

Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts

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Objectives: To evaluate the efficacy and cost effectiveness of self applied podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream, compared to clinic applied 25% podophyllin in the treatment of genital warts over 4 weeks.

Methods: We conducted a randomised controlled trial in 358 immunocompetent men and women with genital warts of 3 months' duration or less.

Results: In the principal analysis both podophyllotoxin solution (OR 2.93, 95% CI 1.56 to 5.50) and podophyllotoxin cream (OR 1.97, 95% CI 1.04 to 3.70) were associated with significantly increased odds of remission of all warts compared to podophyllin. We performed two further analyses. When subjects defaulting from follow up were assumed to have been cured odds of remission of all warts were also significantly increased both for podophyllotoxin solution (OR 3.04, 95% CI 1.68 to 5.49) and for podophyllotoxin cream (OR 2.46, 95% CI 1.38 to 4.40). When subjects defaulting from follow up were assumed not to have been cured odds of remission of all warts were significantly increased for podophyllotoxin solution (OR 1.92, 95% CI 1.13 to 3.27), but not for podophyllotoxin cream (OR 1.17, 95% CI 0.69 to 2.00). Local side effects were seen in 24% of subjects, and recurrence of warts within 12 weeks of study entry in 43% of all initially cleared subjects, without statistically significant differences between the treatment groups. Direct, indirect, and total costs were similar across the three treatment groups. Podophyllotoxin solution was the most cost effective treatment, followed by podophyllotoxin cream, with podophyllin treatment being the least cost effective.

Conclusions: Self treatment of anogenital warts with podophyllotoxin showed greater efficacy and cost effectiveness than clinic based treatment with podophyllin.

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Genital warts are one of the most frequent sexually transmitted diseases worldwide, occurring at incidence rates of 0.6%–1.2% in men and women aged 20–24 years.^{1,2} They represent overt clinical infection with human papillomavirus (HPV) 6 or HPV 11.³ A wide variety of treatments are in use, but failure of treatment and recurrence after initial clearance are seen with all treatments.⁴ The economic burden of the management of genital warts is substantial. In the United States there are estimated to be 500 000–1 million new cases annually with health costs exceeding \$3.8 billion.⁵

The use of podophyllin resin, an extract of the root of *Podophyllum* sp, in alcoholic solution was first described as an effective therapy for genital warts in 1942.⁶ Podophyllin resin contains numerous compounds, but podophyllotoxin has been shown to be the principal active therapeutic component.⁷ Podophyllotoxin offers a number of advantages over podophyllin in treatment of genital warts including purity, stability, and lack of systemic toxicity.^{8,9} Podophyllotoxin was initially formulated as a solution and regimes for self treatment were developed.¹⁰ While this preparation is eminently suitable as a treatment for penile warts such a liquid formulation is less practicable for self treatment of vulval and introital warts in women and for anal warts in either sex. Formulations of podophyllotoxin in cream and gel bases were therefore developed to facilitate self treatment at any anogenital site.^{11–13} A number of trials have also suggested superior efficacy of podophyllotoxin formulations compared to podophyllin, although these trials recruited modest numbers of subjects and not all of the differential treatment outcomes in these trials reached statistical significance.^{14–17} We therefore de-

signed a larger study to compare the efficacy, tolerability, and also the cost effectiveness of self treatment with podophyllotoxin solution 0.5% (Warticon or Wartec7 solution), and with podophyllotoxin cream 0.15% (Warticon or Wartec7 cream), compared to clinic based treatment with podophyllin 25% in the treatment of anogenital warts.

METHODS

Patients

This was an open, randomised, controlled multicentre trial carried out in 11 sexually transmitted disease clinics in the United Kingdom. Inclusion criteria included age 18–65 years and current anogenital warts with a history of 3 months or less and no therapy in that time. Exclusion criteria included known HIV infection or immunosuppression, homosexual men with perianal warts, total lesional area >400 mm², any individual lesion with an area of >100 mm² intrameatal or vaginal warts, ulcerative or inflammatory STDs of the anogenital region, and pregnancy.

The three treatment arms were podophyllotoxin cream 0.15% and podophyllotoxin solution 0.5%, both self applied twice a day for 3 consecutive days with 4 days off therapy, and podophyllin 25% in tincture of compound benzoin applied twice weekly in the clinic. Randomisation to treatment was stratified according to sex, and ≥10 warts or <10 warts using treatment assignment envelopes for each stratum. All therapies were given for 4 weeks, or until clearance if this was earlier. Subjects were evaluated weekly for 4 weeks, and then at 12 weeks after trial entry if complete remission was obtained in the first 4 weeks. Local ethical approval for the

Table 1 Baseline characteristics (figures given are numbers (%))

	Podophyllin (n=116)	Podophyllotoxin cream (n=118)	Podophyllotoxin solution (n=120)	Total (n=354)	p Value
Male	60 (52)	60 (51)	62 (52)	182 (51)	0.9
<10 warts	82 (71)	84 (71)	79 (66)	245 (69)	0.6
White	110 (95)	111 (94)	114 (95)	335 (95)	0.9
Smoker	61 (53)	70 (59)	67 (56)	198 (56)	0.6
Circumcised	3 (3)	1 (1)	9 (8)	13 (4)	0.02

trial was obtained from all participating institutions. Informed consent for the trial was obtained from all patients.

The sample size for the study was based on assumptions regarding complete remission rates of original warts for different treatment groups. Using a two sided χ^2 test without continuity correction at $\alpha = 5\%$ and power = 80%, and assuming the group with the highest efficacy = 80% and the minimum difference that was clinically important to detect was 20%, then 83 patients analysable for efficacy were required per group—that is, 249 in total.

Data

At each study evaluation the number and location of warts were recorded and classified as those present at the study entry (original warts), or those newly occurring during the trial. Adverse events, either self reported or detected on examination, were recorded at each visit. A nurse together with the patient collected data, including information about the use of resources, at each visit.

Analyses

The primary outcome measure of the study was the complete remission of all anogenital warts present at study entry (original warts) after 4 weeks treatment. We investigated the effect of treatment on both original warts and the total number of warts, which included those newly occurring during the 4 weeks of the study (all warts). The percentage of patients with total clearance of all/original warts and the relative reduction in the number of all/original warts were considered. The effect of treatment on clearance of all/original warts was further analysed using logistic regression models, adjusting for the effects of sex, smoking status, and the number of warts at entry (<10 or ≥ 10 warts). The analyses presented are for the odds of having complete remission with podophyllotoxin treatment, compared to podophyllin.

The principal (or per protocol) analysis was of the population of subjects who either had a complete remission, or had documentation of four treatment cycles. We also performed further analyses with two different assumptions regarding the status of cure for subjects who defaulted or were lost to follow up—that is, by setting the missing values to be the number of warts at the last visit (this assumes everybody who defaulted was not cured—“worst case” scenario), or by setting the missing values to zero (this assumes everybody who defaulted was cured—“best case” scenario).

The economic analysis was performed from a general societal point of view. Owing to the short study duration discounting was not performed. We obtained information regarding provider remuneration of costs for outpatient visits from six of the units participating in this study and averaged these. Direct costs consisted of outpatient visits at clinics for which we attribute differing costs for an initial or a follow up visit, drug treatment and travelling costs for the patients. Costs for treatment of adverse events were included for patients who discontinued from the trial because of adverse reactions. Indirect costs related to production losses when patients were absent from work due to treatment of warts were calculated separately. These costs were estimated accord-

ing to average incomes for men and women employees in the United Kingdom in 1998 and were analysed separately.¹⁸

Assumptions for the economic analysis

For patients who had a relapse of warts within 12 weeks, and for those patients who discontinued from study because of adverse events or lack of effect, the same direct and indirect costs as the average cost for all three treatments have been assumed and added to the actual costs calculated for each of these patients. For patients who discontinued for other reasons than adverse events or lack of effect, and who did not subsequently reattend, an assumption has been made that the remission and relapse rates for such patients falling outside the principal analysis population was the same as for patients evaluated in the principal analysis population.

RESULTS

We originally planned a study size of 300 and assumed that 20% of subjects would not provide analysable end point data, and therefore asked six centres to enrol 50 patients each. However, one centre never commenced enrolment, and a higher non-analysability rate of 30% was observed in the first 150 patients. We therefore expanded the study size to 350 and added a further six centres, each to recruit 25 patients. A total of 354 patients were entered according to study criteria and received treatment; 120 patients were randomised to podophyllotoxin solution, 118 to podophyllotoxin cream, and 116 to podophyllin. The study population comprised 182 (51%) men, 95% were white, 56% were smokers, 69% had less than 10 genital warts, and 96% of males were uncircumcised. The characteristics of the subjects in the three treatment arms were well matched at entry (table 1), except that there were slightly more circumcised men in the podophyllotoxin solution arm (9, compared to podophyllin 3, podophyllotoxin cream 1, $p=0.02$). 276 (78%) of patients completed the trial according to the protocol, the principal analysis populations being 96, 82, and 98 subjects in each of the podophyllotoxin solution, podophyllotoxin cream and podophyllin arms respectively. The only significant difference between the principal analysis population and defaulters was that smokers were over-represented in the latter group (52% v 70% respectively, $p=0.004$).

Tables 2 and 3 present both the raw complete remission rates and odds of achieving remission, by treatment group and population (the principal analysis, worst case, and best case populations), for original warts and all warts respectively. Treatment was associated with the odds of remission, with increased odds for both podophyllotoxin solution (for original warts OR 2.88, 95% CI 1.52 to 5.45; for all warts OR 2.93, 95% CI 1.56 to 5.50) and for podophyllotoxin cream (for original warts OR 1.67, 95% CI 0.89 to 3.15; for all warts OR 1.97, 95% CI 1.04 to 3.70) compared to podophyllin. In the analysis where subjects defaulting from follow up were assumed to have been cured we again observed increased odds both for podophyllotoxin solution (for original warts OR 2.91, 95% CI 1.59 to 5.34; for all warts OR 3.04, 95% CI 1.68 to 5.49) and for podophyllotoxin cream (for original warts OR 2.14, 95% CI 1.19 to 3.82; for all warts OR 2.46, 95% CI 1.38 to 4.40)

Table 2 Complete remission of original warts

Population*	Podophyllin % (95% CI)	Podophyllotoxin cream % (95% CI)	Podophyllotoxin solution % (95% CI)
(A) Expressed as % of subjects			
Principal analysis	53.1 (42.7 to 63.2)	64.6 (53.3 to 74.9)	75.0 (65.1 to 83.3)
"Worst case"	44.8 (35.6 to 54.3)	44.9 (35.7 to 54.3)	60.0 (50.7 to 68.8)
"Best case"	60.3 (50.8 to 69.3)	75.4 (66.6 to 82.9)	80.0 (71.7 to 86.7)
Population*	Podophyllotoxin cream Odds (95% CI)	Podophyllotoxin solution Odds (95% CI)	
(B) Expressed as odds of remitting compared to podophyllin (=1) by regression analyses†			
Principal analysis	1.67 (0.89 to 3.15)	2.88 (1.52 to 5.45)	
"Worst case"	1.01 (0.59 to 1.96)	1.96 (1.15 to 3.33)	
"Best case"	2.14 (1.19 to 3.82)	2.91 (1.59 to 5.34)	

*See Methods, analysis for definitions of the populations.

†In regression analyses smoking was not significantly associated with remission, whereas females and having >10 warts at baseline had significantly increased odds of not remitting.

Table 3 Complete remission of all warts

Population*	Podophyllin % (95% CI)	Podophyllotoxin cream % (95% CI)	Podophyllotoxin solution % (95% CI)
(A) Expressed as % of subjects			
Principal analysis	46.9 (36.8 to 57.3)	62.2 (50.8 to 72.7)	70.2 (59.9 to 79.2)
"Worst case"	39.7 (30.7 to 49.2)	43.2 (34.1 to 52.7)	54.2 (44.8 to 63.3)
"Best case"	55.2 (45.7 to 64.4)	73.7 (64.8 to 81.4)	76.6 (68.1 to 83.9)
Population*	Podophyllotoxin cream Odds (95% CI)	Podophyllotoxin solution Odds (95% CI)	
(B) Expressed as odds of not remitting compared to podophyllin (=1) by regression analyses			
Principal analysis	1.97 (1.04 to 3.70)	2.93 (1.56 to 5.50)	
"Worst case"	1.17 (0.69 to 2.00)	1.92 (1.13 to 3.27)	
"Best case"	2.46 (1.38 to 4.40)	3.04 (1.68 to 5.49)	

*See Methods, analysis for definitions of the populations.

compared to podophyllin. These differences therefore reached statistical significance in all analyses for podophyllotoxin solution, but only reached statistical significance for podophyllotoxin cream in the best case analysis where defaulters were assumed to be cured, and in the principal analysis for all warts. In all analyses, males and those with fewer than 10 warts at baseline had significantly increased odds of remitting. Smoking was not associated with the odds of remission, except when considering all warts in the best case analysis when smokers had significantly increased odds of remission. As smokers were significantly over-represented among subjects who defaulted we do not assume this to be of relevance.

We measured the relative reduction in the number of original warts and all warts over the 4 week treatment period for

the three treatment groups. For original warts podophyllotoxin solution (90.0%, 95% CI 85.3 to 94.6) was significantly superior to podophyllin (76.2%, 95% CI 67.4 to 85.1) and podophyllotoxin cream (75.4%, 95% CI 66.5 to 84.3), whereas for all warts podophyllotoxin solution (83.7%, 95% CI 77.0 to 90.4) was only significantly better than podophyllin (62.2%, 95% CI 46.6 to 77.7) (podophyllotoxin cream 64.1%, 95% CI 48.1 to 80.2).

Local side effects were seen in 33%, 24%, and 17% of the podophyllotoxin solution, cream, and podophyllin groups and ulceration in 18%, 12%, and 10%, respectively. Forty five per cent of subjects who were clear of warts at 4 weeks returned for a 12 week follow up or earlier in case of relapse. Relapse rates of 15/33 (45%) in the podophyllotoxin solution group, 12/22 (55%) in the podophyllotoxin cream group, and 5/19

Table 4 Total average direct and indirect costs per patient, in £, 1998 prices

	Podophyllin	Podophyllotoxin cream	Podophyllotoxin solution
Direct costs			
Outpatient visits	172.82	118.44	120.20
Transportation	17.61	13.46	10.75
Drugs	2.44	18.26	15.47
Adverse event increment	1.41	10.63	12.81
Relapse increment	14.47	43.05	29.77
Total direct costs	208.75	203.84	189.00
Indirect costs			
Absence from work	299.15	276.26	254.18
Adverse event increment	2.45	18.44	22.23
Relapse increment	25.12	74.68	51.66
Total indirect costs	326.72	369.38	328.07
Total costs	535.47	573.22	517.07

Table 5 Cost effectiveness of the treatment alternatives (average cost effectiveness rates) for complete remission (CR) with 95% confidence intervals (CIs) for all warts, principal analysis population, in £, 1998 prices

	Podophyllin	Podophyllotoxin cream	Podophyllotoxin solution
Complete remission rates	46.9%	62.2%	70.2%
CIs for CRs	36.8 to 57.3	50.8 to 72.7	59.9 to 79.2
Total average direct costs per patient	208.75	203.84	189.00
Direct costs/CR	445.10	327.72	269.23
CIs for direct costs/CR	364.31 to 567.26	280.39 to 401.26	238.64 to 315.52
Total average direct and indirect costs per patient	535.47	573.22	517.07
Total costs/CR	1141.72	921.58	736.57
CIs for total costs/CR	934.50 to 1455.07	788.48 to 1128.39	652.87 to 863.23

(26%) in the podophyllin group were observed. These differences were not statistically significant. We suggest these figures should be regarded as merely descriptive because of (a) the high proportion of defaulters in each group, and (b) the selection bias for re-attendance if further warts occurred.

Economic results

We obtained information regarding provider remuneration of costs for outpatient visits from six of the units participating in this study. We found that in 1998 the national average for an initial visit was around £70, with a range of costs from £110 to £41. The data showed that a follow up visit cost one third less than an initial visit. Table 4 shows the average direct, indirect, and total costs which were of a similar order across the three treatment groups. The average cost effectiveness of the treatment alternatives in terms of the costs per complete remission for the principal analysis population is shown in table 5. The results from this analysis show a hierarchy of cost effectiveness. Podophyllotoxin solution emerges as the most cost effective treatment, followed by podophyllotoxin cream, with podophyllin treatment being the least cost effective.

DISCUSSION

This is one of the largest randomised trials of treatments for genital warts yet reported. Its size, design, and multicentre nature make it likely that the results are a reasonable reflection of treatment outcomes for first episode genital warts in clinical practice. The patient population was mainly heterosexual, 96% of males were uncircumcised as is usual in the United Kingdom, and the majority of lesions in these men were subpreputial or on the distal penis. The three treatment arms were well matched at entry with no significant differences of relevance.

Although podophyllotoxin solution and gel are generally available at 0.5% strength, evaluations of podophyllotoxin cream have reported the use of 0.5%, 0.3%, and 0.15% strengths.^{11 12 17} Podophyllotoxin 0.3% cream appeared to be associated with a higher frequency of adverse events than 0.15% cream, and it was this latter licensed preparation that we studied.¹² Our data can be compared with other published comparative trials of podophyllin and podophyllotoxin solution and cream.^{11 12 14-17} We found generally similar clearance rates and differences in response rates between the different treatments to the published literature, although the numbers of subjects we studied was larger than those previously reported.

Patients with genital warts in clinical trials not infrequently default from follow up, which previous reports have observed.^{12 14} We explored ways of utilising the data set in a manner where differing assumptions could be made about these "missing values." Sexually transmitted infections in general, and genital warts in particular, have been shown to be

associated with psychological morbidity and concepts of shame.¹⁹ The clinicians who conducted the study were therefore of the opinion that defaulters were more likely to be cured than have persisting disease. The best case analysis therefore has substantial justification, and approaches the real life situation. We also present the response rates for the podophyllotoxin preparations in a novel manner as odds ratios by multivariate regression compared to the efficacy of podophyllin. This illustrates these comparisons (for example, for all warts in the best case analysis) in quite a striking manner, with podophyllotoxin solution and cream being 3.0 and 2.5 times more likely to produce cure than podophyllin. Podophyllotoxin solution was usually associated with numerically better cure rates than podophyllotoxin cream although in none of the regression analyses did this reach significance. Considering that we were comparing a 0.5% podophyllotoxin formulation with a 0.15% formulation the degree of similarity in treatment effects is of note. Although podophyllotoxin solution emerged as significantly superior to podophyllin in all regression analyses, podophyllotoxin cream was only statistically significantly better than podophyllin in the principal analysis for all warts and the best case analysis. Even larger trials than ours would be needed to settle this latter issue definitively. The data with regard to treatment side effects are suggestive of a correlation between side effects and efficacy, as has been observed previously, although the rates of side effects we observed were not statistically different between treatments.¹⁶ Side effects were not a limiting factor for treatments within the trial. Recurrence rates after individual treatments are crucial to overall clinical efficacy in real life. Our ability to reach conclusions about differences in recurrence rates was limited by the rate of patient default we observed at the 12 week visit, and we do not ascribe any significance to these data.

The economic evaluation was also complicated by the frequency of discontinuations during treatment and the reduced proportion of previously cleared patients who returned for the last follow up visit. Health economic analyses sometimes use disease free or healthy days as an effectiveness measure.²⁰ In such studies of genital wart therapy it is not possible to obtain data for disease free days in all patients, and we therefore chose to use complete remission of all warts as the most appropriate effectiveness measure. Arguments can be made concerning the relevance of including indirect costs in such evaluations.^{21 22} In this study the final results regarding which treatments were more cost effective do not differ whether indirect costs are included or not.

In economic evaluations both average costs, effects, and cost effectiveness should be demonstrated, as well as the marginal rates—that is, the additional cost per additional unit of the effect expressed as the marginal cost effectiveness rate. In the main economic analysis the total costs were lower for one of the evaluated drugs (podophyllotoxin solution) compared

with the comparator drug (podophyllin solution) while its treatment effects were superior. It is therefore not necessary nor meaningful to estimate the marginal cost effectiveness rates for podophyllotoxin solution because it is clear that this alternative is more favourable. For podophyllotoxin cream the marginal cost in the main analysis was higher (£37.75) (table 4), but with a better clinical effect expressed as complete remission rate (62.2% compared with 46.9%) (table 5) resulting in a marginal cost effectiveness rate of £246.73 per further cured patient. Podophyllotoxin cream is therefore a cost effective alternative compared with podophyllin solution since the cost of curing one further patient with podophyllotoxin cream is considerably lower than the average cost of curing one patient with podophyllin. In these analyses we have also used the confidence intervals for the complete remission rates associated with the three treatment alternatives as a form of sensitivity analysis. Although economic analyses are not usually evaluated with formal tests of statistical significance, there appears to be a hierarchy of total costs per complete remission with podophyllotoxin solution as the most cost effective and podophyllin as the least cost effective. It is believed that clinicians and patients arrive at choices between podophyllotoxin solution and cream on the grounds that podophyllotoxin cream is a more acceptable treatment for patients with "non-penile anogenital warts." Although it seems common sense that the superior ease of application of cream in less accessible anogenital sites would result in superior acceptability and perhaps effectiveness this has not been formally demonstrated. In the light of this assumption we suggest that the strategy of using podophyllotoxin solution for penile warts and podophyllotoxin cream for other anogenital warts is a cost effective one.

A few previous economic analyses of genital wart therapy have been published.²³⁻²⁵ As in our work, these studies illustrated that one of the central determinants of overall costs is the frequency of clinic visits, and this is inherently reduced with patient applied therapy. An economic evaluation should preferably reflect real clinical practice and it is therefore necessary to identify resource use for the purposes of the trial itself.²⁶ In our trial the patients using podophyllotoxin were asked to attend every week. Assuming only two visits, one at the start of treatment and one after 4 weeks, as in normal clinical practice, would reduce total average costs for patients treated with podophyllotoxin solution and cream by 24% and 22%, respectively.

Although self treatment regimens were developed and analysed some years ago,¹⁰ it is only recently that such therapies have become widely available. Podophyllotoxin is now marketed as a solution in many countries worldwide, and also as a cream formulation in Europe. In North America podophyllotoxin is also available in a 0.5% gel formulation, but the only published evaluation of this preparation in adults with genital warts suggested lower clearance rates that we observed for podophyllotoxin solution and cream.¹³ The primary clearance rates for podophyllotoxin observed in our study of ~70% in both sexes compare well with other treatments.⁴ Both US and UK national guidelines for the treatment of genital warts continue to recommend the use of podophyllin.^{27,28} Our demonstration that treatment of anogenital warts with podophyllotoxin solution and cream shows greater efficacy and cost effectiveness than clinic based treatment with podophyllin, as well the recognised pharmacological deficiencies of podophyllin, suggest that these guidelines may need further modification in due course.^{8,9} However, in clinical practice one of the foremost problems remains recurrence after therapy. Our study observed substantial recurrence rates similar to previous studies of podophyllin and podophyllotoxin, but also illustrates how recurrence after therapy diminishes cost effectiveness. Therefore, treatments, either single or combination, are needed which combine high rates of primary clearance with low recurrence rates. Recently interest

has focused on immunological mechanisms of regression and it is possible that therapies associated with lower recurrence rates may be invoking such cytotoxic immune responses.²⁹ If new treatments satisfying these clinical imperatives are developed they should be evaluated to address the issues of cost effectiveness that we have outlined.

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Competing interests: CL has acted as a consultant to 3M Pharmaceuticals, GlaxoSmithKline, Merck and Xenova. RM has acted as an adviser to Perstorp Pharma, 3M Pharmaceuticals and Stiefel. None of the other authors are consultants for Stiefel, and have no financial interests in Stiefel or podophyllotoxin.

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CONTRIBUTORS

CL was the PI for the study and lead author for the paper; CL, RM, GK, PF, SB, IB, and GRT contributed to the design of the study; RG performed all the statistical analyses; GRT performed all the economic analyses; CL, RM, GK, PF, SB, and IB supervised the conduct of clinical trial; and all authors contributed to the write up.



There are appendices to this paper on the STI website (www.stijournal.com/supplemental).

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ECHO

Pericardial effusion easily misdiagnosed in HIV positive patients with lymphodystrophy



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HIV positive patients, suspected of having pericardial effusion, should undergo further investigation to avoid potentially fatal consequences, warn German researchers. The researchers draw attention to the case of a 52 year old HIV positive man (stage C3), who was being treated with a combination of nelfinavir, nevirapine, and stavudine. He had no history of heart disease, but was admitted because of breathing difficulties on exertion. On admission, his CD4 count was 81 cells/mm³ and his viral load was < 50 copies/ml. But he had evidence of lymphodystrophy syndrome, including reduced subcutaneous fat, increased fatty tissue around the intestine, and increased serum lipid concentrations.

An echocardiogram 10 months previously had indicated diastolic dysfunction and a 4 mm wide epicardial space, which a second echocardiogram showed, had increased to 18 mm, but there were minimal changes to ventricular function.

Because fatty tissue deposits around the heart and pericardial effusion are difficult to distinguish on echocardiography, magnetic resonance imaging was also carried out—computer tomography may be used instead. This clearly showed pericardial fat, but no fat deposits in the myocardium.

A puncture of the epicardial adipose tissue, on the assumption that it is pericardial effusion, risks perforating the ventricles, with potentially fatal consequences, say the authors. Although much more expensive, additional resonance imaging or computer tomography could save lives, they conclude.

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