who were selected as being compliant on the basis of a larger fall in fasting plasma glucose! An additional methodological comment is on the 4-day diet records. It seems clear that, however well validated such a method is, it takes a great stretch of the imagination to believe that a group of people intensively counselled as to what they should be eating might not be influenced in what they recall by the very intervention that is being studied. If one calculates the expected weight loss from the change in total energy intake reported in the 'healthy living' group, these subjects should have lost around 11 kg instead of 2 kg.

The obvious question that comes out of this study is whether we should be screening for impaired glucose tolerance (or even CIGMA glucose intolerance). Screening might be justifiable if one could reduce the incidence of hard end points, these being diabetes (although it is questionable whether even undiagnosed diabetes, let alone impaired glucose tolerance, should be screened for) and cardiovascular disease. Assuming a 2.5% per year deterioration to diabetes, a 20% reduction in incidence of diabetes with treatment would require 200 person–years of treatment per case prevented. Moreover, the benefits on coronary heart disease of intervening for even the standard risk factors (other than smoking) in middle aged subjects can be calculated as producing gains of 9 months or less in life expectancy.[9] It appears, however, that Robert Turner, undaunted by the experience of the UK Prospective Diabetes Study, is now intending to embark on a trial of intervention in glucose intolerant subjects. I can only sit, mouth agape on the touch line, admiring his energy.

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The use and toxicity of didanosine

Sir,

The need for new and more effective therapies for people with HIV disease is keenly felt by the many patients and clinicians who daily face the disease and our limited armamentarium against it. The report by Moyle *et al.*[1] and the recent preliminary announcement of the ALPHA trial using didanosine,[2] also in zidovudine-intolerant patients, highlight some of the difficulties in making progress. They show the tension between providing for today's patients and the need to answer questions for tomorrow's patients, between expectations of new drug therapies and formal data on efficacy.

Zidovudine had made a clear impact on clinical outcomes for HIV disease, but its toxicity meant that a significant proportion were, after a period of therapy, left seemingly unsupported by antiretroviral therapy. Zidovudine causes a fall in p24 antigen and a transient rise in CD4 lymphocyte count; these markers were plausibly viewed as viral and immunological markers of benefit and as a possible means of predicting clinical benefit with similar compounds. The true surrogacy of these markers was not formally established, but new compounds were soon being evaluated in Phase I/II studies almost entirely on such surrogate markers.

As Moyle *et al.* point out, placebo-controlled trials in zidovudine-intolerant patients have been considered impossible because of the perception that drugs showing effects on surrogate markers are better than nothing. Indeed, ALPHA attempted a

limited placebo control by offering patients a choice of a placebo-controlled option or a simple dose comparison option, but it recruited too few to this option for analysis. Thus assessment of the benefits and toxicity of didanosine in such patients is based on observational studies. While much can be learnt about toxicity, efficacy can only be judged by further observations on surrogate markers, by external comparisons with populations that can never be adequately matched or by extrapolations from comparisons between zidovudine and didanosine in those able to tolerate either.

ALPHA highlights the problems. Although there was a highly significant difference in CD4 count rise between the two doses used (which spanned from the lowest dose showing effects on markers to the highest tolerable dose, based on Phase I/II studies), there was no difference in survival, progression or any other clinical end-point. However, the difference in CD4 response was similar to that observed in dose-ranging studies and in direct comparisons between zidovudine and didanosine.[3] If no clinical benefit results from such differences in CD4 response, we must surely question the surrogacy value of such markers. Yet regulatory agencies and others are increasingly relying on them, in lieu of clinical end-points.

The need for new therapies for HIV disease and for early indicators of benefit for the many drugs under evaluation have led to a less than fully critical analysis of what we know, as opposed to what we hope. It is surely time to take stock and for clinicians and patients to appreciate the distinction between knowledge and aspiration, whether of drugs or of markers. Otherwise we will perpetuate our ignorance and uncertainties and thus disenfranchise future patients, while offering those of the present some ambiguously defined treatments. Meanwhile we will have to make the best of careful observational studies such as these and do our best to read between the lines.

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Sir,

We found the paper by Moyle *et al.*[1] describing their experience with didanosine (ddI) in patients intolerant of zidovudine of interest.

The question of this drug's efficacy remains unresolved, and what information there is is based mainly on surrogate markers such as CD4 count and the level of p24 antigenaemia rather than clinical end-points. The potential benefit of ddI therapy must be considered in the context of its toxicity and any decision to start ddI requires careful consideration and discussion, particularly in those with advanced disease where evidence of efficacy is less convincing and in whom toxicity is more common. With regard to patients with less advanced disease who are intolerant of zidovudine, in whom it has been decided that antiretroviral therapy is appropriate, we would agree with Moyle *et al.* that the positive trends in surrogate markers in this patient population suggest that ddI should be considered.

Two recent studies merit consideration. Preliminary data on 1775 patients from the European/Australian Alpha study with advanced disease who were intolerant of zidovudine randomized to either 750 mg/day or 200 mg/day of ddI, showed no difference between the treatment groups in either survival or disease progression, but the incidence of side effects was more frequent in the higher dose group.[2]

Recent data from the AIDS Clinical Trials Groups (ACTG) 116B/117 indicated that, in patients with AIDS-related complex and asymptomatic disease who were tolerating zidovudine and who had received a minimum of 16 weeks zidovudine (median 13.9 months), changing to ddI in doses of 500 mg and 750 mg/day had no significant benefit in terms of survival compared with continued zidovudine, but that there was a delay in new AIDS defining events in those with asymptomatic disease or AIDS-related complex on the lower dose. The lack of benefit of the higher dose was attributed partly to the increased dropout rate at this dose level.[3]

In our institution we have found ddI to be poorly tolerated by patients with advanced disease. Of 70 patients receiving named-patient ddI with advanced disease, 53 are currently attending and 17 have died. Of 44 case notes that were reviewed 25/44 (57%) stopped therapy within 6 months as a result of drug-related toxicity or disease progres-