Double blind dose-response study of zidovudine in AIDS and advanced HIV infection

Nordic Medical Research Councils' HIV Therapy Group

Abstract

Objective—To compare the efficacy and side effects of 400 mg, 800 mg, and 1200 mg zidovudine daily in patients with AIDS or advanced HIV infection.

Design—Randomised, double blind, parallel group multicentre study.

Setting—Hospital departments of infectious diseases and dermatology in Denmark, Sweden, Norway, Finland, and Iceland.

Subjects—474 patients: 126 (27%) with AIDS; 248 (52%) with HIV related symptoms; 100 (21%) with low CD4+ cell counts.

Interventions—Zidovudine 400 mg (160 patients), 800 mg (158), or 1200 mg (156) daily. All patients received one capsule from each of three bottles four times daily.

Main outcome measures—Survival; incidence of new HIV related events; CD4+ cell count; quality of life; incidence of haematological side effects.

Results—460 (97%) of the 474 patients had not received zidovudine previously. The median follow up period was 19 months, during which the death rates in the three treatment groups were 23% (36/160 patients), 23% (36/158), and 19% (30/156) respectively ($p=0{\cdot}49$; log rank test). One year after the trial was terminated the death rates were 38% (61/160), 41% (64/158), and 44% (68/156) respectively ($p=0{\cdot}54$). There was no significant difference between the groups in time to a new AIDS defining event or death, average number of events per patient, decline in CD4+ cell counts, wellbeing (visual analogue scale), or Karnofsky score. Zidovudine was withdrawn in 132 (28%) patients, mainly because of side effects (71 cases; 15%). The incidences of anaemia and leucopenia, time to first dose reduction, and numbers of patients withdrawn were all dose related.

Conclusion—Zidovudine should be limited to 400-600 mg daily in patients with AIDS or advanced HIV infection.

Introduction

Zidovudine (azidothymidine; AZT) is a nucleoside analogue active in vitro and in vivo against HIV-I.[1,2] Its clinical effect, however, is limited to delaying progression of the HIV infection, and toxicity is substantial when 1500 mg of the drug is given daily.[3-5] We therefore carried out a pragmatic study comparing the currently recommended dose of 1200 mg zidovudine daily with 800 mg and 400 mg to see whether lower doses might cause fewer adverse effects without loss of efficacy.

Patients and methods

Patients were recruited between 1 February 1988 and 31 December 1989. The trial was completed in all patients on 1 July 1990 (additional information on survival after one year of open zidovudine treatment was obtained as on 1 July 1991). Patients were eligible for the study if they were at least 18 years old, resided in one of the five Nordic countries (Denmark, Sweden, Norway, Finland, or Iceland), had AIDS[6] or current or previous symptomatic HIV related infection, and were or had been HIV antibody positive. Symptomatic HIV related infection was defined as the presence of one or more of the following: severe oral candidiasis or hairy leucoplakia in patients not treated with antibiotics, herpes zoster, extensive mucocutaneous herpes simplex of less than one month's duration, unexplained fever for one month, unexplained diarrhoea for one month, and unexplained weight loss of at least 7 kg or 10% of the body weight. Hence the HIV wasting syndrome was not an AIDS defining diagnosis.

As the study was pragmatic we decided three weeks after it had started that other HIV infected patients who in the investigators' opinion were candidates for zidovudine could also be enrolled. These patients should preferably have a CD4+ cell count below $0{\cdot}2\times10^9$/l.

Patients were excluded if they had a life expectancy of less than three months; were unlikely to abstain from drug misuse; were pregnant, lactating, or wished to become pregnant; or if they had previously been entered into the study. Patients who fulfilled the criteria for the trial but did not enter were listed in a reject log.

ETHICS AND STUDY DESIGN

Informed consent was obtained after oral and written information. The protocol was approved by the national research ethics committees and drug agencies in each country.

The study was designed as a randomised, double blind, fully coordinated multicentre trial. The investigators met at regular intervals before and during the trial. Patient eligibility was assessed at the statistical centre before randomisation. Randomisation to 400 mg, 800 mg, or 1200 mg zidovudine daily was carried out by means of a computer generated program of random numbers in blocks of six (three for three small centres contributing only three to six patients each). Zidovudine was purchased at market price from Wellcome (Beckenham, England). The company supplied active drug and placebo but otherwise did not take part and did not contribute financially.

Each patient received three bottles of capsules, labelled A, B, and C. The capsules contained 100 mg zidovudine or placebo, identical in appearance and with a similar taste. All patients took one capsule from each bottle four times daily. In every case bottle C contained zidovudine. Bottle B contained zidovudine for the 800 mg and 1200 mg groups, and bottle A contained zidovudine for the 1200 mg group only. The efficiency of blinding was tested by asking patients and investigators to guess the dose when the trial

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medication was permanently discontinued or at the end of the trial.

The case report forms were sent on a weekly basis to the coordination centre, where they were checked for accuracy and completeness by two people.

DOSE REDUCTIONS

Dose reductions, or temporary interruptions of treatment, were allowed if necessitated by adverse reactions or concomitant treatment with other toxic drugs and were recommended in cases of severe anaemia despite blood transfusions or a progressive fall in leucocyte count to $<1{\cdot}5\times10^9$/l or neutrophil count to $<1{\cdot}0\times10^9$/l.

Dose reductions were made by removing either bottle A or bottles A and B. If bottle C alone was not tolerated or the patient became pregnant or refused further participation treatment was permanently discontinued. As bottle A contained placebo in the 800 mg and 400 mg groups, and bottle B in the 400 mg group, dose reductions were sometimes shams. Therefore, temporary interruption rather than a dose reduction was encouraged when an adverse reaction was severe.

COMPLIANCE CONTROL AND EVALUATION OF PATIENTS

Compliance was controlled by interview and capsule count at each visit. Non-compliance was defined as intake of less than three quarters of the prescribed dose. All patients were followed up throughout the study, continuing with the trial drug if possible, irrespective of the level of compliance.

At admission and at monthly follow up visits a medical history was taken and a physical examination performed with emphasis on HIV related diagnoses, signs, and symptoms. Quality of life was assessed by the patients using a 10 cm visual analogue scale ranging from "I have never been better" to "Worst possible condition." The patients had access to their previous results. The physician used the Karnofsky scale for the quality of life assessment without referring to the results on the analogue scale.[7] Monthly laboratory measurements included haemoglobin concentration, packed cell volume, total red cell count, mean corpuscular volume, platelet count, total and differential white cell count, aspartate or alanine aminotransferase activity, alkaline phosphatase activity, and bilirubin concentration. The haematological tests were also done after two and six weeks. CD4+ lymphocyte count was performed monthly for the first six months, then every three months. Serum vitamin B-12 and folate concentrations were measured every three months.

TABLE I—*Baseline characteristics of zidovudine treatment groups. Diagnoses listed were those recorded in 10 or more patients. Data expressed as numbers (percentages) of patients and median values (non-parametric 95% ranges)*

	Zidovudine dose		
	400 mg (n=160)	800 mg (n=158)	1200 mg (n=156)
Age (years)	37 (24-64)	38 (24-62)	38 (22-66)
Male	143 (89)	143 (91)	147 (94)
AIDS	37 (23)	53 (34)	36 (23)
Pneumocystis carinii pneumonia	20 (13)	28 (18)	22 (14)
Kaposi's sarcoma	6 (4)	12 (8)	8 (5)
Candidiasis	7 (4)	7 (4)	3 (2)
Herpes simplex infection	1 (1)	7 (4)	2 (1)
Symptomatic HIV infection	87 (54)	72 (46)	89 (57)
Oral candidiasis/hairy leucoplakia	63 (39)	53 (34)	71 (46)
Herpes zoster	24 (15)	33 (21)	30 (19)
Fever	12 (8)	8 (5)	9 (6)
Weight loss	21 (13)	21 (13)	10 (6)
Diarrhoea	12 (8)	9 (6)	9 (6)
Low CD4+ count	36 (23)	33 (21)	31 (20)
Previous zidovudine	2 (1)	9 (6)	3 (2)
CD4+ cells ($\times10^9$/l)	0·15 (0-0·50)	0·15 (0·01-0·60)	0·15 (0-0·58)
Weight (kg)	70 (45-94)	69 (50-92)	69 (50-92)
Karnofsky score	90 (60-100)	90 (50-100)	90 (53-100)
Visual analogue score (mm)	32 (0-82)	30 (0-93)	32 (0-88)
Haemoglobin (g/l)	135·2 (101·4-162·6)	135·2 (96·6-165·8)	138·5 (96·6-167·4)

Adverse events were those reported spontaneously or observed and those elicited by indirect questioning. They were classified by seriousness and intensity. A severe reaction was life threatening, decreased life expectancy, caused prolonged interference with lifestyle, or impaired ability to cope with future health problems. Intensity was graded as mild (not interfering with usual activity), moderate (interfering with but not preventing usual activity), or severe (preventing usual activity). The number of blood transfusions was noted.

STATISTICS

Assuming an annual mortality of 10% in patients receiving 1200 mg zidovudine daily and an average follow up period of 18 months, we calculated that the number of patients required to assure that an annual death rate in the 400 mg or 800 mg groups of 20% was not overlooked was 90 per group with $2\alpha=0{\cdot}05$ and $\beta=0{\cdot}2$. As the actual mortality in the study was lower than expected, the target sample was later adjusted to 150 patients per group.

During the trial two interim analyses were performed by the chairman of the coordinating committee. A χ^2 test was done on the three death rates without breaking the code. The trial was to be stopped early if $p<0{\cdot}001$ was recorded with df=2. The investigators were not informed about the calculated p values or the death rates.

All randomised patients were included in the analyses provided they had taken the first dose of the trial drug (intention to treat). The main end point was survival. Secondary variables were the incidence of new infections, malignancies, or other events related to AIDS or HIV infection and not reported at baseline; CD4+ cell count; quality of life; and incidence of haematological side effects.

Data analysis was blinded and the randomisation code not broken before the results were presented at a meeting of investigators. The code was not broken for any individual patients during the study.

The Kaplan-Meier method and a log rank test which took the order of the doses into account[8] were used for analysis of time to events. The decline in CD4+ cell count over time was estimated by linear regression for each patient and the average slope for the treatment groups compared by analysis of variance.[9] Other quantitative variables were analysed by analysis of variance, taking the order of the doses into account. Binomial frequencies were analysed by the Mann-Whitney test for 2×3 tables. Medians and non-parametric 95% ranges were used for descriptive purposes; 95% confidence intervals were used to estimate the uncertainty of observed differences.

Results

A total of 474 patients were enrolled in the study. The main reasons for not enrolling a further 108 eligible patients were: patient refused (51 cases; 47% (most were satisfied with current zidovudine treatment)); open or high dose wanted (13; 12%); high dose not tolerated (12; 11%); severe disease (12; 11%); zidovudine refused (9; 8%). Risk factors for acquiring HIV infection were homosexuality or bisexuality (368 cases; 78%), intravenous drug misuse (23; 5%), blood transfusion (15; 3%), haemophilia (7; 1%), heterosexuality (66; 14%), and unknown or other (16; 3%).

Of the 474 patients, 160 were randomised to receive 400 mg zidovudine daily, 158 to receive 800 mg daily, and 156 to receive 1200 mg daily. Table I shows that the three treatment groups were well matched for important prognostic factors. Only 14 patients (3%) had received zidovudine previously. AIDS at admission was reported for 126 patients (27%). Comparatively more patients in the 800 mg group had

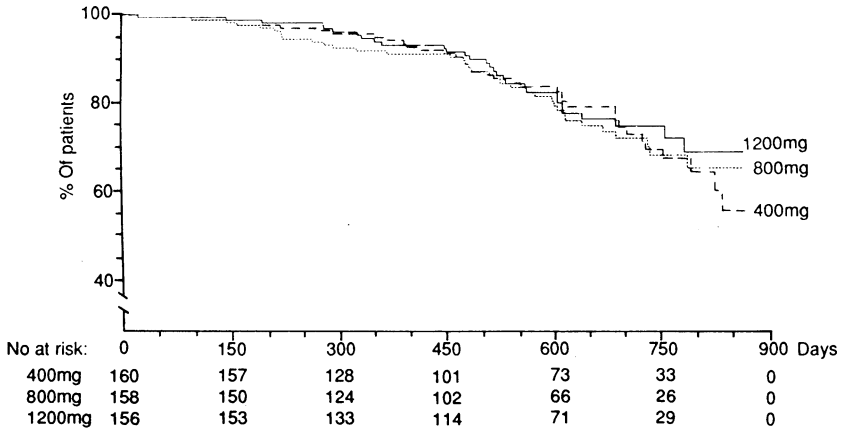

FIG 1—*Survival of patients in three zidovudine treatment groups during period of trial*

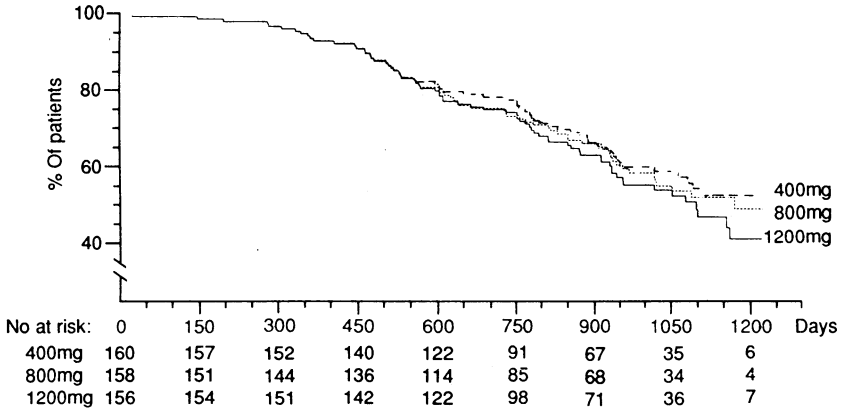

FIG 2—*Survival of patients in three zidovudine treatment groups up to one year after termination of trial*

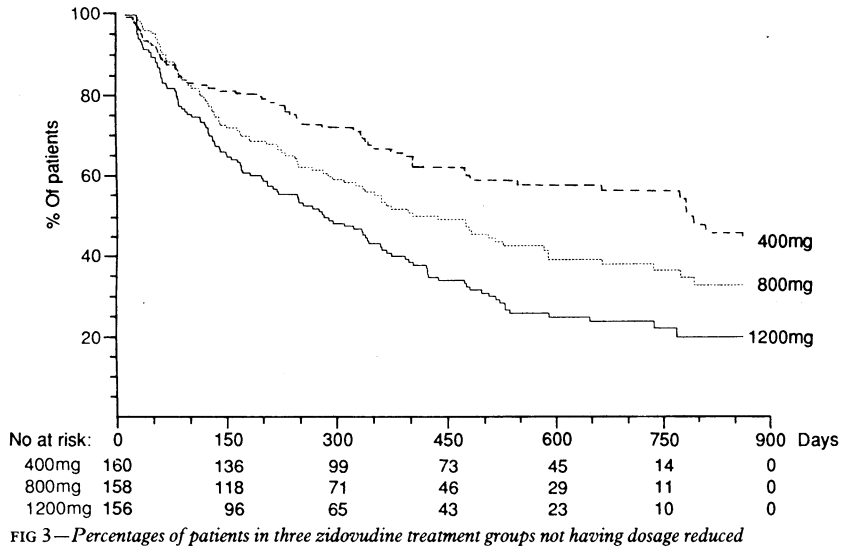

FIG 3—*Percentages of patients in three zidovudine treatment groups not having dosage reduced*

AIDS, but the median CD4+ cell count was the same in all three groups ($0{\cdot}15\times10^9$/l). The CD4+ count in patients who did not have AIDS was similar whether they had asymptomatic or symptomatic infection (median 0·16 (95% range 0·10-0·50) $\times10^9$/l *v* 0·18 (0·10-0·55) $\times10^9$/l).

The median follow up period was 19 months, and compliance was high. Although 132 patients (28%) discontinued treatment prematurely, most did so because of side effects (71 cases; 15%). Other main reasons were poor compliance or severe disease (29 cases; 6%), zidovudine refused (12; 3%), and open or high dose wanted (6; 1%). The drop out rate was dose related: 33 patients (21%) receiving the 400 mg dose, 49 (31%) receiving the 800 mg dose, and 50 (32%) receiving the 1200 mg dose left the study (p=0·02). The numbers of patients with a mean corpuscular volume above 100 fl at any time during the study were similar in the three treatment groups (145 (91%), 139 (88%), and 138 (88%) respectively; p=0·73) whereas the proportion of visits when the patient was non-compliant was highest in the 800 mg group (6%, 10%, and 6%). The latest follow up information was obtained for all but 12 patients (2·5%; two, six, and four respectively) within the last two months before the study cut off.

There was no difference in survival between the three treatment groups (fig 1, table II; p=0·48 (Mann-Whitney test), p=0·49 (log rank test)). The 95% confidence interval for the true difference in death rates between the 400 mg and 1200 mg groups was −5·6% to 12·2%. One year after termination of the study the mortality had increased to 61 patients (38%) in the 400 mg group, 64 (41%) in the 800 mg group, and 68 (44%) in the 1200 mg group (fig 2; p=0·54) (survival status was known for all but two patients). There was no difference between the groups with respect to time to death or a new AIDS defining event (p=0·18; numbers of patients shown in table II).

TABLE II—*Numbers (percentages) of patients in each zidovudine treatment group who died or had new AIDS defining events or HIV related infections not reported at baseline. Events listed were those that occurred in 10 or more patients in whole series*

	Zidovudine dose			
	400 mg (n=160)	800 mg (n=158)	1200 mg (n=156)	p Value
Died	36 (23)	36 (23)	30 (19)	0·48
Died or had new AIDS event	71 (44)	68 (43)	60 (38)	0·29)
Average No of events per patient	0·74	0·59	0·53	0·17
AIDS defining events:				
Pneumocystis carinii pneumonia	31 (19)	23 (15)	21 (13)	0·15
Candidiasis	18 (11)	12 (8)	14 (9)	0·48
Kaposi's sarcoma	12 (8)	13 (8)	13 (8)	0·79
Dementia complex	13 (8)	10 (6)	5 (3)	0·06
Toxoplasmosis	9 (6)	10 (6)	6 (4)	0·48
Cytomegalovirus infection	12 (8)	7 (4)	7 (4)	0·24
Atypical mycobacteriosis	7 (4)	9 (6)	3 (2)	0·27
Non-Hodgkin's lymphoma	7 (4)	3 (2)	3 (2)	0·18
HIV related infections:				
Severe oral candidiasis/ hairy leucoplakia	57 (36)	54 (34)	67 (43)	0·18
Herpes zoster	21 (13)	8 (5)	17 (11)	0·49
Diarrhoea	12 (8)	18 (11)	12 (8)	0·94

The average number of new AIDS defining events per patient did not differ significantly between the groups (p=0·17), although there was a tendency towards more events with lower doses (table II; 95% confidence interval for difference between 400 mg and 1200 mg groups −0·02 to 0·43). *Pneumocystis carinii* pneumonia was diagnosed in 75 patients (16%) in whom it was not reported at baseline. Prophylactic use of antipneumocystis drugs was similar in the three groups (co-trimoxazole given to 42 (26%), 38 (24%), and 40 (26%) patients; pentamidine to 65 (41%), 54 (34%), and 56 (36%) patients).

The monthly decline in CD4+ cell count did not differ between the groups. In the 400 mg, 800 mg, and 1200 mg groups the mean (SD) counts were 0·007 (0·011), 0·006 (0·012), and 0·010 (0·021) $\times10^9$/l respectively (p=0·13).

The incidences of anaemia (p=0·006) and leucopenia (p=0·008) and numbers of patients with fewer than $1{\cdot}0\times10^9$ neutrophils per litre at any time (p=0·0005) were dose related (table III; 95% confidence intervals for differences between 400 mg and 1200 mg groups 4% to 24%, 3% to 22%, and 9% to 31% respectively). Time to first dose reduction was significantly longer with lower doses (fig 3; p<0·0001). The prescribed mean daily doses in the 400 mg, 800 mg, and 1200 mg treatment groups while patients continued with the trial drugs were 314 mg, 596 mg, and 920 mg respectively; the cumulative doses were 162 g,

281 g, and 465 g. Forty two patients (26%) in the 400 mg group received blood transfusions (average 9 units per patient), as did 49 (31%) patients in the 800 mg group (average 9 units) and 44 (28%) patients in the 1200 mg group (average 10 units) (p=0·57 for difference between groups in numbers transfused). The incidence of other adverse reactions or side effects or of other abnormal laboratory values was similar in the three groups, apart from a trend towards more neuropathy with higher dosage (p=0·03; table III).

TABLE III—*Incidences of adverse effects in each zidovudine treatment group. Events listed were those that occurred in 10 or more patients in whole series. Figures are numbers (percentages) of patients*

	Zidovudine dose			
	400 mg (n=160)	800 mg (n=158)	1200 mg (n=156)	p Value
Anaemia	32 (20)	48 (30)	53 (34)	0·006
Leucopenia	29 (18)	35 (22)	48 (31)	0·008
Nausea	57 (36)	51 (32)	55 (35)	0·94
Weakness/fatigue	28 (18)	31 (20)	25 (16)	0·74
Headache	26 (16)	27 (17)	26 (17)	0·92
Muscle pain	19 (12)	16 (10)	14 (9)	0·40
Diarrhoea	8 (5)	12 (8)	9 (6)	0·76
Fever	11 (7)	7 (4)	8 (5)	0·49
Abdominal pain	7 (4)	9 (6)	7 (4)	0·96
Rash	8 (5)	7 (4)	8 (5)	0·96
Neuropathy	2 (1)	5 (3)	9 (6)	0·03
Malaise	3 (2)	4 (3)	4 (3)	0·68
Neutrophils ≤1·0×10⁹/l	66 (41)	71 (45)	95 (61)	0·0005
Thrombocytes ≤50×10⁹/l	22 (14)	23 (15)	22 (14)	0·93
Aspartate or alanine aminotransferase ≥5× normal	21 (13)	18 (11)	21 (13)	0·94
Alkaline phosphatase ≥2× normal	35 (22)	40 (25)	38 (24)	0·60
Bilirubin ≥2× normal	15 (9)	7 (4)	7 (4)	0·07
Vitamin B-12 ≤100 pmol/l (≤136 ng/l)	21 (13)	13 (8)	17 (11)	0·52
Serious adverse reaction	57 (36)	54 (34)	63 (40)	0·38
Severe or moderate reaction	92 (58)	100 (63)	111 (71)	0·01

The incidence of moderate or severe adverse reactions was dose related (p=0·01) whereas the incidence of serious reactions was not (p=0·38; table III).

The groups showed no differences in quality of life as assessed by the visual analogue scale and Karnofsky score.

Most of the patients (268; 57%) and the physicians in 354 cases (75%) provided guesses on the daily dose. In the 400 mg, 800 mg, and 1200 mg groups correct guesses were made by 36% (34/94), 35% (29/83), and 42% (38/91) of the patients, while 34% (42/122), 49% (55/113), and 38% (45/119) of their physicians guessed correctly.

Discussion

This trial of three dosages of zidovudine in patients with AIDS or advanced HIV infection showed no significant differences in death rate, time to death or a new AIDS defining event, average number of new AIDS events per patient, or rate of decline in CD4+ cell count.

There was a trend towards fewer cases of the AIDS dementia complex with higher doses (table II). Numbers of patients were small, however, and the finding should be weighed against a similar trend towards more neuropathic side effects with higher doses (table III). In a study with historical controls zidovudine seemed to have an effect on the dementia complex.[10] The possibility of dose related effects on dementia and neuropathy should be examined in prospective studies specifically addressing these issues.

Results from other studies support our findings. In a non-randomised study of 365 patients no significant difference in clinical effect was noted between 600 mg and 1200 mg zidovudine daily.[3]

In an open trial in 524 patients with AIDS the death rate was significantly higher in those receiving 1500 mg daily than in those randomised to receive 600 mg daily (p=0·02) whereas there was no difference in the occurrence of new AIDS defining events (p=0·91).[11] The mean total dose did not differ appreciably between the 1500 mg and 600 mg groups (266 g *v* 192 g) whereas there were considerable differences between the three treatment groups in our series. Another difference was the lower death rate in our series, only a quarter of our patients having AIDS at admission to the trial.

In a double blind study of 1338 asymptomatic patients with a CD4+ cell count below 0·5×10⁹/l disease progression was reported in 38 patients taking placebo, 17 taking 500 mg zidovudine, and 19 taking 1500 mg zidovudine.[12]

The incidence of anaemia and neutropenia and of adverse events considered severe or moderately severe was significantly dose related in our trial, which agrees with other studies.[11,12]

The history of zidovudine supports the view that randomised dose-response studies are needed early in drug development.[13,14] The initially approved dose of 1200 mg zidovudine seems to correspond to the upper plateau in the drug's dose-response curve. Although small dose escalation studies with surrogate markers may help in suggesting a reasonable range of doses to choose among for dose-response studies,[15] probably it is not possible to predict the optimal dose of a drug in that way. HIV infection seems to be no exception, especially as viral resistance may occur.[16,17] Hence we suggest that more than one dose level of a drug should be used when an anti-HIV drug is studied for the first time in a large sample of patients.

The success of blinding in our study was acceptable and should not have influenced recording of the hard end points.

Based on the results of this and other studies, it seems clear that high doses of zidovudine—that is, 1000-1500 mg daily—offer no clinical advantages over lower doses. Furthermore, as zidovudine is not curative we conclude that the routine dose should be 400-600 mg daily. This reduction from the current recommendation would decrease the risk of adverse reactions and lower the cost of treatment considerably.

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Psychological aspects of lower urinary tract infections in women

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Abstract

***Objective*—To determine whether women with the urethral syndrome can be distinguished from those with urinary tract infection by case notes, clinical symptoms, or psychiatric state.**

***Design*—Longitudinal survey of consecutive women presenting with dysuria and frequency.**

***Setting*—General practice and community.**

***Subjects*—58 patients with the urethral syndrome and 44 patients with a urinary tract infection, mean age 39·9 years.**

***Main outcome measures*—Results of analysis of serial midstream urine specimens, patients' self rated physical symptoms and responses to 60 item general health questionnaire at presentation and after resolution of symptoms, and results of psychiatric assessment with the clinical psychiatric interview.**

***Results*—4 of 42 patients with a urinary tract infection had recently changed sexual partner compared with none of 58 with the urethral syndrome. Dysuria and nocturia were more common in patients with urinary tract infections than those with the urethral syndrome (mean (SD) score for dysuria 5·37 (2·39) *v* 4·57 (2·13), $p<0·05$; nocturia in 39/44 (88%) patients *v* 40/58 (69%), $\chi^2=5·5$, $p<0·02$). Both groups showed transient high levels of distress which resolved with the physical symptoms, but no psychiatric difference distinguished them.**

***Conclusion*—The urethral syndrome is not associated with increased psychiatric morbidity.**

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Introduction

Urinary tract disorders comprise 6% of all consultations in general practice.[1] Most general practitioners treat dysuria and frequency with antibiotics after collecting a midstream urine specimen without waiting for the result.[2] However, in up to 50% of women specimens are sterile or contain insignificant numbers of bacteria.[3,4] These women have the urethral syndrome rather than a urinary tract infection, which is defined as a pure growth of $\geq 10^5$ conventional urinary tract pathogens per ml of urine.[5]

General practitioners might prescribe antibiotics more appropriately if they could predict significant bacteriuria before they had the midstream urine result. One study suggested that patients with the urethral syndrome exhibited less severe dysuria and their case notes were more likely to include "psychosomatic markers" such as anxiety, recurrent abdominal pain, and use of minor tranquillisers.[6] We studied the psychiatric morbidity in women presenting with urinary tract disorders. We also examined other putative aetiological factors, including sexual and hygiene practices, as well as demographic characteristics.

Subjects and methods

General practitioners entered into the study all female patients aged 18 to 55 years presenting with dysuria and frequency over nine months. Exclusion criteria were pregnancy, complicated urinary tract disorder, receipt of antibiotics within 14 days, and insufficient command of English. A midstream urine specimen was obtained, co-trimoxazole prescribed, and the doctor predicted the result of analysis of the urine specimen.

The practice nurse completed an "aetiology schedule" by referring to the case notes and interviewing the patient. Information included demographic details; days elapsed since last period; degree of dysuria and frequency of micturition (both on seven point self rating scales); presence of nocturia; recent change of sexual partner; time since last sexual intercourse; number of sexual partners in the previous year; presence of an abnormal vaginal discharge; type of contraception used; preferences for bath or shower, tights or stockings, natural or synthetic underwear; and use of bath additives and biological or standard washing powder. The nurse determined the total number of consultations in the preceding two years for episodes of abdominal pain, anxiety, use of minor