

## Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study)

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### ABSTRACT

**Objective** To determine whether ultraviolet B phototherapy at home is equally safe and equally effective as ultraviolet B phototherapy in an outpatient setting for patients with psoriasis.

**Design** Pragmatic multicentre single blind randomised clinical trial (PLUTO study).

**Setting** Dermatology departments of 14 hospitals in the Netherlands.

**Participants** 196 patients with psoriasis who were clinically eligible for narrowband (TL-01) ultraviolet B phototherapy. The first 105 consecutive patients were also followed for one year after therapy.

**Intervention** Ultraviolet B phototherapy at home using a TL-01 home phototherapy unit compared with standard narrowband ultraviolet B phototherapy in an outpatient setting. Both therapies were done in a setting reflecting routine daily practice in the Netherlands.

**Main outcome measures** The main outcome measure was effectiveness as measured by the proportion of patients with a 50% or more reduction of the baseline psoriasis area and severity index (PASI) or self administered psoriasis area and severity index (SAPASI), called the PASI 50 and SAPASI 50 (relevant treatment effect). Another outcome of effectiveness was the percentage reduction in median scores on the PASI as well as SAPASI. Also the proportion of patients reaching the PASI 75 and SAPASI 75 (successful treatment effect), and the PASI 90 and SAPASI 90 (almost complete clearance) were calculated. Other secondary outcomes were quality of life (SF-36, psoriasis disability index), burden of treatment (questionnaire), patients' preferences and satisfaction (questionnaire), and dosimetry and short term side effects (diary).

**Results** 82% of the patients treated at home compared with 79% of the patients treated in an outpatient setting reached the SAPASI 50 (difference 2.8%, 95% confidence interval -8.6% to 14.2%), and 70% compared with 73% reached the PASI 50 (-2.3%, -15.7% to 11.1%). For patients treated at home the median SAPASI score decreased 82% (from 6.7 to 1.2) and the median PASI score decreased 74% (from 8.4 to 2.2), compared with 79% (from 7.0 to 1.4) and 70% (from 7.0 to 2.1) for

patients treated in an outpatient setting. Treatment effect as defined by the mean decline in PASI and SAPASI scores was significant ( $P < 0.001$ ) and similar across groups ( $P > 0.3$ ). Total cumulative doses of ultraviolet B light were similar ( $51.5$  v  $46.1$  J/cm<sup>2</sup>, difference 5.4, 95% confidence interval -5.2 to 16.0), and the occurrence of short term side effects did not differ. The burden of undergoing ultraviolet B phototherapy was significantly lower for patients treated at home (differences 1.23 to 3.01, all  $P \leq 0.001$ ). Quality of life increased equally regardless of treatment, but patients treated at home more often rated their experience with the therapy as "excellent" (42%, 38/90) compared with patients treated in the outpatient department (23%, 20/88;  $P = 0.001$ ).

**Conclusion** Ultraviolet B phototherapy administered at home is equally safe and equally effective, both clinically and for quality of life, as ultraviolet B phototherapy administered in an outpatient setting. Furthermore, ultraviolet B phototherapy at home resulted in a lower burden of treatment and led to greater patients' satisfaction.

**Trial registration** Current Controlled Trials ISRCTN83025173 and [Clinicaltrials.gov](http://Clinicaltrials.gov) NCT00150930.

### INTRODUCTION

Ultraviolet B phototherapy is indicated for psoriasis and is generally offered in an outpatient clinic, requiring patients to travel for treatment. To overcome this drawback, equipment for use at home was introduced.<sup>1-4</sup> Although home phototherapy has been used since the late 1970s,<sup>3-10</sup> its safety and effectiveness have been debated. Non-evidence based fears are often expressed about higher attendant risks such as inaccurate dosimetry, phototoxicity, and unsupervised continuation after the treatment has finished.<sup>7-16</sup> These risks are thought to influence the occurrence of acute side effects and lead to an increased cumulative dose and hence promote photocarcinogenesis and photo-ageing. Little attention has been paid to the possible positive effects of home therapy on quality of life, patients' satisfaction, and the burden of treatment.<sup>13</sup>

We aimed to establish that treatment effect, safety, and quality of life of home ultraviolet B phototherapy

do not differ substantially from that of ultraviolet B phototherapy in an outpatient clinic. We also expected a lower burden from home treatment and higher patient satisfaction.

## METHODS

From 2002 to 2005 we carried out a pragmatic multicentre single blinded randomised trial comparing narrowband ultraviolet B phototherapy at home with narrowband ultraviolet B phototherapy in an outpatient setting ([www.biomedcentral.com/content/pdf/1471-2288-6-39.pdf](http://www.biomedcentral.com/content/pdf/1471-2288-6-39.pdf)).<sup>17</sup> A pragmatic design tackles questions on effectiveness in daily practice as opposed to efficacy in a “controlled” setting.<sup>18-20</sup> Blinding participants to treatment was not possible, and because of the pragmatic design it was undesirable to blind the dermatologists. The extent and severity of the psoriasis was, however, assessed by an independent research nurse blinded to the treatment arm.<sup>17</sup>

We invited patients with plaque or guttate psoriasis to participate if they were considered clinically eligible for narrowband ultraviolet B phototherapy. The treatment with ultraviolet B light had to be prescribed by the patient’s own dermatologist.

### Sample size

We expected the treatments to be equally effective.<sup>5</sup> The sample size was therefore calculated in accordance with a negative trial approach.<sup>21</sup> We considered a 50% or more improvement in the severity of psoriasis from baseline to be a relevant clinical response. From the literature we expected about 85% of the treated patients to show at least a 50% improvement.<sup>22</sup> We determined that we would need 90 patients per group.<sup>17</sup> To allow for missing data and losses to follow-up we aimed to recruit 100 patients per group.

### Randomisation and therapy

After baseline data had been collected each patient was randomised by a computer generated list to ultraviolet B phototherapy either at home or in an outpatient department.<sup>17</sup> After randomisation both the patient and the dermatologist were informed of the assigned treatment.

Patients randomised to outpatient treatment received narrowband (TL-01) ultraviolet B phototherapy in their local hospital. The hospitals used their own treatment schedules and full circle units. Some types of units had indicators to measure the intensity of irradiation ( $\text{mW}/\text{cm}^2$ ); others measured treatment time. Accordingly, treatments were prescribed in dose ( $\text{J}/\text{cm}^2$ ) or in seconds.<sup>17</sup> Patients were treated two or three times a week, depending on the hospital.

Patients randomised to home ultraviolet B phototherapy were provided with a semicircular TL-01 home phototherapy unit (UV 100; Waldmann, Villingen-Schwenningen, Germany), without an intensity indicator. Therefore treatments were prescribed in seconds. The unit was delivered and collected by the home care institutions. On delivery, a nurse from the institution provided training in the use of the unit. The

patients received a treatment schedule, set in seconds. Irradiation took place three to four times a week. The irradiation schedules for both groups were those normally used by the hospitals and home care institutions. Neither equipment nor schedules were modified for the trial.

### Outcome measures

We determined the severity of disease using the psoriasis area and severity index (PASI)<sup>23</sup> and the self administered psoriasis area and severity index (SAPASI),<sup>24</sup> with scales ranging from 0 (no lesions) to 72 (extensive erythroderma of the severest degree). The main outcome measure was effectiveness, as measured by the proportion of patients with a 50% or more improvement of the baseline PASI or SAPASI (called PASI 50 and SAPASI 50), considered a relevant treatment effect. Another outcome measure was the percentage reduction in median PASI and SAPASI scores. Also the PASI 75 and SAPASI 75 (a “successful treatment effect”), the PASI 90 and SAPASI 90 (almost complete clearance), and a patient assessed visual severity assessment scale ranging from 0 (no psoriasis) to 100 (most severe psoriasis imaginable) were measured.

To verify whether the treatments were equally safe we assessed the incidence of acute side effects and measured the total cumulative dose of ultraviolet B light. The patients recorded any short term side effects for every irradiation in a diary. We considered four side effects of interest: mild erythema and burning sensation (mild and expected) and severe erythema and blistering (serious).

To calculate cumulative doses of ultraviolet B light we measured light intensity ( $\text{J}/\text{cm}^2$ ) of all equipment from the hospitals using portable ultraviolet light meters. If the unit had an irradiation intensity indicator, we compared its reading with our own measurements. The home care institutions measured the light intensity of every unit before the first irradiation and after the last irradiation, using their own ultraviolet light meters. At the end of the trial we collected these measurements and also compared their ultraviolet light meters with our own ultraviolet light meter (see [bmj.com](http://bmj.com)). Participants in both groups recorded treatment times in their diary. We also took copies of the charts of the patients treated in hospital. We calculated standardised cumulative doses ( $\text{mW}/\text{cm}^2$ ) for all patients using the intensity measurements and data from the charts or diaries, or both.

To measure the perceived burden of treatment we designed a four item questionnaire using visual analogue scales ranging from 0-10. We also assessed health related quality of life using the short form 36 general health survey<sup>25</sup> and the psoriasis disability index.<sup>26</sup> We also developed a questionnaire on patients’ satisfaction and preferences.<sup>17</sup>

Measurements for the 196 participants coincided with inclusion in the study, start of therapy, the 23rd irradiation, and the end of therapy. When treatments exceeded 46 irradiations, we defined 46 irradiations as the end of therapy.<sup>17</sup>

### Statistical analysis

The main principle of our analysis was non-inferiority—that is, we hypothesised that there would be no differences between both treatment groups. The non-inferiority margin ( $\Delta$ ) for the primary outcome measures PASI 50 and SAPASI 50 was set at  $-15\%$ . Non-inferiority of home phototherapy was accepted if the lower bound of the two sided  $95\%$  confidence interval around the estimated difference in proportion of patients reaching PASI 50 or SAPASI 50 was above  $-15\%$ . We also analysed the secondary outcome measures for non-inferiority, using evaluation of the lower bounds of the  $95\%$  confidence intervals for clinical relevance. The differences at group level are presented with their  $95\%$  confidence intervals.

We used statistical methods in accordance with the type of data to analyse the superiority of patients' satisfaction and burden of treatment. From independent samples we carried out the unpaired *t* test for normally distributed continuous data. For ordinal data and data with a skewed distribution we used the Mann-Whitney U test. All analyses were done according to the intention to treat principle.

### RESULTS

Overall, 98 patients were randomised to home ultraviolet B phototherapy and 98 to outpatient ultraviolet B phototherapy (see [bmj.com](http://bmj.com)). The severity of psoriasis at baseline between those who completed the study and those who dropped out did not differ. Baseline

**Main outcome measures for patients with psoriasis randomised to ultraviolet B phototherapy at home or in an outpatient department. Values are percentages (numbers) of patients unless stated otherwise**

Variables	Home phototherapy	Outpatient phototherapy	Difference (95% CI)
<b>Effectiveness</b>			
SAPASI 50, 75, and 90*:	(n=94)	(n=91)	—
SAPASI 50	81.9 (77)	79.1 (72)	2.8 (−8.6 to 14.2)
SAPASI 75	69.1 (65)	59.3 (54)	9.8 (−4.0 to 23.6)
SAPASI 90	43.6 (41)	29.7 (27)	13.9 (0.002 to 27.8)
PASI 50, 75, and 90†:	(n=91)	(n=84)	—
PASI 50	70.3 (64)	72.6 (61)	−2.3 (−15.7 to 11.1)
PASI 75	40.7 (37)	41.7 (35)	−1.0 (−15.6 to 13.6)
PASI 90	19.8 (18)	19.0 (16)	0.8 (−10.9 to 12.5)
<b>Safety</b>			
Irradiations:	(n=98)	(n=98)	—
Mean No of irradiations	34.4	28.6	5.8 (2.7 to 9.0)
Mean cumulative dose (J/cm <sup>2</sup> ):	(n=85)	(n=68)	—
At 23 irradiations	21.2	26.9	−5.7 (−10.3 to −1.1)
At end of therapy	(n=91)	(n=93)	—
At end of therapy	51.5	46.1	5.4 (−5.2 to 16.0)
Proportion of side effects per irradiation (%):	(n=93)	(n=92)	—
Severe erythema	5.5	3.6	1.9 (−1.1 to 4.9)
Blistering	0.3	0.6	−0.3 (−0.9 to 0.3)
Burning sensation	7.1	10.0	−2.9 (−7.1 to 1.2)
Mild erythema	28.8	28.6	0.3 (−7.4 to 8.0)
<b>Use of adjuvant drugs‡</b>			
During waiting time§:	(n=94)	(n=95)	—
Topical steroids	25.5 (24)	6.3 (6)	19.2 (8.8 to 29.6)
Vitamin D derivatives	18.1 (17)	6.3 (6)	11.8 (2.5 to 21.1)
During phototherapy:	(n=92)	(n=92)	—
Topical steroids	31.5 (29)	52.2 (48)	−20.7 (−35.0 to −6.4)
Vitamin D derivatives	19.6 (18)	40.2 (37)	−20.6 (−33.8 to −7.4)
<b>Waiting time§ and duration of therapy</b>			
	(n=93)	(n=95)	—
Mean waiting time§ (weeks)	5.8	2.2	3.6 (2.9 to 4.4)
Mean duration of therapy (weeks)	11.4	14.1	−2.7 (−4.1 to −1.2)
Mean time from inclusion to end of therapy (weeks)	17.2	16.2	1.0 (−0.6 to 2.5)

SAPASI=self administered psoriasis area and severity index; PASI=psoriasis area and severity index. When treatments exceeded 46 irradiations, 46 irradiations is defined as end of therapy. Values shown are calculated from data not exceeding 46 irradiations.

\*Proportion of patients achieving at least a 50%, 75%, or 90% decline of baseline SAPASI at end of therapy.

†Proportion of patients achieving at least a 50%, 75%, or 90% decline of baseline PASI at end of therapy.

‡Proportion of patients using adjuvant drugs during two consecutive phases of trial.

§Time between inclusion in trial and starting phototherapy.

psoriasis severity ranged from mild to severe, with individual PASI scores up to 48.6. Eight patients had experience of home ultraviolet treatment: three were allocated to home ultraviolet B phototherapy and five to outpatient ultraviolet B phototherapy.

#### Treatment effect

Four of the six outcome measures for effectiveness (PASI 50, 75, and 90 and SAPASI 50, 75, and 90; table) indicated that home ultraviolet B phototherapy was not inferior—that is, was equally effective as (SAPASI 50 and PASI 90), at least equally effective as (SAPASI 75), or even superior to (SAPASI 90) outpatient ultraviolet B phototherapy. The remaining two measures (PASI 50 and PASI 75) had point estimates suggesting equal effectiveness, but non-inferiority could not be confirmed by the 95% confidence intervals, of which the lower bounds were slightly lower than -15%.

The treatment effect as defined by the mean decline in SAPASI and PASI scores was statistically significant within (all  $P < 0.001$ ) and similar across ( $P > 0.3$ ) both treatment groups.

During therapy the median SAPASI score decreased from 6.7 to 1.2 for the home ultraviolet B group and from 7.0 to 1.4 for the outpatient ultraviolet B group; a decline of 82% and 79%, respectively. Essentially similar results were observed for decline in median PASI scores, from 8.4 to 2.2 compared with 7.0 to 2.1; a decline of 74% and 70%.

Mean self assessed scores for psoriasis severity using a visual severity assessment scale (range 0-100) were 70.6 and 70.2 at inclusion and 18.1 and 18.0 at the end of therapy (90 patients in home group *v* 88 in outpatient group).

#### Safety

Patients treated at home had a higher mean total number of irradiations than patients treated in the outpatient setting (table). Yet the point estimate of the mean cumulative dose of TL-01 ultraviolet B light at the end of therapy was only slightly higher for patients treated at home (difference 5.4 J/cm<sup>2</sup>, 95% confidence interval -5.2 to 16.0).

Information on side effects was available for 6111 irradiations in 185 patients. Regardless of treatment group, 87% (n=161) of the patients had at least one occurrence of mild erythema during the treatment, 58% (n=107) a burning sensation, 39% (n=73) severe erythema, and 6% (n=11) blistering. No differences were observed between the treatment groups. The mean probability per irradiation of experiencing a particular side effect did not differ between the groups (table), and the patients' perception of safety also did not differ between the groups (see bmj.com).

#### Waiting time, adjuvant drug use, and burden of treatment

Waiting time (between inclusion in the trial and the start of phototherapy) was longer for patients treated at home than for patients treated in the outpatient department (table). This did not result in a clinically relevant difference in total duration until the end of

treatment. During waiting time, a higher proportion of patients treated at home used topical steroids and vitamin D derivatives, whereas during phototherapy a higher proportion of patients treated in the outpatient department used these two types of drugs (table).

Results for the burden of treatment measured after 23 irradiations and at the end of therapy were virtually identical. The overall average burden of treatment was significantly higher for patients treated in the outpatient department than for those treated at home. Differences in mean scores for the four domains were 1.23 to 3.01 ( $P \leq 0.001$  for all; see bmj.com).

#### Quality of life

The psoriasis disability index values decreased from 32.8 in the home ultraviolet B group (n=98) and 34.3 in the outpatient ultraviolet B group (n=98) at inclusion to 20.9 and 22.0 (n=93, and n=91) at the end of therapy. At all three time points of measurement, psoriasis disability index values were similar across groups ( $P > 0.45$ ). The eight SF-36 domain scores and the two components scores were also similar across the groups. The values were, however, lower than the values observed in an unaffected population sample.<sup>27</sup>

#### Patients' satisfaction and preferences

Patients treated at home evaluated their therapy more positively than patients treated in the outpatient department ( $P = 0.001$ ; see bmj.com). Patient satisfaction was categorised as satisfaction with the treatment result (appearance of skin), the rate of improvement, and nursing care and supervision (see bmj.com).

Waiting time before phototherapy was sometimes considerable. However, 26% (22/86) of the patients treated at home and 45% (26/58) treated as an outpatient thought the waiting time was not a problem, and 48% (41/86) compared with 35% (20/58) thought the waiting time was acceptable. Only a minority thought it was too long (17% *v* 16%) or far too long (9% *v* 5%;  $P = 0.038$ ). Despite the waiting times, most of the participants in both groups said that they would prefer home ultraviolet B phototherapy in the future: 92% (83/90) of patients treated at home compared with 60% (53/88) treated in the outpatient department (difference 32%, 95% confidence interval 19.5% to 44.5%).

#### DISCUSSION

Ultraviolet B phototherapy at home is equally effective for treating psoriasis as ultraviolet B phototherapy in an outpatient setting and implies no additional safety hazards in a setting precluding possible non-prescribed irradiations. Furthermore, home treatment poses a lower burden, is better appreciated, and gives similar improvements in quality of life. Most of the patients said that they would prefer future ultraviolet B treatment at home over phototherapy in an outpatient setting.

Four of six measures of the SAPASI 50, 75, and 90 and PASI 50, 75, and 90 indicated that home ultraviolet B phototherapy for psoriasis is at least equally effective as, or even superior to, ultraviolet B phototherapy in an outpatient department. The remaining two

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Two observational studies indicated that ultraviolet B phototherapy at home might be equally effective as ultraviolet B phototherapy in an outpatient setting

Randomised evidence and evidence based guidelines on home ultraviolet B phototherapy are lacking, and general consensus suggests being prudent

Half of dermatologists think home ultraviolet B phototherapy is inferior to outpatient treatment, and almost a third think it carries higher risks

**WHAT THIS STUDY ADDS**

Randomised evidence shows that ultraviolet B phototherapy at home is at least equally effective as and equally safe as treatment in an outpatient setting

Home treatment was associated with a lower burden of treatment and greater patients' satisfaction

Home ultraviolet B phototherapy provides a good alternative to outpatient ultraviolet B treatment

measures had point estimates suggesting equal effectiveness, but from the 95% confidence intervals possible inferiority of home ultraviolet B phototherapy could not be entirely excluded. Also, the similar decrease in the PASI and SAPASI scores and the visual severity assessment score adds to the conclusion of similar effectiveness. The proportion of patients reaching the SAPASI 90 shows that home ultraviolet B phototherapy may be more effective than such treatment as an outpatient. This was not, however, confirmed by the PASI 90 score. Possibly, the patients' responses may have been biased, resulting in optimistic assessment.

The treatments were also equally safe, as judged by the similar proportion of acute side effects and the perceived safety of the treatment.

The final cumulative dose of ultraviolet B light was not significantly different between the groups. As the attributive long term risk for skin cancer caused by ultraviolet B phototherapy is believed to correlate directly with the experience of acute side effects and with the total cumulative dose of ultraviolet B light,<sup>28-30</sup> we conclude that the risk of skin cancer from treatment would also be similar across the groups. Moreover, a possible difference of 5.4 J/cm<sup>2</sup> in total cumulative dose (95% confidence interval -5.2 to 16.0) corresponds to a difference of about 9 minimal erythema doses (95% confidence interval values correspond to -9 and 26). In the Netherlands the mean solar exposure is 75 minimal erythema doses annually for indoor workers and 170 minimal erythema doses annually for outdoor workers.<sup>31</sup> Therefore a mean difference of 9 minimal erythema doses per year seems insignificant and insufficient to favour outpatient ultraviolet B phototherapy over home treatment.

The considerable waiting time before home treatment partly resulted from capacity problems at the home care institutions during winter. Duration of

home phototherapy was, however, shorter than outpatient treatment, supposedly due to the difference in irradiation frequency and the resulting difference in rate of improvement.<sup>32,33</sup> Thus, despite the longer waiting time for home ultraviolet B treatment, the mean time from inclusion up to the end of the treatment was similar for both groups.

The results of the burden of treatment questionnaire showed more comfort and a lower burden for patients treated at home. Improvement in quality of life, however, was similar for both groups. This was because the quality of life questionnaires were disease specific (psoriasis disability index) and generic (SF-36). Disease severity decreased similarly in both groups, hence it might be expected that general or disease specific quality of life would improve similarly in the groups.

Patients treated in hospital were in general slightly more satisfied with nursing care and supervision. However, the longer waiting time for home ultraviolet B treatment was not an issue for most patients and 92% of patients treated at home and 60% treated in hospital would prefer home treatment over hospital based treatment in the future. Most patients found home phototherapy comfortable, flexible, and less time consuming than hospital based treatment, leading to higher reported satisfaction.

**Comparison with other studies**

We found only two observational parallel group studies on ultraviolet B phototherapy at home,<sup>7,13,14</sup> with home treatment seeming to be effective. No information about severity of psoriasis at baseline was provided, however, and neither study had a randomised design.<sup>7,14</sup> Patients in our trial had mild to severe disease. The average severity of psoriasis was comparable to that of a non-selected group of 23 patients receiving ultraviolet B phototherapy in our hospital from August 2006 to July 2007 (median SAPASI score 7.55).

Effectiveness in terms of percentage decline in baseline PASI and SAPASI score was similar to that of three other trials studying the effect of narrowband ultraviolet B light.<sup>34-36</sup> Overall our results may be considered representative and can be extrapolated to many other settings.

Four of six published guidelines on the safety of home ultraviolet B phototherapy for psoriasis presume that such treatment leads to inaccurate dosimetry, sub-optimal treatment, phototoxicity, and higher attendant risks.<sup>11-13,15,16</sup> We showed that home ultraviolet B treatment was equally effective and equally safe as ultraviolet B treatment in an outpatient setting, and that eligibility criteria for home ultraviolet B phototherapy can be broad.

**Strengths and weaknesses of the study**

A major strength of this study is that it is the first randomised trial on the effectiveness, quality of life, and burden of treatment of home ultraviolet B phototherapy for psoriasis compared with ultraviolet B phototherapy in an outpatient setting.<sup>13</sup> We used a pragmatic design to be able to compare the treatments under conditions in which they would be applied in

daily practice. The design ensured broad inclusion of patients who were eligible for ultraviolet B phototherapy. We believe that our participants adequately represent patients with psoriasis receiving ultraviolet B phototherapy outside the trial.

A potential weakness may be the manner in which data collection was planned. This was organised such that both groups could be compared without important differences in the number of irradiations. However, this aspect of the design made it impossible to compare the groups at fixed times. Another point of consideration might be that it was not possible to keep a record of all patients with psoriasis who were prescribed narrow-band ultraviolet B phototherapy but were not referred for inclusion in the trial. We therefore do not know the reasons for non-referral and cannot entirely exclude selection bias. Such bias would, however, be minimal as the included patients matched a consecutive sample of patients offered ultraviolet B phototherapy in our hospital at a later period.

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# Surgical treatments for men with benign prostatic enlargement: cost effectiveness study

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## ABSTRACT

**Objective** To determine which surgical treatment for lower urinary tract symptoms suggestive of benign prostatic enlargement is cost effective.

**Design** Care pathways describing credible treatment strategies were decided by consensus. Cost-utility analysis used Markov modelling and Monte Carlo simulation.

**Data sources** Clinical effectiveness data came from a systematic review and an individual level dataset. Utility values came from previous economic evaluations. Costs were calculated from National Health Service (NHS) and commercial sources.

**Methods** The Markov model included parameters with associated measures of uncertainty describing health states between which individuals might move at three monthly intervals over 10 years. Successive annual cohorts of 25 000 men were entered into the model and the probability that treatment strategies were cost effective was assessed with Monte Carlo simulation with 10 000 iterations.

**Results** A treatment strategy of initial diathermy vaporisation of the prostate followed by endoscopic holmium laser enucleation of the prostate in case of failure to benefit or subsequent relapse had an 85% probability of being cost effective at a willingness to pay value of £20 000 (€21 595, \$28 686)/quality adjusted life year (QALY) gained. Other strategies with diathermy vaporisation as the initial treatment were generally cheaper and more effective than the current standard of transurethral resection repeated once if necessary. The use of potassium titanil phosphate laser vaporisation incurred higher costs and was less effective than transurethral resection, and strategies involving initial minimally invasive treatment with microwave thermotherapy were not cost effective. Findings were unchanged by wide ranging sensitivity analyses.

**Conclusion** The outcome of this economic model should be interpreted cautiously because of the limitations of the data used. The finding that initial vaporisation followed by holmium laser enucleation for failure or relapse might be advantageous both to men with lower urinary tract symptoms and to healthcare providers requires confirmation in a good quality prospective clinical trial before any change in current practice. Potassium titanil phosphate laser vaporisation was unlikely to be cost effective in our model, which argues against its unrestricted use until further evidence of effectiveness and cost reduction is obtained.

## INTRODUCTION

In men, benign prostatic enlargement caused by hyperplasia of the gland is the main cause of lower urinary tract symptoms, such as frequency and poor flow. Prevalence is about 30% in men aged over 60, amounting to 1.8 million cases in the United Kingdom.<sup>1</sup> Endoscopic removal of prostate tissue, typically by transurethral resection (TURP), is usually recommended for men who have not benefited from behavioural or drug treatment as it offers a high (70-80%) chance of benefit and a low (1% per year) risk of retreatment. About 25 000 such procedures are carried out annually in England at a cost of £53m (€57m, \$76m). However, it carries the risk of major haemorrhage and myocardial stress<sup>2</sup> and so alternative surgical options have been trialled.

In a systematic review of effectiveness we concluded that newer technologies, such as microwave thermotherapy and diathermy or laser vaporisation, improve symptoms and reduce risk but have higher rates of retreatment than transurethral resection.<sup>3,4</sup> Men seeking treatment might trade off this reduced effectiveness for the reduced risk and for most this would result in successful treatment but a minority would need another more effective but potentially more morbid procedure. Previous studies of health economics focused on single treatments.<sup>5-7</sup> We modelled the use of plausible strategies of sequential treatments to determine which is most likely to be cost effective.

## METHODS

### Model design

We investigated cost utility of each considered treatment option with effects measured by quality adjusted life years (QALYs) and costs (£) at 2006 prices.<sup>8</sup> The perspective was the UK's National Health Service, with treatments in appropriately equipped hospitals with specialist urologists already competent to carry out the procedures.

*Treatment options and care pathways*—The standard procedure was transurethral resection, with failure to benefit or relapse managed by a second transurethral resection if urodynamics confirmed obstruction of the bladder outlet. Alternative treatments were categorised into three groups: minimally invasive, characterised by no tissue removal and ambulatory care; tissue ablative, signifying the use of differing energy sources to partially remove prostate tissue; and near total removal of prostate by holmium laser enucleation (HoLEP). Transurethral microwave thermotherapy (TUMT) and diathermy vaporisation (TUVV) typified

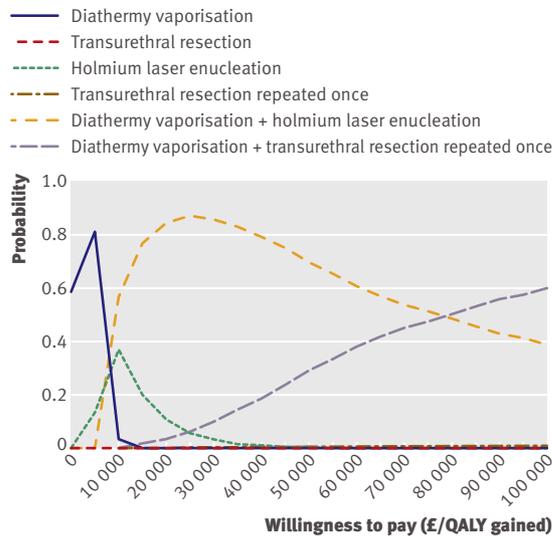


Figure 1 Cost effectiveness acceptability curve showing probability of being cost effective for non-dominated and reference strategies for increasing limits of willingness to pay

the minimally invasive and tissue ablative groups, respectively. We included potassium titanyl phosphate (KTP) laser vaporisation in the model as a substitute for diathermy vaporisation given its current clinical popularity.<sup>9</sup> Treatments always proceeded from less to more invasive; minimally invasive treatments could be repeated only once; tissue ablative and holmium laser enucleation procedures could not be repeated; and transurethral resection could be repeated only once and only after confirmation of obstruction of the bladder outlet

**Population of patients**—The population was men with symptoms (international prostate symptom score (IPSS) >7) with presumed benign prostatic enlargement and no existing relevant complications, who required transurethral resection. The mean age was set at 70, the midpoint of the age range for men undergoing this surgery.

**Model structure**—We constructed a Markov model describing the sequence of events and main health states that men might find themselves in after the defined treatment strategies. The cycle length was set at three months, the period over which benefit would occur and short term adverse events resolve. We chose a time horizon of 10 years as this was the period over which the population would be likely to seek active treatment and current technologies would remain relevant.

**Definition of health states**—We defined six health states: treatment, remission, no remission, remission with incontinence, no remission with incontinence, and death. Remission was defined as a more than 10% improvement in the international prostate symptom score. The number of cycles spent by each individual in this state was determined by the probability of relapse after an initially successful treatment derived from long term observation data. Incontinence was the only complication we included in the model and if this occurred no further treatment was possible. If

the state of no remission-no incontinence was entered and further treatments were possible in the defined sequence then transition to the next treatment was allowed.

## Data sources

### Probabilities

**Remission**—We calculated the probability of individual men entering the remission state after treatment as 1–probability of relapse. The probability of failure for subsequent treatments was estimated as if there had been no previous treatment. If an individual treatment was used twice in a strategy then the risk of a second failure was decided by consensus of the clinical expert group.

**Relapse**—We calculated this for each treatment by subtracting the respective initial failure rate derived by meta-analysis from the total retreatment rate documented in studies with long term follow-up. Long term data were available only for transurethral resection and microwave thermotherapy and we therefore derived rates for other treatments from these according to the weighted mean difference in symptom score at 12 months found on meta-analysis. We calculated probabilities of subsequent relapse after initial treatment success for each three month cycle, assuming a constant rate over 10 years.

**Complications**—We estimated probabilities for complications after transurethral resection by summing events across treatment arms of studies carried out in the UK. Probabilities for other treatments were calculated with the relative risk reported in the meta-analysis.

**Mortality**—We applied age specific population mortality rates for English men, irrespective of treatment or treatment sequence in line with previous economic evaluations in this area.<sup>6</sup>

### Costs

We considered only hospital costs because primary care costs would be low and similar for each procedure. Endoscopic procedures (diathermy or laser vaporisation, laser enucleation, and transurethral resection) were assumed to incur the same basic costs. We added appropriate extra costs for equipment, such as optical fibres for laser transmission and tissue morcellators for laser enucleation, using data provided by UK based manufacturers or distributors. The costs of short term complications were calculated by summing costs of extra interventions, such as blood transfusion or bladder neck incision, and extra bed days. The cost of incontinence was derived from the drug tariff for oxybutynin multiplied by the proportion of men (95%) having urge incontinence. For the 5% of men with stress incontinence the cost was that for insertion of an artificial urinary sphincter (£6000).

### Sensitivity analysis

**Probabilistic**—To test for the effect of uncertainty in parameter estimates, we used Monte Carlo simulation to select values for each parameter within the model

according to a distribution around each parameter. These values were then combined in the Markov model to estimate the outcome for each treatment strategy by calculating the expected cost and effectiveness of each treatment sequence as the mean across all samples.

*Deterministic analysis*—We also conducted one way sensitivity analysis to test the effect on outcome of assumptions in the model.

## RESULTS

### Cost effective treatment strategies

The strategy of initial diathermy vaporisation followed by holmium laser enucleation for men whose symptoms fail to improve or relapse after initial benefit was cost effective with a probability of 0.85 at a willingness to pay threshold of £20 000/QALY gained (table, figure). In general, the use of escalating multiple treatment strategies, starting with the option of diathermy vaporisation, showed increased effectiveness and decreased cost. Both diathermy vaporisation followed by holmium laser enucleation and diathermy vaporisation followed by transurethral resection, repeated if necessary, dominated (that is, were more effective and less costly) other strategies, including the reference standard of transurethral resection. The strategy of diathermy vaporisation followed by transurethral resection repeated if necessary became cost effective if the willingness to pay threshold was >£80 000/QALY gained. Diathermy vaporisation as a single treatment was highly likely to be cost effective at a willingness to pay threshold of £5000/QALY gained. Holmium laser enucleation as a single treatment dominated transurethral resection, but the probability of it being the most cost effective strategy never exceeded 0.37. All strategies starting with microwave thermotherapy were dominated, as were those involving potassium titanyl phosphate laser vaporisation.

### Sensitivity analysis

*Model parameters*—Use of a single cohort of 25 000 men generally showed similar incremental cost effectiveness ratios (ICER) for non-dominated strategies,

except for diathermy vaporisation followed by transurethral resection, repeated if necessary. Variation of all other parameters did not alter conclusions.

*Effect of disaggregation*—Most time was spent in remission and this was shortest after either microwave thermotherapy or potassium titanyl phosphate laser vaporisation and longest for sequences starting with diathermy vaporisation.

## DISCUSSION

### Cost effective treatment

Ablation with diathermy vaporisation followed by holmium laser enucleation is cost effective given a willingness to pay threshold of £20 000/QALY gained. This conclusion was unchanged by extensive sensitivity analysis. The model did not show any advantage for strategies involving microwave thermotherapy. Diathermy vaporisation as a single treatment was less effective than transurethral resection. Single treatment with holmium laser enucleation was cost effective only at a threshold of between £7600 and £9500 and might be best used as the final part of a treatment sequence, administered in a few specialist centres for men who relapse after transurethral resection or vaporisation.

The finding that potassium titanyl phosphate laser vaporisation was unlikely to be cost effective, either as a single treatment or within a treatment sequence, is important as the procedure has gained wide popularity around the world because of its perceived ease of use and reduced risk of bleeding and despite lack of evidence of equivalent or improved effectiveness over transurethral resection. Current evidence does not therefore support its unrestricted use in clinical practice.

### Use of strategies

Sequences of escalating treatments were more effective than single treatments. This supports widespread use of a less morbid, technically less demanding, and cheaper option, such as diathermy vaporisation as the initial treatment in various settings, with holmium laser enucleation available in a limited number of

Cost and effectiveness data derived by Monte Carlo simulation with associated probabilities. All other non-reference strategies were dominated

Treatment strategy	Cost (£1000s)	Incremental cost (£1000s)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	Incremental cost effectiveness ratio (£/QALY)	Probability of being cost effective at set willingness to pay threshold*				
						£5000	£10 000	£20 000	£40 000	£80 000
<b>Non-dominated strategies</b>										
Diathermy vaporisation	380 775	0	917 082	0	N/A	0.82	0.03	0	0	0
Holmium laser enucleation	400 550	19 775	919 656	2574	7682	0.14	0.37	0.11	0.01	0
Diathermy vaporisation + holmium enucleation	413 713	13 163	921 041	1385	9505	0	0.57	0.85	0.80	0.49
Diathermy vaporisation + TURP repeated once if necessary	418 264	4551	921 091	50	90 576	0	0.01	0.04	0.19	0.5
<b>Reference strategy</b>										
TURP repeated once if necessary	457 866	39 602	920 340	-751	Dominated	0	0	0	0.01	0.01

QALY=quality adjusted life year; N/A=not applicable; TURP=transurethral resection of prostate.

\*Excludes other strategies dominated at a willingness to pay threshold of £20 000/QALY.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Benign enlargement of the prostate is a common chronic health condition for ageing men, with 25 000 undergoing surgical treatment in England each year at a cost of £53m

Newer surgical techniques such as laser or diathermy vaporisation show similar efficacy to the standard treatment of transurethral resection with reduced morbidity

The trade-off for this benefit is higher retreatment rates, which might incur higher costs

**WHAT THIS STUDY ADDS**

A treatment strategy of initial diathermy vaporisation followed by laser enucleation for those who fail to benefit or subsequently relapse seems cost effective

The currently popular option of potassium titanyl phosphate laser ablation was unlikely to be cost effective in this model

In the absence of strong evidence in favour of newer methods, transurethral resection, repeated if necessary, remains clinically effective and is well established

specialised units to treat the small number of men who fail to benefit or relapse after vaporisation.

**Uncertainties**

Although we have used the best available methods to define the likely outcomes of each treatment, limitations in the current evidence base lead to inevitable uncertainty regarding parameter values. Reassuringly, sensitivity analysis around appropriately selected variables did not radically change key outcomes of the model.

**Strengths of the model**

We have considered a wide variety of treatment sequences of relevance to healthcare consumers and providers in differing healthcare systems. Our model was based on a rigorous systematic review of the international literature. The use of a multiple cohort model allowed consideration of the diseconomies associated with using a costly, capital intensive second or third line treatment by simulating the purchasing of new equipment as required over time.

**Limitations of the model**

We focused on technologies in current wide use or those with an extensive evidence base. Vaporisation techniques with different energy sources were run in the model and the result in terms of cost effectiveness was markedly in favour of diathermy over potassium titanyl phosphate laser treatment. The probability of failure for treatments under study was a key parameter but difficult to quantify with certainty.

Costs were deliberately based on the setting of the NHS in England because this provided the most comprehensive source of data. We did not consider costs associated with staff retraining and service reconfiguration required to change practice away from the standard of transurethral resection, but these are likely to be small if the cost effective strategy of vaporisation followed by holmium resection in the case of failure or relapse is adopted as sufficient capacity already exists. The population studied in the model was sufficiently healthy to undergo any of the procedures. In practice, men with comorbidities resulting in an

excessive risk of bleeding or fluid imbalance tend to be advised against transurethral resection. We focused on surgical treatment and therefore assumed that men entering the model had already tried and failed conservative management in the form of advice on fluid management or drug treatment.

**Conclusion**

Current evidence suggests a sequence of treatments consisting of initial diathermy vaporisation followed by either holmium laser enucleation or transurethral resection, repeated if necessary on failure or relapse, are cost effective strategies for surgical treatment of symptoms presumed to be caused by benign enlargement of the prostate. Single treatment with either diathermy vaporisation or holmium laser enucleation could also be cost effective.

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**Ethical approval:** Not required.

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# Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study

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## ABSTRACT

**Objective** To examine the relation between plasma HIV-1 RNA concentrations in the community and HIV incidence among injecting drug users.

**Design** Prospective cohort study.

**Setting** Inner city community in Vancouver, Canada.

**Participants** Injecting drug users, with and without HIV, followed up every six months between 1 May 1996 and 30 June 2007.

**Main outcome measures** Estimated community plasma HIV-1 RNA in the six months before each HIV negative participant's follow-up visit. Associated HIV incidence.

**Results** Among 622 injecting drug users with HIV, 12 435 measurements of plasma HIV-1 RNA were obtained. Among 1429 injecting drug users without HIV, there were 155 HIV seroconversions, resulting in an incidence density of 2.49 (95% confidence interval 2.09 to 2.88) per 100 person years. In a Cox model that adjusted for unsafe sexual behaviours and sharing used syringes, the estimated community plasma HIV-1 RNA concentration remained independently associated with the time to HIV seroconversion (hazard ratio 3.32 (1.82 to 6.08,  $P < 0.001$ ), per  $\log_{10}$  increase). When the follow-up period was limited to observations after 1 January 1998 (when the median plasma HIV RNA concentration was  $< 20\,000$  copies/ml), the median viral load was no longer statistically associated with HIV incidence (1.70 (0.79 to 3.67,  $P = 0.175$ ), per  $\log_{10}$  increase).

**Conclusions** A longitudinal measure of community plasma HIV-1 RNA concentration was correlated with the community HIV incidence rate and predicted HIV incidence independent of unsafe sexual behaviours and sharing used syringes. If these findings are confirmed, they could help to inform both HIV prevention and treatment interventions.

## INTRODUCTION

As highly active antiretroviral therapy (HAART) is known to reduce a patient's plasma HIV RNA concentration,<sup>1</sup> it has been debated whether antiretroviral therapy can also reduce HIV transmission.<sup>2-5</sup> While several mathematical models have suggested this might be the case, researchers have suggested that the increasing use of HAART might lead to increased HIV risk behaviour, which could overwhelm the possible protective effect of HAART.<sup>2-5</sup> Empirical data are urgently needed to inform this controversy, particularly given the recent

negative results of clinical trials involving leading candidates in the microbicide and vaccine specialties.<sup>6,7</sup>

To date, no study has described the real world relation between community plasma HIV RNA concentrations and HIV incidence. We tested the hypothesis that a longitudinal estimate of community plasma HIV-1 RNA concentration would be associated with an estimate of community HIV incidence independent of HIV risk behaviours.

## DESIGN

Between 1 May 1996 and 30 June 2007, injecting drug users with and without HIV were recruited into a prospective cohort study from the Downtown Eastside neighbourhood of Vancouver, Canada. Those without HIV at baseline made up the Vancouver Injection Drug Users Study (VIDUS), an open prospective cohort of injecting drug users.<sup>8,9</sup> Those with HIV-1 made up another cohort known as the Barriers to Accessing Antiretroviral Therapy (BART).<sup>10,11</sup> At baseline participants gave blood samples for HIV serology and completed a questionnaire and then returned every six months for follow-up evaluation. Outreach methods with snowball sampling techniques<sup>12,13</sup> were used to derive a representative sample. The estimated refusal rate for participation in the study was under 10%.<sup>14</sup>

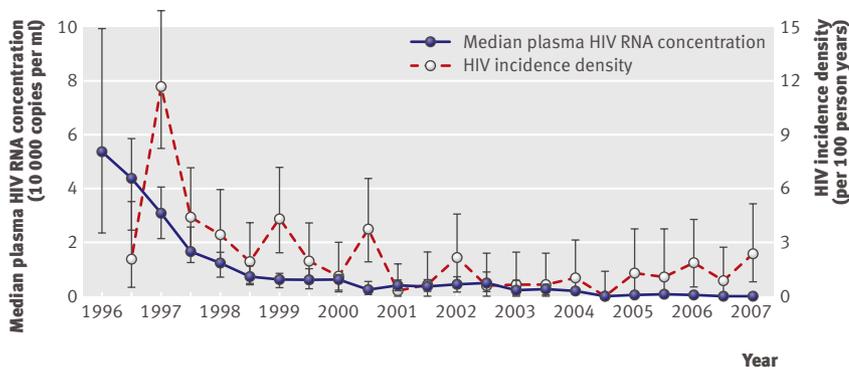
## Community plasma HIV-1 RNA concentrations

We estimated community plasma HIV-1 RNA concentrations every six months and longitudinally using data from BART cohort participants. The local setting has a centralised antiretroviral dispensation programme and HIV/AIDS laboratory, allowing for a complete prospective profile of plasma HIV-1 RNA levels and use of antiretroviral therapy among cohort participants.

We assessed use of antiretrovirals among BART participants during each year of the study and analysed changes during the study period.

## Community HIV-1 incidence

HIV infection was assessed in the VIDUS cohort at each follow-up visit, and the date of HIV seroconversion was estimated with the midpoint between the last negative and the first positive antibody test result.



Estimated community plasma HIV-1 RNA concentrations and HIV incidence density, with 95% confidence intervals, among two parallel cohorts of injecting drug users. HIV incidence first estimated in second half of 1996 as enrolment started in May 1996 and repeat HIV tests to assess incidence were available only after six months of follow-up

### Statistical analyses

We tested for a crude correlation between the twice a year estimates of community plasma HIV-1 RNA and the twice a year estimates of community HIV incidence. We plotted the median plasma HIV RNA concentrations and the incidence density every six months for each year of the study.

We used Cox proportional hazards regression to assess factors associated with the time to HIV infection and examined whether the estimated community plasma HIV-1 RNA concentration in the six months before each participant's follow-up visit was associated with HIV-1 incidence, while adjusting for HIV risk behaviour. To assess for potential confounding, we calculated unadjusted and adjusted hazard ratios of HIV infection per  $\log_{10}$  increase in the estimated community plasma HIV-1 RNA concentration. We adjusted the model for sharing used syringes, unsafe sex (insertive or receptive anal or vaginal intercourse without a condom versus no unsafe sex), ethnicity, cocaine use, heroin use, and unstable housing. All behavioural variables refer to the six months before the latest follow-up interview. We linked participants to the local province-wide antiretroviral dispensation programme to examine patterns of antiretroviral use during the study period.

### Cox proportional hazards regression of time to HIV infection among 1429 HIV negative injecting drug users followed from 1 May 1996 to 30 June 2007

Characteristic	Relative hazard (95% CI)	P value
Plasma HIV RNA (per $\log_{10}$ increase)*	3.32 (1.82 to 6.08)	<0.001
Unsafe sex† (yes v no)‡	1.09 (0.77 to 1.54)	0.619
Used syringe sharing (yes v no)	1.45 (0.99 to 2.12)	0.058
Ethnicity (white v other)	0.65 (0.47 to 0.91)	0.011
Heroin injection ( $\geq$ daily v <daily)‡	1.35 (0.97 to 1.90)	0.079
Cocaine injection ( $\geq$ daily v <daily)‡	2.50 (1.76 to 3.54)	<0.001
Unstable housing (yes v no)§	1.41 (1.00 to 1.98)	0.049

\*Plasma HIV RNA was time updated based on median value in BART cohort during six months before each HIV negative participant's follow-up visits.

†Defined as insertive or receptive vaginal or anal intercourse.

‡All behavioural data time updated based on data from follow-up every six months.

§Living in single room occupancy hotel, shelter, recovery or transition house, jail, on street, or having no fixed address.

## RESULTS

The baseline age was similar between the two cohorts (36.6 v 36.1 years), whereas those with HIV were more likely to be female (250 (40.2%) v 464 (32.5%)) and of non-white ethnicity (270 (43.4%) v 530 (37.1%)).

### Community plasma HIV-1 RNA

During the study period, 622 BART participants underwent plasma HIV-1 RNA assessments. Among the 622 participants, there were 12 435 plasma HIV-1 RNA assessments, with a median of 17 (8-31) measurements per person. The figure shows the estimated median plasma HIV-1 RNA concentrations every six months for 1996-2007.

### HIV-1 incidence

During the study period, 1796 individuals who were HIV negative at baseline were enrolled into the VIDUS cohort. Of these, 367 (20.4%) were lost to follow-up. Among the 1429 individuals included in the HIV incidence analyses the median number of follow-up visits was 8 (3-16). During the study period, there were 155 HIV seroconversions, resulting in an overall incidence density of 2.49 (95% confidence interval 2.09 to 2.88) per 100 person years. The figure also shows the incidence density for every six months for 1996-2007.

### HIV-1 RNA and HIV incidence

When we divided the 11 year study period into 22 six month intervals, the median plasma HIV-1 RNA concentration and the HIV-1 incidence were correlated (Spearman correlation coefficient 0.48;  $P=0.024$ ).

In unadjusted Cox regression analyses, we found that the median estimated community plasma HIV-1 RNA concentration during the six months before each HIV negative participant's follow-up visit was associated with HIV seroconversion (hazard ratio 3.57 (2.03 to 6.27),  $P<0.001$ , per  $\log_{10}$  increase). A multivariate model that adjusted for sharing used syringes, unsafe sex, ethnicity, daily cocaine use, daily heroin use, and unstable housing showed that the median plasma HIV-1 RNA concentration during the six months before each HIV negative participant's follow-up visit remained independently associated with the time to HIV seroconversion (hazard ratio 3.32 (1.82 to 6.08),  $P<0.001$ , per  $\log_{10}$  increase) (table). In a post-hoc analysis, which limited follow-up to the period after 1 January 1998 (when the median plasma HIV RNA concentration was  $<20\,000$  copies/ml), we found that the median viral load was no longer significantly associated with HIV incidence (1.70 (0.79 to 3.67),  $P=0.175$ , per  $\log_{10}$  increase).

We found that the number of individuals who had started antiretroviral therapy increased during the study period from 42.5% in 1996 to 69.6% in 2007 (Mantel test for trend across all 11 years  $P<0.001$ ). Among those receiving antiretroviral drugs, we found that the number using at least three antiretroviral drugs (versus fewer than three drugs) in their antiretroviral

regimen increased during the study period from 8.4% in 1996 to 98.8% in 2007 (Mantel test for trend across all 11 years  $P < 0.001$ ).

## DISCUSSION

In a small urban neighbourhood with high rates of injecting drug use, we found that estimated community plasma HIV-1 RNA concentration predicted estimated community HIV incidence, and that this association was independent of HIV risk behaviours and other potential confounders. Previous studies have suggested that injecting drug users might be less likely to access antiretroviral therapy.<sup>15</sup> If our findings are confirmed, outreach strategies could be used to improve access to HAART among this population. Any benefit of earlier use of HAART, however, must be balanced with antiretroviral toxicities and potential for increased antiretroviral resistance.<sup>16</sup>

### Comparison with other studies

Our study was observational, and the observed declines in HIV incidence in the community might not be causally related to the observed decline in the estimated community plasma viral load. Several lines of evidence, however, suggest a causal link. HAART has been shown to reduce HIV-1 RNA concentrations in blood,<sup>17</sup> the female genital tract,<sup>18</sup> the rectum,<sup>19</sup> and semen,<sup>20</sup> which might make those with HIV less likely to transmit the virus.<sup>4</sup> A study from Uganda, which examined couples serodiscordant for HIV, found no cases of HIV transmission where the index case had an HIV-1 RNA concentration below 1500 copies/ml.<sup>21</sup> We found that the association between plasma viral load and HIV incidence was no longer significant in subanalyses restricted to the period when the median viral load reached  $< 20\,000$  copies/ml. This finding introduces some uncertainty into our overall finding as

it suggests that our results are largely driven by the early years, during which the plasma viral load was high. The relation between viral load and HIV incidence might be less strong when viral load is below a certain threshold.

### Strengths and limitations

Our analyses were limited by the fact that there is a known delay between HIV exposure and seroconversions and we had to estimate an individual's date of HIV seroconversion as the midpoint between the last negative HIV test and the first positive test.<sup>9</sup> As a result, HIV seroconversions might have happened slightly earlier than the year to which they were assigned in our study. It is interesting that the highest rate of HIV seroconversion was observed in the year after the highest community plasma HIV-1 RNA concentration. Antiretroviral resistance is unlikely to explain our findings as increased resistance is associated with use of less potent antiretrovirals and increasing viral load,<sup>22,23</sup> whereas we observed the use of more potent antiretroviral therapy and decreased plasma HIV RNA concentrations. Finally, injecting drug users are a highly marginalised and hidden population, and we do not know with certainty that our cohort is representative of injecting drug users in the community.

### Conclusions and policy implications

Our findings should prompt a re-examination of arguments that dichotomise HIV prevention and HIV treatment, as they might not be independent strategies to reduce the rate of new HIV infections.<sup>5,24</sup> These data should help to inform the debates regarding global increase in use of antiretrovirals, and HIV risk behaviour and new HIV infections, as expanded HAART use in the community was associated with both reduced community plasma HIV RNA concentrations and subsequent HIV incidence.<sup>2-5</sup>

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**Ethical approval:** The research was approved by the University of British Columbia's research ethics board at St Paul's Hospital.

#### WHAT IS ALREADY KNOWN ON THIS TOPIC

Antiretroviral therapy reduces plasma viral load and reduces HIV related mortality

Its potential role in reducing HIV transmission by reducing an individual's infectivity is controversial

Drug misusers with HIV are less likely to access HAART (highly active antiretroviral therapy) than other people with HIV

#### WHAT THIS STUDY ADDS

A longitudinal measure of community plasma HIV-1 RNA correlates with the community HIV incidence rate and predicts HIV incidence independent of unsafe sexual behaviours and sharing syringes

These data should prompt a re-examination of arguments that dichotomise HIV prevention and HIV treatment, which might not be independent strategies for reducing the rate of new HIV infections

Injecting drug users can be successfully attracted to and retained in HAART programmes

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## A room with a view

Like any doctor being admitted to the hospital in which he or she works, I was pleased to have a side room away from the curious eyes of colleagues and friends. Free to sleep in peace, read in peace, and have personal medical discussions in private. But as the weeks passed while I waited for a diagnosis, boredom and loneliness set in—DVD box-sets all watched and attention span for crosswords, Sudoku, solitaire, and books exhausted. Time slowed to a standstill. Having stared at the same four windowless walls for a whole month, I found little new to talk about with visiting friends. Despite excellent medical care and staff who always had time to listen, I couldn't help becoming a short tempered, tearful, impatient patient.

Then I was referred to a tertiary centre for further investigation. My heart sank when I arrived at my bed, in a bay of six, to the sound of a confused elderly woman having a conversation with her "invisible friend." I imagined the inevitable sleepless nights that lay ahead and, had I not been so far from home, would have started planning my escape immediately. That was before the arrival of June, a sprightly 68 year old cancer patient who introduced herself and all the members of "Bay 2" as if they had been lifelong friends. She explained how they were there to talk to if needed, for support or advice. The complex diagnoses and conditions of these patients resembled a PACES exam, yet each one deemed themselves better off than the next and offered their help. Relatives showed concern for other patients, and the breaking of bad news was followed by respectful offers of space or comfort.

At meal times June would make sure the older women were eating their food, or would press her buzzer if they needed help. She would motivate them to sit in their chairs rather than on their beds and congratulate them on their

work with the physiotherapists. She offered comfort to those going for investigations or treatment and would make sure their favourite drink was waiting on return. Ironically, despite being a rock for others, her own health deteriorated. Bad news was broken to her on several occasions, and she exhibited the classic responses of selective hearing and poor information recall.

The illusion of privacy that bedside curtains offer reminded me of a child who covers her eyes and says, "You can't see me." Although you can't see facial expressions, you can hear the words and imagine the tears. I couldn't help overhear June's discussions with the doctors, and after they left I could offer her support as a sounding board, repeating what had been said to her or even answering simple questions. As time passed, I found myself not minding that others could overhear what was said to me, and I rarely drew the curtains.

During my stay I witnessed a degree of camaraderie among the patients that I am convinced improved both their speed of recovery and psychological wellbeing. My views regarding ward layout changed. Although not every ward will have a catalyst—an inspiring motivator like June—communal bays offer more than simple clinical convenience compared with side rooms. As doctors, we may pass in and out of side rooms and bays somewhat oblivious to the interpersonal dynamics that govern psychological wellbeing. The way we treat one patient affects a web of relationships that we ignore to our, and our patients', detriment.

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p i c o

# Prognostic value of N-terminal pro-brain natriuretic peptide in elderly people with acute myocardial infarction: prospective observational study

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**STUDY QUESTION** Does age influence the ability of N-terminal pro-brain natriuretic peptide (NT-proBNP) assay to predict cardiovascular mortality among older people after myocardial infarction?

**SUMMARY ANSWER** In this large contemporary non-selected cohort of patients with myocardial infarction, NT-proBNP concentration had incremental prognostic value even in the oldest patients, above and beyond the GRACE risk score and traditional biomarkers after acute myocardial infarction.

## Participants and setting

Consecutive patients admitted for an acute myocardial infarction to intensive care units, from the RICO survey (a French regional survey for acute myocardial infarction).

## Design, size, and duration

The 3291 participants recruited to this prospective observational study were divided into quarters according to age. We calculated the Global Registry of Acute Coronary Events (GRACE) risk score with admission variables including age, heart rate, serum creatinine, systolic blood pressure, Killip class, cardiac arrest, ST segment deviation, and cardiac markers and determined plasma NT-proBNP concentrations by electrochemiluminescence immunoassay. We used multivariate Cox regression analysis to identify independent predictors of cardiovascular mortality at one year.

## Main results and the role of chance

The mean age of the 3291 participants was 68 (SD 14) years, and 2356 (72%) were men. The median NT-proBNP concentration was 1053 (interquartile range 300-3472) pg/ml. Median values for age quarters 1 to 4 were 367 (119-1050), 696 (201-1950), 1536 (534-4146), and 3774 (1168-9724) pg/ml ( $P < 0.001$ ). Multiple linear

regression analysis determined that NT-proBNP was mainly associated with age, left ventricular ejection fraction, creatinine clearance, female sex, hypertension, diabetes, and anterior wall infarction. At one year's follow-up, 384 (12%) patients had died from all causes and 372 (11%) from cardiovascular causes. In multivariate analysis, NT-proBNP remained strongly associated with cardiovascular death, beyond traditional risk factors including creatinine clearance and left ventricular ejection fraction, in each age group except those aged under 54 years (the small number of deaths ( $n=25$ ) in this age group may have resulted in insufficient statistical power). The addition of NT-proBNP significantly improved the performance of the statistical model in the overall study population ( $-2\log$  likelihood 3179.58 *v* 3099.74,  $P < 0.001$ ) and in each age quarter including the upper one (1523.52 *v* 1495.01,  $P < 0.001$ ). Diagonal stratification using the median value of the GRACE score and NT-proBNP in older patients (upper quarter) identified a high risk group—patients from the higher NT-proBNP group and with a high risk score—characterised by a risk of death of almost 50% at one year.

## Generalisability to other populations

The population of the RICO survey is almost exclusively white, and thus we were unable to investigate the influence of ethnicity on NT-proBNP. Adjustment for these factors would be unlikely to change the main conclusion, but the cut-off points determined may not be applicable in other community cohorts.

## Study funding/potential competing interests

This work was supported by the University Hospital of Dijon and the Association de Cardiologie de Bourgogne and by grants from the Union Régionale des Caisses d'Assurance Maladie de Bourgogne and the Agence Regionale d'Hospitalisation de Bourgogne.

## NT-proBNP AS A PREDICTOR OF ONE YEAR CARDIOVASCULAR MORTALITY BY COX REGRESSION ANALYSIS

Quarter (age)	Cardiovascular death—No (%)	Unadjusted hazard ratio (95% CI)	P value	Adjusted hazard ratio* (95% CI)	P value
Overall	372/3291 (11.3)	2.55 (1.99 to 3.26)	<0.001	2.82 (2.22 to 3.59)	<0.001
Q1	25/822 (3.0)	1.77 (0.61 to 5.13)	0.29	1.45 (0.52 to 3.88)	0.50
Q2	45/823 (5.5)	5.11 (2.42 to 10.81)	<0.001	4.52 (2.05 to 9.98)	<0.001
Q3	103/823 (12.5)	2.53 (1.61 to 3.98)	<0.001	1.92 (1.24 to 2.98)	0.003
Q4	199/823 (24.2)	2.34 (1.66 to 3.29)	<0.001	2.55 (1.79 to 3.64)	<0.001

\*Adjusted for sex, previous myocardial infarction, left ventricular ejection fraction <40%, C reactive protein >3 mg/l, diabetes, peak troponin, and GRACE (Global Registry of Acute Coronary Events) score