

## **Zidovudine treatment for anti-HIV positive haemophiliacs**

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**Summary** Twenty haemophiliacs (17 CDC group IV and 3 CDC group II) were treated with zidovudine for a median of 37 weeks (range 10–66). Eight (40%) tolerated zidovudine without a dose change. Two patients died and five patients (29%) developed opportunist infections. Haematological toxicity occurred in ten CDC IV patients (59%) but only one case of sepsis occurred in 101 episodes of documented granulocytopenia. Thrombocytopenia responded to treatment with zidovudine in four of five patients. It is concluded that zidovudine is beneficial for symptomatic haemophiliacs and although the haematological toxicity is high, it is mostly asymptomatic, reversible and well tolerated. Two of the three CDC II patients treated with zidovudine progressed to CDC IV, but had low initial T4 lymphocyte counts and were P24 antigen positive.

**Keywords:** zidovudine, HIV infection, haemophilia

Following the first case of transfusion induced acquired immunodeficiency syndrome (AIDS) described in 1982, there has been a steady increase in the number of AIDS cases among the haemophilic population (Darby *et al.* 1989). Currently, the only anti-viral drug that has proven clinical benefits is zidovudine.

Zidovudine (AZT, azidothymidine, retrovir<sup>®</sup>), a thymidine analogue, acts as a chain terminator in human T cells, and is a potent inhibitor of reverse transcriptase, as well as reducing DNA polymerases and this is probably the mechanism of its bone marrow toxicity (Jeffries *et al.* 1989).

In a placebo controlled study in 1986, zidovudine was shown to be effective in the treatment of AIDS and AIDS-related complex (ARC) with improved survival, decreased opportunist infections and improved clinical well-being over a 24 week period (Fischl *et al.* 1987), but at the cost of considerable haematological toxicity (Richmann *et al.* 1987). The problem of toxicity has concerned both health professionals working in the area (Dournon *et al.* 1988; Richman *et al.* 1988; Pinching *et al.* 1989) and also people with the disease (Deer 1989).

The following study assesses side-effects of zidovudine in a small haemophilic population and a retrospective comparison is made of the results of zidovudine therapy in different patient groups.

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### Patients and methods

The Haemophilia Centre at the Royal Free Hospital has had 111 regularly attending anti-HIV positive haemophiliacs under its care, and the course of this patient population has been described elsewhere (Lee *et al.* 1989). Ten deaths due to AIDS occurred between 1984 and the introduction of zidovudine in late 1987. Details of the 20 patients treated with zidovudine are shown in Table 1, and Table 2 shows their centre of disease control classification [CDC] (MMWR 1987) at the time of commencing zidovudine. The group included three asymptomatic patients who had purchased their own zidovudine privately. Royal Free Hospital policy as from February 1990, is for NHS-prescribed zidovudine to be started in patients with T4 counts  $< 0.2 \times 10^9/l$ , or those with symptomatic HIV disease.

### MONTHLY REVIEWS

Clinical assessment, blood tests including full blood count, serum biochemistry, liver function tests (LFTs), T4 lymphocyte count and P24 antigen were performed monthly. Further investigation and review were undertaken if indicated.

**Table 1.** Patients treated with zidovudine

Patients	20
Median age	33 years (range 21–69)
Time since first anti-HIV positive (median)	72 months (range 42–107)

(Six patients have had no prior negative anti-HIV test).

**Table 2.** CDC classification of patients (CDC classification 9)

	CDC IV	CDC II
	No. of patients	No. of patients
PCP	3	
PCP + oral candida	2	
PCP + cryptococcal meningitis	1	
+ oral candida		
PCP + HIV neurological disease	1	
+ oral candida		
PCP + thrombocytopenia	1	
Constitutional disease	3	
Oral candida	2	
Oral candida + thrombocytopenia	3	
Thrombocytopenia	1	
Total	17	3

## PROPHYLAXIS

Nebulized pentamidine 150 mg fortnightly was given to nine patients with previous pneumocystis carinii pneumonia (PCP). Eleven patients with previous oropharyngeal candidiasis received fluconazole at 50 mg/day for two weeks and then were randomized to 150 mg fluconazole/placebo weekly as part of an ongoing double blind fluconazole trial of prophylaxis for oropharyngeal candidiasis.

## ZIDOVUDINE

Five of the 20 patients were included in a 24 week multicentre trial of zidovudine and acyclovir/placebo (three patients received acyclovir) that has now been completed, and whose results will be separately reported. These five patients were started on 2000 mg/day of zidovudine as a loading dose for two weeks (in four divided doses) and then decreased to 1000 mg/day (in four divided doses), at the same time receiving acyclovir/placebo 3.2 g/day (in four divided doses). The other patients were commenced on 1000 mg/day (in five divided doses). Dose modification was instituted to the following haematological criteria: (1) Reduction to 400 mg/day if: (a) anaemia ( $< 10$  g/dl) or (b) granulocytopenia ( $< 1.0 \times 10^9/l$ ); (2) temporary cessation of medication if: (a) anaemia ( $< 7.5$  g/dl) or (b) granulocytopenia ( $< 0.80 \times 10^9/l$ ).

Zidovudine was generally increased to full dose as soon as blood counts permitted. Repeated attempts (greater than three) to increase to full dose were usually abandoned if haematological toxicity invariably occurred on each occasion. These patients were usually maintained on long term reduced dose (e.g. 400 mg/day) zidovudine as illustrated by patients 3 & 4 (see Figure 1).

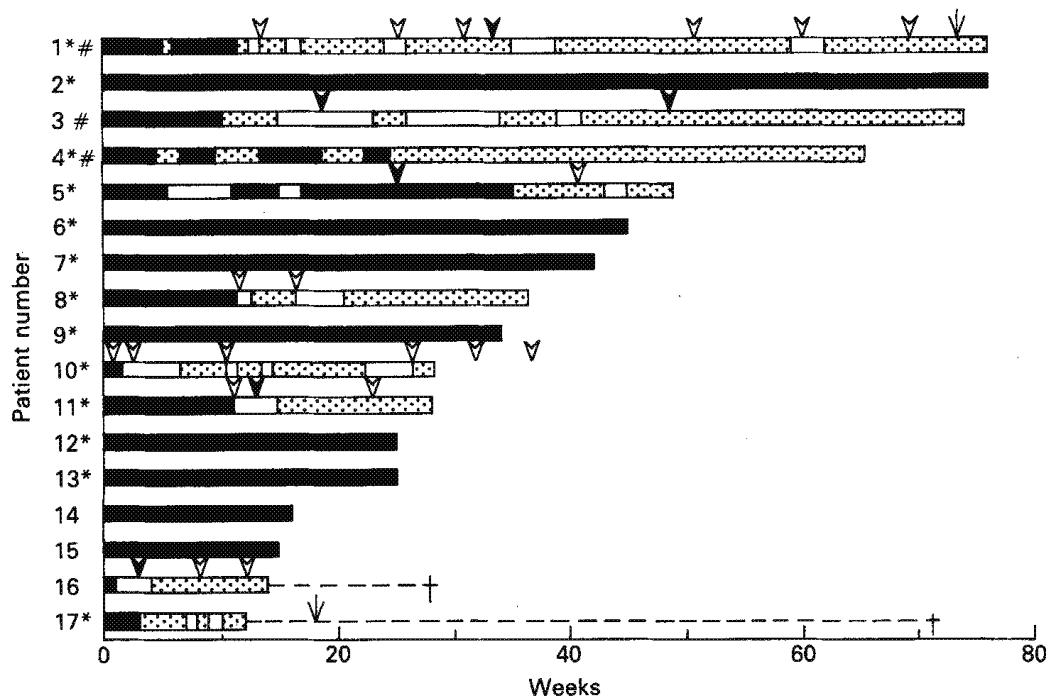
Liver function tests were assessed prior to starting therapy and were followed on each subsequent review. Dose modification occurred if the LFTs were markedly abnormal ( $> 10$  times the normal range), although the previous pattern of abnormality was also taken into consideration as most patients had been infected with non-A, non-B hepatitis.

## Results

### CLINICAL

Twenty patients took zidovudine for 10–66 weeks (median 37 weeks) of whom 8 (40%) tolerated zidovudine without a dose change while the majority required intermittent or reduced therapy (Figure 1).

Six opportunist infections occurred in 5 patients (Table 3), two of these patients were temporarily off zidovudine at the time, one of whom had a granulocytopenia contributing to sepsis with *Salmonella typhimurium*, and one patient had zidovudine for only three weeks before symptoms of abdominal



\*CMV positive patients. # Received acyclovir in AZT/acyclovir trial.

■ Full; ▨ Reduced; □ Nil; ▼ Opportunist infection; ▽ Transfusion; ψ Malignancy; † Death.

**Figure 1.** Duration of zidovudine therapy and its relation to opportunist infection, frequency of blood transfusion, development of malignancy and death in CDC IV patients.

discomfort due to increasing hepatosplenomegaly attributable to atypical mycobacteriosis developed.

Two patients developed non-Hodgkin's lymphoma: a Burkitt-like lymphoma occurring after 11 weeks of zidovudine, infiltrating the bone marrow and invading the right axilla; and the other, a large cell lymphoma occurring 73 weeks after

**Table 3.** Opportunist infections during zidovudine therapy

Pneumocystis carinii pneumonia	1
Atypical mycobacteria*	1
Cryptosporidiosis	1
<i>Salmonella typhimurium</i> sepsis†**	1
Oral candidiasis	1
Lobar pneumonia§†	1
Total	6 opportunist infections in 5 patients out of 17 (29%)

\*On zidovudine for 3 weeks prior to diagnosis (abdominal discomfort due to hepatosplenomegaly).

†Patients temporarily off zidovudine.

\*\*Concurrent granulocytopenia  $0.6 \times 10^9/l$ .

§No organism found.

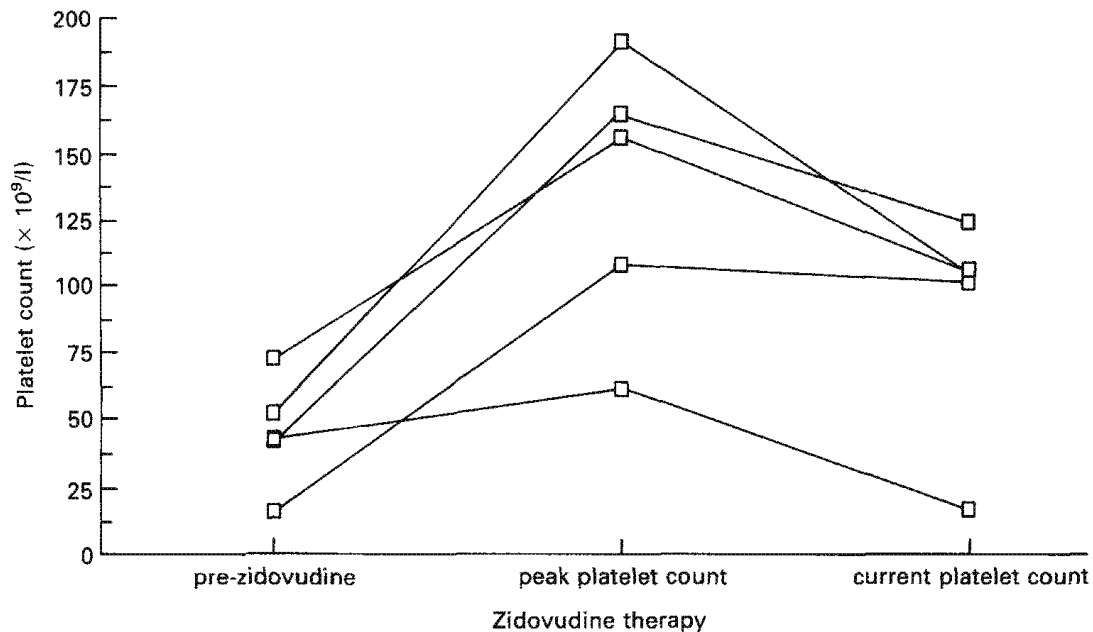


Figure 2. The effect of zidovudine on thrombocytopenia.

starting zidovudine therapy initially localized to the cervical nodes. Kaposi's sarcoma was not seen in any of our patients in this study nor in the other 111 HIV seropositive patients.

The two deaths occurred in patients with atypical mycobacteria and Burkitt-like lymphoma who had received 10 and 11 weeks of zidovudine treatment respectively (Figure 1). Zidovudine had to be stopped due to pancytopenia from bone marrow infiltration by mycobacteria, and chemotherapy-induced haematological toxicity in the patient with lymphoma.

#### LABORATORY

Thrombocytopenia  $< 100 \times 10^9/l$  occurred in five patients (29%), the median platelet count being  $52 \times 10^9/l$ ; 4/5 patients responded to zidovudine with a median peak response of  $100 \times 10^9/l$ , as shown in Figure 2.

A response in T4 cell count was defined as an increase in T4 lymphocyte count greater than  $0.05 \times 10^9/l$  from baseline, within six weeks of starting zidovudine. There were 11 responders (65%), but after 37 weeks of treatment with zidovudine only 1 patient maintained a T4 count above baseline. The median rise and fall in T4 counts over 37 weeks is shown in Figure 3.

Nine patients were P24 antigen positive, and four patients cleared P24 antigen but in two patients P24 returned 11 and 13 months later. 2/3 CDC II and 13/16 CDC IV patients were positive for cytomegalovirus (CMV) antibodies as illustrated in Figure 1. In addition, 1/3 CDC II and 10/15 CDC IV patients were positive for antibodies to herpes simplex virus (HSV).

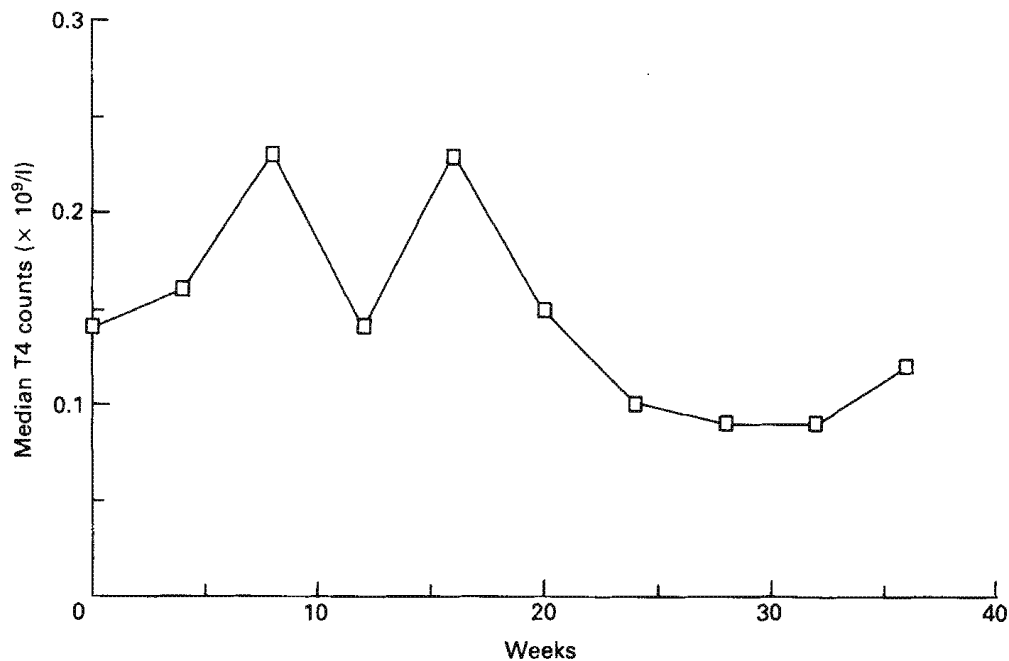


Figure 3. Median T4 lymphocyte counts over 37 weeks of zidovudine therapy.

## Side-effects

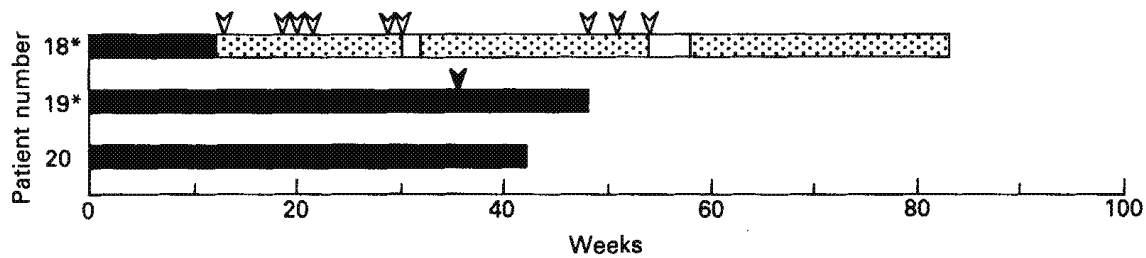
### ANAEMIA

Anaemia (defined as Hb  $< 10.0$  g/dl) with a median haemoglobin of 8.7 g/dl occurred in 5/17 CDC IV patients (23%), and one CDC II patient (Figures 1 & 4). Anaemia occurred within three months of starting zidovudine in all affected patients as shown in Figure 1. Three patients required frequent transfusion needing a total of 15, 21 and 28 units of blood respectively, and the patient 5 had mild anaemia prior to zidovudine, which was exacerbated by the drug.

Macrocytosis (MCV  $> 100$ ) occurred in 12/20 patients, usually within 3 months (median) of starting therapy (range 2 weeks–4 months). Of the 12 patients with macrocytosis, two developed haematological toxicity, namely anaemia and pancytopenia. Of the eight patients who did not develop macrocytosis during their entire course of zidovudine therapy, four developed anaemia.

### GRANULOCYTOPENIA

Five CDC IV patients (29%) and one CDC II patient developed 8 episodes of granulocytopenia  $< 0.5 \times 10^9/l$ , and 132 episodes of granulocytopenia of  $0.5\text{--}1.0 \times 10^9/l$ , which necessitated dose reduction and intermittent therapy. There was only one case of sepsis (*Salmonella typhimurium*) associated with granulocytopenia ( $0.6 \times 10^9/l$ ), in a patient with an indwelling Hickman catheter for treatment of cryptococcal meningitis.



\*CMC positive patients.

■ Full; ▨ Reduced; □ Nil; ∇ Transfusion; ▼ Opportunist infection.

**Figure 4.** Zidovudine therapy in CDC II patients and its relation to blood transfusion and opportunist infections.

#### PANCYTOPENIA

This occurred in one CDC IV patient (6%) [Hb 5.6 g/dl, granulocyte count  $0.6 \times 10^9/l$ , platelet count  $50 \times 10^9/l$ ] and resolved after stopping zidovudine.

Thus haematological toxicity (i.e. anaemia and/or granulocytopenia) occurred in a total of 10 CDC IV (59%) patients (one patient having both anaemia and granulocytopenia), and one CDC II patient.

#### LIVER FUNCTION TESTS

Only one patient developed markedly abnormal LFTs ( $> 10$  times the normal range) 11 weeks after starting zidovudine, that required cessation of therapy (together with concurrent granulocytopenia). However, this patient had documented abnormal LFTs prior to starting zidovudine and hepatomegaly due to atypical mycobacteria. His LFTs did fall to twice the normal range after stopping zidovudine and was not rechallenged due to granulocytopenia.

Only 2 patients had completely normal LFTs before and during the course of zidovudine treatment, whilst 15 patients had mild abnormalities, and 2 patients had moderately elevated transaminases that were unrelated to zidovudine treatment.

#### DISEASE PROGRESSION

Two asymptomatic (CDC II) patients progressed to symptomatic disease (CDC IV): patient 18 after 28 weeks and patient 19 after 35 weeks of zidovudine therapy. Both these patients had T4 lymphocyte counts  $< 0.2 \times 10^9/l$  and were P24 antigen positive at the start of therapy.

#### Discussion

The only double blind placebo controlled trial of zidovudine in AIDS and ARC patients was performed by Fischl (Fischl *et al.* 1987), and showed a considerable

Table 4. Comparative results of mortality and opportunist infection from six other centres

Author	Centre	Length of AZT therapy	Patient number	Mortality	Opp. infection
Fischl M. A. <i>et al.</i>	AZT collaborative working Group, USA	24 weeks (median 18 weeks)	145 AZT/ 137 placebo	1% AZT/ 14% placebo	17% AZT/ 33% placebo
Dourmon E. <i>et al.</i>	Claude Bernard Hospital AZT Study Group, Paris	30 weeks (median)	365	16%	33%
Williams I. <i>et al.</i>	Middlesex Hospital, London	34 weeks (mean)	81	17%	40%
Stambuk D. <i>et al.</i>	St Stephen's Hospital, London	26 weeks (mean)	145	14%	22%
Jones P.	Newcastle Haemophilia Centre, UK	50 weeks (median)	22	18%	9%
Pinching A. J. <i>et al.</i>	St Mary's Hospital, London	22 weeks (median)	113	not stated	not stated
Current study	Royal Free Haemophilia Centre, London	37 weeks (median)	20 (17 CDC IV)	12%	29%



improvement in mortality and decrease in opportunist infection in those patients treated with zidovudine compared to placebo. On this basis, zidovudine was licensed for use in AIDS and ARC patients. Subsequently, it has been difficult to ascertain the efficacy of zidovudine in the absence of controlled trials, particularly in the light of reports of considerable haematological toxicity (Richman *et al.* 1987; Dournon *et al.* 1988). In view of the small numbers of haemophiliacs with AIDS in each centre, and the difficulties of conducting controlled trials, there is a paucity of statistically significant data on the use of zidovudine in AIDS and ARC in this patient group.

Table 4 is a summary of a literature search of the results of treatment of CDC IV patients with zidovudine (Fischl *et al.* 1987; Dournon *et al.* 1988; Pinching *et al.* 1989; Jones, 1989; Stambuk *et al.* 1989; Williams *et al.* 1989). The mortality figures (all under 20%), despite the considerable variety of studies, are remarkably similar. However, the different rates of opportunist infection may be partly explained by the different criteria for definition, the differing durations of zidovudine treatment, and the differing clinical practices for prophylaxis of opportunist infection, particularly for pneumocystis carinii pneumonia and oral candidiasis. The incidence of opportunist infection in our study appears to compare favourably with those of other centres despite these differences. Thus, patients in our small study population are deriving similar benefit from the use of zidovudine as other groups. This benefit is particularly noticeable in patients with HIV associated thrombocytopaenia where four of five patients had a sustained response, and is supported by other studies on HIV associated thrombocytopenia using zidovudine (Oksenhendler *et al.* 1987; The Swiss Group, 1988).

The benefits of zidovudine therapy need to be balanced by the side-effects (mainly haematological) which are high (Table 5) in all the studies listed.

**Table 5.** Comparative haematological toxicity from six other centres

Author	Length of AZT therapy	Patient number	Anaemia	Neutropenia	Haematol. toxicity
Richman D. D. <i>et al.</i>	24 weeks (median 18 weeks)	145 AZT/ 137 placebo	24% AZT/ 4% placebo	40% AZT/ 7% placebo	45% (AZT)
Dournon E. <i>et al.</i>	31 weeks (mean)	365	23%	52%	58%
Williams I. <i>et al.</i>	34 weeks (mean)	81	22%	33%	42%
Stambuk D. <i>et al.</i>	26 weeks (mean)	145	32%	6%	not stated
Jones P.	50 weeks (median)	22	18%	not stated	not stated
Pinching A. J. <i>et al.</i>	22 weeks (median)	113	47%	37%	not stated
Current study	37 weeks (median)	20 (17 CDC IV)	23%	29%	59%

However, granulocytopenia is often asymptomatic and reversible, as exemplified by only one case of sepsis (in our study) amongst 140 episodes of documented granulocytopenia, although only in eight of these was the granulocyte count below  $0.5 \times 10^9/l$ . This finding is supported by a prospective study showing that the incidence of bacterial infections in AIDS or ARC patients was significantly higher only when the neutrophil count fell below 500 cells/ $\mu l$  [ $0.5 \times 10^9/l$ ] (Shaunak *et al.* 1989), and which concludes that zidovudine therapy can be continued in neutropenic patients providing the neutrophil count remains above 500 cells/ $\mu l$ . Similarly, anaemia requiring frequent transfusion (more than two occasions or more than six units of blood) occurred in only three patients. Macrocytosis occurred frequently in our patients but the lack of macrocytosis seemed to be associated with a higher risk of developing anaemia. The lack of macrocytosis in zidovudine-induced anaemia points to development of 'early' anaemia (within three months) associated with isolated erythroid aplasia or hypoplasia (Cohen *et al.* 1989). Most of our patients tolerated these haematological side-effects and dose modifications well despite the reported high incidence of haematological toxicity. Dournon and colleagues found no significant differences in clinical well-being and major events between patients treated within six months of continuous half-dose, or full dose zidovudine, suggesting that half dose treatment may be preferable to avoid the toxicity and interruptions to therapy.

Abnormalities in LFTs can occur with zidovudine, but uncommonly (Dubin *et al.* 1989). The situation is compounded in haemophiliacs who have underlying non-A, non-B hepatitis. In our patient, abnormal liver function tests were present at the start of therapy but worsened after 11 weeks, although this did not cause any symptoms. As there was doubt about the cause, therapy was withdrawn.

There is no doubt that zidovudine needs to be used cautiously in AIDS and ARC patients, but the problem of toxicity must be weighed against the continuing benefits derived from its use. The question of efficacy of half-dose zidovudine is currently being examined in a number of studies.

Preliminary results announced by the National Institute of Allergy and Infectious Diseases (NIAID) of trial ACTG 016 showed patients with early symptomatic HIV disease and with less than 500 CD4 cells/ $\mu l$  [ $0.5 \times 10^9/l$ ] benefited from zidovudine. In addition, patients who were asymptomatic (CDC II) in the ACTG 019 trial also showed significant reduction (by 50%) in the risk of progression to AIDS or ARC (Lancet, 1989). Both trials were double blind placebo controlled studies and, if confirmed, will certainly alter prescribing policy in patients with HIV disease. Additionally, the incidence of toxicity was less than 5% in the first trial (ACTG 016) and low in the second study, although no figures were given. This low toxicity in asymptomatic patients has previously been suspected from a small study of 18 asymptomatic anti-HIV positive homosexuals (de Wolf *et al.* 1988) using zidovudine with or without acyclovir, which showed a low incidence of toxicity (11%) after 24 weeks of treatment.

The possibility that co-infection with other viruses like CMV may accelerate the progression to full blown AIDS has been assessed using this cohort in another study (Webster *et al.* 1989). The role of acyclovir may take an increasing

prominence in this regard and we await with interest the results of the multicentre trial of zidovudine +/– acyclovir in haemophiliacs. The recent report of in-vitro resistance to zidovudine (Larder *et al.* 1989) needs to be clinically addressed in future well-controlled studies.

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