Albendazole chemotherapy for treatment of diarrhoea in patients with AIDS in Zambia: a randomised double blind controlled trial

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Abstract

***Objective*—To determine the value of short course, high dose albendazole chemotherapy in the treatment of persistent diarrhoea related to HIV in unselected patients in urban Zambia.**

***Design*—A randomised double blind placebo controlled trial of albendazole 800 mg twice daily for two weeks. Patients were monitored intensively for one month and followed for up to six months.**

***Setting*—Home care AIDS services in Lusaka and Ndola.**

***Patients*—174 HIV seropositive patients with persistent diarrhoea (defined as loose but not bloody stools three or more times a day for three weeks or longer). No investigations were undertaken except HIV testing after counselling.**

***Main outcome measures*—Proportion of time periods during which diarrhoea was experienced after completion of treatment; proportion of patients with full remission after completion of treatment; mortality.**

***Results*—The patients taking albendazole had diarrhoea on 29% fewer days than those taking placebo (P<0.0001) in the two weeks after treatment. The benefit of albendazole was maintained over six months. In patients with a Karnofsky score of 50 to 70 (needing help with activities of daily living and unable to work, but not needing admission to hospital) diarrhoea was reduced by 50%. Remission was obtained in 26% of all patients who received albendazole (P=0.004 against 9% receiving placebo), and this difference was maintained over six months (log rank test, P=0.003). Albendazole had no effect on mortality. Minimal adverse effects were noted.**

***Conclusions*—For HIV infected Zambians with diarrhoea of more than three weeks' duration albendazole offers substantial relief from symptoms and may be used empirically, without prior investigation.**

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BMJ 1996;312:1187–91

Introduction

The HIV pandemic continues to have a major impact on public health in sub-Saharan Africa.[1-3] Many health care institutions are overwhelmed by the burden of disease, and the morbidity and mortality of AIDS is having social and economic consequences throughout the region.[4 5] A major contributor to this morbidity and mortality is diarrhoeal disease; in studies from Zaire, Uganda, and Tanzania the lifetime occurrence of diarrhoea in AIDS patients varied from 40% to 75%.[6] HIV prevalence in antenatal clinics in Lusaka has recently been estimated at 36%.[7] A study conducted in a district hospital in southern Zambia showed that 11% of all adult inpatient days (including medical, surgical, and gynaecological admissions) were for treatment of diarrhoea, and 89% of these admissions were related to HIV (S Foster, personal communication, 1991).

The approach to AIDS related diarrhoea in industrialised countries follows a strategy of investigation to determine, when possible, the nature of the infecting opportunist, with treatment aimed at its eradication.[8] In sub-Saharan Africa this is often not possible owing to constraints of technology and time. We recently carried out an intensive parasitological survey of 75 inpatients at the University Teaching Hospital in Lusaka and found infections in 81% of cases.[9] The most common potential pathogens were microsporidia (23-35%), *Isospora belli* (28%), and *Cryptosporidium parvum* (25%).[9 10] The microsporidia species, when identified, were *Enterocytozoon bieneusi* and *Septata intestinalis* in a ratio of 5:2. *Strongyloides stercoralis* and *Giardia intestinalis* were present in 5% and 1% of cases respectively . Geohelminth infections and schistosomes were each found in 3% of cases. Conlon *et al*, however, found microsporidia in only 2% of Zambian patients with AIDS and chronic diarrhoea using a Brown-Brenn Gram stain.[11] Given the intensive investigations needed to establish diagnosis in AIDS related diarrhoea and the frequency of multiple infections, treatments designed on an empirical basis for the population in question and given to all comers may be more logical than investigating each patient, certainly in many parts of Africa.

In Zambia much attention has been paid to developing services to enable patients with AIDS to receive care at home.[12] Several models of delivery have evolved, but all health care staff realise that the number of cases is too great for the hospitals and that the delivery of acceptable care to this group of patients has to be at primary health care level.

We therefore designed and carried out a randomised double blind placebo controlled study to determine the extent to which diarrhoea as a symptom of AIDS can be treated or suppressed by a chemotherapeutic agent that can be given in the community setting without prior investigation. We chose albendazole as this agent acts against microsporidia,[13] *S stercoralis*,[14] and *G intestinalis*,[15] although whether albendazole acts against *I belli* is not known.

Patients and study design

SETTING

The trial was conducted in three centres in urban Zambia where primary AIDS care is delivered. The home care service of the University Teaching Hospital in Lusaka deals mainly with patients referred from the clinics and wards of that hospital. The patients of this service are transported to their homes on discharge from hospital and visited at home regularly. The second study centre (with a similar service) was at Ndola Central Hospital in the north, in Zambia's second most populated city. The third centre was at the Kara Counselling and Training Trust in central Lusaka—the Kara HIV Counselling and Testing project provides a drop in advice and primary care service. The trust also runs several other prevention, training, and counselling projects.

Karnofsky scores[16]

100	Normal (no complaint or evidence of disease)
90	Able to carry on normal activity; minor signs of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Needs occasional help and some medical care
50	Needs considerable help and frequent medical care
40	Disabled; needs special care and help
30	Severely disabled; admission to hospital indicated, although death not imminent
20	Very sick; admission to hospital and active support treatment necessary
10	Moribund; fatal process progressing rapidly
0	Dead

PATIENTS

We recruited patients consecutively. Patients were eligible for enrolment if they were aged over 18 years, were HIV seropositive by enzyme linked immunosorbent assay (ELISA) (Wellcozyme HIV 1 and 2), and had had persistent diarrhoea—loose but not bloody stools three or more times a day for three weeks or longer. We excluded patients if they were pregnant, unable to give informed consent, had received antibiotics in the preceding week, or were deteriorating clinically (Karnofsky score of 20 or less[16] (see box). Patients in all three centres had already been counselled and tested for serum antibodies to HIV as part of their care. Consent was sought in the patient's own language by the counsellor or nurse, and a written explanation of the study was provided. We gave each patient a Karnofsky score as a measure of overall severity of illness at the time of entry into the study. The only generally available anthelminthic drug, mebendazole, is not used widely among adults, and none was prescribed to the patients during the study.

RANDOMISATION

After the study objectives had been explained and consent obtained the patients were randomised by allocation of a study pack containing either albendazole or placebo, which had been prepared in London according to a randomisation code. The code (constructed so that the numbers of patients randomised to albendazole and placebo balanced every 20 patients) was kept in London during the study; it was broken during the study only for individual cases when we were concerned about adverse drug reactions. Each pack contained 112 tablets of albendazole or placebo, which were indistinguishable.

STUDY PROTOCOL

Albendazole was administered in a dose of 800 mg twice daily for 14 days. Patients were allowed to receive codeine phosphate (which was supplied if the nurse thought it necessary) or loperamide as required, but the administration of such drugs was recorded. We provided all patients with oral rehydration salts (Unicef formula) and folic acid 5 mg daily. As well as the treatment pack we gave each patient a card on which to record the number of loose stools during each 24 hour period. The patients kept this record for the first month, after which we collected the cards, and the home care staff recorded for the next five months whether diarrhoea occurred in each two week period. The study was terminated after a total of six months of follow up. We asked patients not to take antibiotics for the diarrhoea, but if antibiotics were used for any other indication during the first month of follow up this was recorded. Any potential adverse effects were notified by the home care staff. If there was a potentially serious event the drug was withdrawn, the code broken in London, and the team advised if any further action was needed. Deaths were all notified, together with an assessment of the circumstances to allow assessment of whether death was due to the underlying disease or to an unexpected event.

STATISTICAL EVALUATION

We evaluated efficacy by estimating *(a)* the proportion of days (in the first month) or fortnights (for the rest of the follow up) during which diarrhoea was experienced; *(b)* the proportion of patients in remission two weeks after completing treatment and their progress over follow up; and *(c)* mortality. The presence or absence of diarrhoea was evaluated daily during the first month and then over periods of two weeks during the next five months of follow up. We also assessed the frequency of adverse events. We compared these outcomes by determining the relative risk (and 95% confidence intervals) of experiencing diarrhoea during a day or fortnight conferred by treatment with albendazole. Significance was evaluated with two approaches—firstly, with Fisher's exact test, which assumes independence of the periods during which symptoms were recorded as being present or absent, and, secondly, by calculating the probability of experiencing diarrhoea during each period of follow up of each patient and by carrying out a Mann-Whitney non-parametric comparison. This does not make the independence assumption except in as much as the individual patients are assumed to be independent, but is insensitive during the later periods of follow up as many patients are given the same rank. For this reason, in one case the last five months of follow up were grouped together. Mortality and the probability of relapse after remission were compared with Kaplan-Meier analysis and the log rank statistic. Calculations were carried out with EPI-INFO, version 6 (Centers for Disease Control, Atlanta) and STATA, version 4.0 (Stata, Texas).

Approval for the study was obtained from the national AIDS research ethics committee of Zambia.

Table 1—*Demographic and clinical characteristics of patients at randomisation, according to centre and to treatment*

	Centre			Treatment	
	University Teaching Hospital, Lusaka	Ndola Hospital	Kara Trust, Lusaka	Albendazole	Placebo
No	58	74	42	87	87
Age (years)	34.1	31.9	30.1	31.9	32.5
Sex (male:female)	29:29	38:36	30:12	45:42	52:35
Mean duration of diarrhoea (months)	9.7	7.1	6.3	7.8	7.4
Mean frequency of diarrhoea (per 24 h)	7.1	6.0	5.6	6.7	6.0
Mean Karnofsky score*	66	61	77	67	65
Receiving treatment for tuberculosis	10	5	4	8	11
Oral candidiasis	2	24	2	11	17
Fever	4	46	5	26	29
Receiving antibiotics	2	0	1	0	3
Receiving codeine	12	34	0	23	23

*See box for meaning of scores.

Results

In all, 174 patients were randomised. Six enrolment errors occurred during randomisation: in four patients diarrhoea had been present for less than three weeks, and two patients were inadvertently enrolled by both the University Teaching Hospital's team and the Kara Trust's team and therefore received two treatment packs. In 30 cases (16 in the group taking albendazole and 14 in the group taking placebo) the records were lost before any data were retrieved. These losses

Table 2—*Proportion of time periods with and without diarrhoea in groups receiving albendazole or placebo over six months of follow up*

	Weeks of follow up				
	1-2*	3-4*	5-8†	9-16†	17-24†
Albendazole (n=52):					
With diarrhoea	530	291	34	35	21
Without diarrhoea	279	439	55	102	74
Placebo (n=53):					
With diarrhoea	563	409	40	55	33
Without diarrhoea	228	318	47	70	55
Relative risk (95% confidence interval)	0.92 (0.86 to 0.98)	0.71 (0.63 to 0.79)	0.83 (0.59 to 1.18)	0.58 (0.41 to 0.82)	0.59 (0.37 to 0.94)
P (Fisher's exact test)	0.016	<0.0001	0.36	0.002	0.02
P (Mann-Whitney rank test)‡		0.028		0.011	

*No of patient days.
†Number of two weekly periods.
‡Probability of experiencing diarrhoea during weeks 3-4 and 5-24 (see methods).

Table 3—*Number of patients who achieved remission of diarrhoea after completion of treatment**

	Weeks of follow up			
	3-4	5-8	9-16	17-24
Albendazole (n=69)	18	15	13	10
Placebo (n=69)	6	5	5	1
Relative risk (95% confidence interval)	3.0 (1.3 to 7.1)	3.0 (1.2 to 7.8)	2.6 (1.0 to 6.9)	10.0 (1.4 to 82.0)
P (Fisher's exact test)†	0.008	0.017	0.048	0.005

*Analysis includes non-compliers, those lost to follow up, deaths, and withdrawals, but not those incorrectly randomised or those whose records were lost before any data were retrieved. Remission was defined as having no more than one day of diarrhoea in the two weeks after treatment; any further diarrhoea at all was regarded as relapse.
†Kaplan-Meier analysis and log rank test confirmed overall significance (P=0.003).

Table 4—*Reduction in diarrhoea, expressed as relative risk (95% confidence interval) of experiencing diarrhoea in group taking albendazole compared with group taking placebo, with respect to Karnofsky score**

	Weeks of follow up				
	1-2	3-4	5-8	9-16	17-24
Karnofsky score 50-70:	0.83 (0.75 to 0.92)	0.55 (0.47 to 0.63)	0.59 (0.39 to 0.89)	0.38 (0.23 to 0.61)	0.52 (0.27 to 1.01)
No of patients	65	65	59	41	31
P (Fisher's exact test)	<0.001	<0.001	0.019	<0.001	0.06
P (rank test)	0.19	<0.001	0.02	0.007	0.12
Karnofsky score 80-90:	1.0	1.05	1.22 (0.64 to 2.34)	0.89 (0.55 to 1.45)	0.81 (0.41 to 1.59)
No of patients	38	38	34	32	23

No assessment of efficacy could be made in the group with Karnofsky scores of 40 or below as the mortality in this small group was very high. Effect of albendazole was not significant at any time during follow up with either test for group of patients with score of 80-90.
*See box for meaning of scores.

occurred because of patients moving house, natural catastrophes (for example, domestic fire, roof collapse), or unexplained factors. Records that for at least the first month were complete and could be evaluated were available for 138 patients (69 patients taking albendazole, 69 placebo).

Of the 138 correctly randomised patients with adequate records for the first month, four patients (two taking albendazole, two placebo) failed to complete the treatment course, as determined by inspection of the treatment pack. Eight patients withdrew from the study (five taking albendazole, three placebo); withdrawal was attributed to worsening diarrhoea or vomiting in (five patients) and to adverse effects (three patients receiving albendazole). Twenty one patients died (10 taking albendazole, 11 placebo) during the first 14 days of the trial and therefore did not complete treatment.

Table 1 shows the demographic and clinical data for the 174 patients according to treatment centre and treatment. No differences existed in the entry characteristics or in the recorded consumption of codeine or antibiotics between the patients allocated to albendazole and those allocated to placebo.

REDUCTION IN DIARRHOEA

Diarrhoea was less common in the group taking albendazole than in the group taking placebo during the entire six month period of follow up; this was significant at all time points except during weeks 5 to 8. Table 2 shows the relative risk of experiencing diarrhoea conferred by albendazole (0.71 in weeks 3-4 (a reduction in the proportion of days with diarrhoea of 29%) and 0.58 to 0.83 over the rest of follow up).

Table 3 shows the proportions of patients who were in remission after completion of treatment (26% in the group taking albendazole, 9% in that taking placebo), and their progress over follow up. A significant difference between the two groups was seen at each time point and when the whole period of follow up was compared with a Kaplan-Meier analysis and log rank test (P=0.003). The proportion of patients lost to follow up over the six months was similar in both groups (albendazole, 23/69; placebo, 19/69).

The reduction in diarrhoea was seen in all treatment centres, but the magnitude and significance of the benefit varied. In weeks 3 to 4—that is, after completion of treatment—the patients at the Kara Trust who could be evaluated (n=29) achieved a 31% reduction (P=0.004), those in Ndola (n=57) a 41% reduction (P<0.0001), but those at University Teaching Hospital (n=18) only a 10% reduction (not significant).

The outcome was found to be poor in those few patients who had been given a score of 40 or less at the time of randomisation; at one month eight out of 12 patients in this group had died—no meaningful conclusions could be drawn. The other patients were divided into those with scores of 80 or 90 (able to work) and those with scores of 50 to 70 (needing help with activities of daily living and unable to work, but not needing admission to hospital). Table 4 shows that the benefit of albendazole is conferred on patients with Karnofsky scores of 50 to 70.

DEATH

Death was known to have occurred in 49 patients (in 22 patients taking albendazole and 27 placebo). Log rank analysis showed that albendazole had no significant effect on mortality at any time during follow up (P=0.55).

ADVERSE EVENTS

Adverse events were recorded in 10 patients (in seven taking albendazole and three taking placebo). Five patients had an exacerbation of diarrhoea, together with vomiting. One patient (taking albendazole) had a cutaneous reaction; this was a transient morbilliform rash that resolved within one week of discontinuing the drug. Four other patients taking albendazole complained of dizziness (1), headache (1), cough (1), and difficulty swallowing (1), but these symptoms are indistinguishable from symptoms due to the underlying illness.

Discussion

EFFICACY OF ALBENDAZOLE

This trial has shown that albendazole reduces the proportion of time that patients with AIDS in urban Zambia have diarrhoea. Remission was achieved in 26% of patients (compared with 9% of those taking placebo), but this proportion rose to 35% (18/52) if the analysis

excluded deaths and withdrawals from treatment. The empirical approach adopted in this study shows that patients can expect benefit from treatment without having undergone a search for specific pathogens. The therapeutic benefits were obtained in a setting that applies to many African patients with AIDS and may have been underestimated in our study, as we allowed, for ethical reasons, the concomitant use of codeine phosphate and similar agents. If codeine, antibiotics, or traditional herbal medicines were used more freely than was admitted to, this might lead to a further reduction in apparent efficacy, and we know that the use of herbal remedies is common.

We cannot comment on the value of albendazole in seriously ill patients as in our patients the mortality was high, but we have clear evidence that it is beneficial in patients who cannot work and need help with activities of daily living. In these patients albendazole confers a protection against experiencing diarrhoea at any one time of about 50% over six months. Some of the patients who were given Karnofsky scores of 50 to 70 at randomisation would already have shown improvement after treatment with oral rehydration and codeine in hospital and may have been more seriously ill even a few days previously. Patients with persistent diarrhoea—that is, non-responders—would have probably been more likely to be lost to follow up, and this may partly explain the improvement in symptoms in both groups over time (table 2). This effect would not explain, however, the difference between the group taking albendazole and that taking placebo.

MORTALITY

Albendazole had no effect on mortality. Perhaps this is not surprising as early deaths are likely to have been determined before enrolment, whether by nutritional deficiency, systemic infection, or the severity of immunosuppression. Albendazole may have an effect on late (after the first two months) mortality, but our study may not have had sufficient power to detect it in that some of the patients who were lost to follow up would have died. Local customs dictate that seriously ill people are taken back to their ancestral home to die, and at death many of their personal belongings are destroyed. This suggests that deaths would be overrepresented in the group whose record cards were not returned despite the efforts of the home care staff to trace their whereabouts. This was a particular problem in the patients attending University Teaching Hospital in Lusaka, which has a high proportion of residents who consider themselves to have a true domicile elsewhere. Patients at the Kara Trust centre were less unwell, and follow up was more successful. Another possible explanation for the lack of effect on mortality could be infection with other pathogens: Lucas *et al* in Abidjan found unsuspected advanced tuberculosis to be responsible for much mortality in patients with slim disease,[17] and septicaemic complications are almost certainly responsible for many deaths.[18] Unexpectedly, five of the 21 early deaths occurred in patients with Karnofsky scores of 60 or more.

IMPLICATIONS OF FINDINGS

We surmise that much of the effectiveness of albendazole in the patients in our study was due to its effect in eradicating or suppressing infection with microsporidia. *S intestinalis* is sensitive to albendazole,[19,20] and we have previously reported the presence of this organism in Zambia.[10] Infections with other parasites (*G intestinalis* and *S stercoralis*) also respond to albendazole, but these infections are less common in patients with AIDS in Zambia. We do not know the response of *C parvum* or *I belli* to albendazole. The regimen that we used could probably be improved further with the addition of other chemotherapeutic agents, but antibiotic resistance is very common among isolates of enteric bacteria in Lusaka at the moment.

Key messages

- Persistent diarrhoea is an important cause of morbidity and mortality in patients with AIDS in Zambia
- Enteric intracellular protozoa can be identified in most of these patients in hospital in Lusaka
- Albendazole (800 mg twice daily for two weeks) reduced the time with diarrhoea over six months
- The Karnofsky score, a simple clinical assessment, identified patients most likely to benefit
- Albendazole had no measurable effect on mortality

We know of no other placebo controlled studies that have shown efficacy of a treatment for diarrhoea in patients with AIDS in Africa. Current practice in many areas is to give co-trimoxazole and metronidazole in standard doses, with or without loperamide. In a previous study a substantial response to placebo showed considerable variability in the natural course of the diarrhoea,[21] and so the use of a placebo in a blinded study was important and fully justified.[22] If the results of our study (including the apparent safety of high dose albendazole) are confirmed, the following recommendations would seem reasonable. On presentation, patients with salt and water depletion should have fluid and electrolyte replacement, usually with an oral glucose electrolyte solution containing potassium. If the diarrhoea has been present for over three weeks then albendazole 800 mg twice daily may be given. If the patient is moribund or if the diarrhoea is of less than three weeks' duration then codeine phosphate should be used to try to control the diarrhoea, as in these situations we have no direct evidence of benefit. In the light of our findings patients with Karnofsky scores of 80 or more should probably be treated in the same way.

Albendazole chemotherapy for AIDS in Africa seems to be beneficial, with minimal adverse reactions, and is effective in empirical use in a community setting. Individuals infected with HIV, and their families, often spend much of their resources on treatments,[23] many of which are of doubtful value. We believe that treatment with albendazole, which is effective over six months, is likely to have a high benefit:cost ratio in this devastating disease. Further work is urgently needed to corroborate these findings, to compare albendazole with cheaper antibiotic regimens, and to improve the regimen by addition of other agents.

We acknowledge the dedicated work of the following nursing and counselling staff of the home care services for their careful monitoring of the patients: Mrs N Chiselo, Mrs J Chimoto, Mr J Daka, Mrs G Goma, Mrs A Kapaya, Mrs P Kapembwa, Mrs V Kunda, Mr R Makulele, Mrs Q Moyowanyambe, Mrs S Phiri, Mrs R Sakala, Mr S Silomba, Mrs M Tonha, and Mrs R Zulu. We thank Mr John Young for valuable help with packaging and pharmaceutical quality control, Dr Joan Morris for statistical guidance, and our patients for their willingness and cooperation.

Funding: SmithKline Beecham for financial support and provision of drugs.

Conflict of interest: None.

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(Accepted 27 February 1996)

Role of patients' view of their illness in predicting return to work and functioning after myocardial infarction: longitudinal study

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Abstract

***Objective*—To examine whether patients' initial perceptions of their myocardial infarction predict subsequent attendance at a cardiac rehabilitation course, return to work, disability, and sexual dysfunction.**

***Design*—Patients' perceptions of their illness were measured at admission with their first myocardial infarction and at follow up three and six months later.**

***Setting*—Two large teaching hospitals in Auckland, New Zealand.**

***Subjects*—143 consecutive patients aged under 65 with their first myocardial infarction.**

***Main outcome measures*—Attendance at rehabilitation course; time before returning to work; measures of disability with sickness impact profile questionnaire for sleep and rest, social interaction, recreational activity, and home management; and sexual dysfunction.**

***Results*—Attendance at the rehabilitation course was significantly related to a stronger belief during admission that the illness could be cured or controlled (t=2.08, P=0.04). Return to work within six weeks was significantly predicted by the perception that the illness would last a short time (t=−2.52, P=0.01) and have less grave consequences for the patient (t=−2.87, P=0.005). Patients' belief that their heart disease would have serious consequences was significantly related to later disability in work around the house, recreational activities, and social interaction. A strong illness identity was significantly related to greater sexual dysfunction at both three and six months.**

***Conclusions*—Patients' initial perceptions of illness are important determinants of different aspects of recovery after myocardial infarction. Specific illness perceptions need to be identified at an early stage as a basis for optimising outcomes from rehabilitation programmes.**

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BMJ 1996;312:1191–94

Introduction

Recent developments in treatment during the acute stage of myocardial infarction have resulted in improved survival and fewer complications for patients.[1] However, these gains in the acute phase of the illness contrast with the small progress that has been achieved in understanding and improving the rehabilitation phase of the illness.[2] The difficulties patients face after leaving hospital in terms of changing their lifestyle and regaining their vocational, sexual, and other functioning may be considerable. As more patients survive myocardial infarction this aspect has become even more important.

Much of the available evidence suggests that psychological factors become more important than medical factors in directing the recovery process after a myocardial infarction.[3,4] Recently, more attention has been directed to how patients' cognitive representations of their illness are associated with adjustment and rehabilitation in several medical conditions.[5,6] Research suggests that patients group their ideas about illness around five coherent themes or components, which health psychologists have called illness perceptions.[7] These provide a framework for patients to make sense of their symptoms, assess health risk, and direct action during recovery. The five main cognitive components are:

- Identity—the label the person uses to describe the illness and the symptoms the patient views as being part of the disease
- Cause—personal ideas about the cause of the illness
- Time line—how long the patient believes the illness will last
- Consequences—expected effects and outcome of the illness
- Cure or control—how the patient recovers from or controls the illness.

Previous research on heart disease has highlighted the importance of personal models of illness to recovery after myocardial infarction. Clinicians have noted that patients may develop quite idiosyncratic ideas about what has happened to their heart and their likelihood of recovery[8]—an extreme example is cardiac invalidism. Researchers have noted that patients' negative expectations about their illness and future work capacity while in hospital have been associated with slower return to work and impaired functioning.[9,10] Attendance at rehabilitation programmes and adoption of changes in lifestyle are ongoing issues—some patients do not attend such programmes[11] or they cannot make the long term changes to diet and lifestyle after them. One recent study found that patients who were judged by staff to view their illness less seriously were less likely to attend cardiac rehabilitation.[12] This has prompted some to