markers suggesting progression) while others remain well. Thus one may be treating those who would not progress to AIDS. Though this would be acceptable with an agent of proved safety, major toxicity has been seen with zidovudine in the two to three years of clinical experience. It has been suggested that haematological toxicity may be less in symptomless subjects, but it certainly can occur; and other problems, such as myopathy, may well be equally common. If cumulative toxicity is similar, patients may be able to take the drug for only a limited period. Furthermore, the mechanism of action of zidovudine depends on active viral replication for its efficacy. Yet many symptomless individuals are at a phase where replication may be at a very low level. This could lead to a worse therapeutic ratio. Thus if zidovudine can be taken for only a limited period it may prove to be more appropriate to use it for symptomatic disease.

The risk-benefit ratio of zidovudine in symptomless infection cannot therefore be predicted with any confidence. Early small studies on antigenaemic patients have shown a reduction in antigen levels and apparently less toxicity,³² but these are short term and have not yet shown clinical benefit. Several large studies now under way are comparing zidovudine with placebo in symptomless HIV positive subjects, stratified for adverse prognostic markers. The study designs appropriately recognise that there is genuine uncertainty about whether zidovudine helps, has no effect, or harms in this setting. Pending the results of such studies, it seems inadvisable to prescribe zidovudine to patients with asymptomatic infection; those who wish should be entered into the trials. Probably results will become available piecemeal, the effect of zidovudine on those with adverse prognostic markers

being likely to become apparent before the effects on those without. Again, it would be unwise to extrapolate any benefits or hazards from one subgroup to another. Indeed, it has very recently been announced that a trial of zidovudine in asymptomatic HIV infection has shown reduced progression to AIDS in treated patients with CD4 cell counts below 500. The data are so far unpublished, however, and it would be premature to draw conclusions about the general use of the drug in these circumstances.⁵²

Other antiretroviral strategies

Several other reverse transcriptase inhibitors are being evaluated and some, having shown useful in vitro activity, are being tested in early clinical trials. Foremost among these has been dideoxycytidine (DDC), which has shown some in vivo activity in phase I studies.³⁵ Unfortunately, at the doses used in these studies it caused peripheral neuropathy in most subjects, though it did not seem to cause serious marrow toxicity. A regimen in which DDC and zidovudine were used alternately for two weeks was explored in the hope of ameliorating the toxicity of both compounds, while retaining their efficacy.³⁵ Early results were encouraging and longer term studies are awaited. Other studies, using lower doses of DDC, are in progress. There have as yet been no published reports of the early clinical investigations on other reverse transcriptase inhibitors of similar type. But preliminary evidence on dideoxyinosine (DDI) seems encouraging. Reports suggest that phosphonoformate, a reverse transcriptase inhibitor working by a different mechanism, may inhibit HIV replication in vivo as well as in vitro³⁶⁻³⁸; clinical benefits have yet to be established and the difficulties of its administration may limit its usefulness.

Several studies have shown that α interferon may inhibit HIV replication in vivo.³⁹⁻⁴² These were generally retrospective analyses of patients given α interferon for Kaposi's sarcoma or for hepatitis B infection and the doses used were frequently accompanied by important symptomatic side effects. Further studies are needed to evaluate the role of this approach alone or in conjunction with zidovudine,⁴² and in particular to define if possible a dose that can achieve antiviral effects without producing serious long term toxicity.

Many other approaches have been advocated on the basis of in vitro studies or on theoretical grounds (reviewed by Oberg⁴³), but substantive data to support their clinical use are so far lacking. One of the most ingenious is the use of soluble CD4 as a decoy with which to bind free HIV.⁴⁴⁻⁴⁸ It depends on inhibiting cell to cell infection within the infected subject and on the presupposition that this occurs predominantly through the fluid phase. If cell to cell infection occurs

between adjacent cells to any significant degree its value would be restricted. The early in vitro study suggesting that its use would not impair immune responses was limited in scope.⁴⁶ Nevertheless, phase I clinical trials are in progress and the results on efficacy and on immune responses in these subjects are awaited with interest. A potential drawback of this approach is the relatively short half life of soluble CD4 and the high levels likely to be required to achieve a decoy effect in vivo. To circumvent this problem, a hybrid molecule of CD4 and antibody (an "immuno-adhesin") has been made which has a longer half life.⁴⁹ A disadvantage of this ingenious approach, however, is that such molecules would be less effective in reaching the central nervous system and hence in preventing cell to cell infection there; lack of effectiveness at this site would seriously compromise the clinical value of such a strategy.

Another approach suggested recently is the use of high titre antibody from HIV infected subjects who are well to treat those with advanced disease.^{50,51} This could enhance the neutralising effects or possibly enhance anti-HIV antibody dependent cellular cytotoxicity, though the latter could in principle increase rather than decrease CD4 cell damage. The data so far show that p24 antigen levels decrease, but this is not surprising as the administration of p24 antibody to people who typically lack it will complex free antigen. Changes in serum p24 antigen cannot therefore be used to evaluate the efficacy of this approach. Clinical benefit has not been clearly shown with the passive administration of antibody; an apparent reduction in early attack rate of pneumocystis pneumonia in one of the studies⁵⁰ almost certainly resulted from a carry over effect of recent successful treatment of pneumocystis infection.

Conclusions

It is abundantly clear that agents that can inhibit the replication of HIV are an essential component of treatment strategies for HIV infection and disease, but only one agent, zidovudine, is of proved efficacy in the clinical setting. The use of this drug, though undoubtedly valuable and effective in the medium term for people with symptomatic HIV infection, is seriously limited by its medium and long term toxicity. This raises serious questions about the risk-benefit ratio of early intervention for symptomless HIV infection, and data from controlled trials are eagerly awaited.

The natural enthusiasm and impatience of clinicians and patients for effective antiretroviral treatment must be tempered with a realistic appraisal of the available evidence. In vitro effects do not automatically translate into in vivo efficacy. The clinical efficacy and toxicity of putative agents must be evaluated in formal

clinical trials before they are widely applied in clinical practice. Premature use of inadequately evaluated agents may do more harm than good, either directly or by diverting attention from more suitable agents.

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