# COMMENTARY

## Surrogacy in HIV-1 clinical trials

*See page 543*

In today's *Lancet* William Cameron and colleagues report that in advanced HIV disease the addition of a potent anti-HIV-1 drug (the protease inhibitor ritonavir) to established dual-nucleoside therapy reduced the risk of death or progression of AIDS by 47% at a median follow-up of 28·9 weeks, compared with deferring the ritonavir for 16 weeks or more. Even at 1 year the difference in mortality was significant—16% *vs* 23%.

In a subset of patients plasma HIV-1 RNA was measured, and for those on ritonavir there was a mean fall of 1·3 $\log_{10}$ copies, together with modest increases in CD4 and CD8 lymphocyte numbers. These values started to return to baseline after a few weeks and were within 0·6 $\log_{10}$ copies of baseline by 4 months. Is the striking clinical effect surprising, in view of the moderate and poorly sustained suppression of plasma HIV-1 RNA ?

The trial was designed to simulate clinical practice. Subsequent work has shown that, for the regimens tested, the rapid return of the markers of infection towards baseline could be a consequence of ritonavir resistance. In patients with advanced HIV-1 infection dual-nucleoside combinations will not suppress viral replication sufficiently to prevent the development of resistant HIV-1 mutations and are deemed to be suboptimum therapy. The addition of ritonavir to such a regimen might not be contemplated today because it would be considered equivalent to giving monotherapy, with the risk of development of ritonavir resistance and potential cross-resistance to other protease inhibitors.

Nevertheless, surrogate markers are much used as endpoints in clinical trials of HIV-1 infection. How should changes in plasma HIV-1 RNA and CD4 counts be interpreted in these trials? Are surrogate markers acceptable replacements for clinical endpoints, to reduce the cost and duration of phase III clinical trials? Are the present surrogates good enough?

Baseline pretreatment plasma HIV-1 RNA load is a strong predictor of progression of HIV-1 disease,[1–3] and currently the goal of therapy is to reduce the HIV-1 RNA load to below the limit of detectability. There seems to be a linear relation between the reduction in viral load and short-term clinical benefits. The lowest viral load achieved seems to predict the duration of viral suppression,[4] and the time to "virological response" (when HIV-1 RNA becomes undetectable) is related to baseline value of HIV-1 RNA, type of treatment, and sensitivity of the HIV-1 RNA assay.

CD4 counts and plasma HIV-1 RNA are used as markers of biological activity in phase I/II trials. Favourable responses—ie, decline in plasma HIV-1 RNA and rises in CD4 counts—have led to accelerated licensing for many antiretroviral agents, on grounds of the impracticability of waiting years for large clinical-endpoint trials to be completed before drugs are approved. From experience in advanced treatment-naive patients, the antiretroviral activity profile can be established from 24-week data and the durability of the response can be examined at 48 weeks. Most clinicians would accept this licensing policy as reasonable and humanitarian, but it is important to realise that the approval for these drugs is based on their short-term biological activity and safety profile.

Clinical efficacy cannot be extrapolated from surrogacy data unless the surrogate fits two criteria. First, the surrogate must be a correlate of the true clinical outcome and, second, and more importantly, it must capture the net effect of treatment on clinical outcome—ie, the effect aggregated over all mechanisms of action of the treatment on the clinical endpoint.[5] Most drugs operate through several mechanisms, which need to be understood so that surrogate markers can be interpreted reliably.[6]

Surrogate markers must be robust enough for the estimation of a clinical effect that occurs much later than the short-term changes seen with switching or discontinuation of treatment,[7] and they must predict outcome whatever the past exposure to therapy, or stage of disease. Accumulating evidence suggests that HIV-1 RNA or a combination of this and the CD4 count[8] might account for a substantial part of the treatment benefit obtained with antiretroviral therapy, but this view is based on short-term data only.[8,9] In the MRC Delta Trial, although suppression of plasma HIV-1 RNA was highly predictive of clinical progression and overall survival, it consistently overestimated the expected clinical benefit from combination therapy. Furthermore, the proportion of treatment effect predicted by changes in plasma HIV-1 RNA differed between the two combination arms.[10] With more potent regimens of newer classes of drugs the relevance of these analyses of the Delta Trial might be questioned. Methods for validating surrogate endpoints need to be applied across populations and across studies before the markers can be used with confidence.

Two recent trials with similar designs show how effectively identical protease-containing combination therapy lowers HIV-1 RNA viral load. In one (ACTG 320)[11] clinical endpoints were measured, and there was a 50% reduction in deaths or progression to AIDS or both over a median follow-up of 38 weeks. In the other, much smaller, study[12] clinical endpoints were not reported because they were not part of the design of the study, but the researchers implied that the reduction in viral RNA in

90% of patients at 24 weeks will translate into clinical benefit. This assumption is reasonable because the trial design and drug combinations were similar to those in the clinical-endpoints study. However, the same assumptions of clinical efficacy equivalence cannot be made when two different drugs are compared, even if they are of the same class (eg, two different protease inhibitors) and have similar biological effects on surrogate markers in phase I/II trials and similar tolerability profiles. Two drugs of the same class might not have the same long-term clinical efficacy because drugs can work through causal pathways of the disease process that are not mediated by the surrogate endpoint and may have unintended mechanisms of action that are independent of the disease process.[5] The true clinical outcome would then be inconsistent with that expected solely from evaluation of surrogate endpoints. One sobering example is the use of antiarrhythmic drugs to prevent ventricular arrhythmia after myocardial infarction. Instead of the expected reduction in mortality, death rates were increased.[13]

The follow-up periods in the clinical and virological endpoint studies that have formed the basis for combination regimens intended to keep viral replication persistently below detectable levels fall short of the 10 years for which patients have been observed in natural-history studies of HIV-1 infection. So many unknowns remain, including when to start therapy and how long any benefit will last. Disorders thought to be long-term adverse effects of these drugs are beginning to be reported: diabetes, lipodystrophy, and haemolytic uraemic syndrome are but a few.

However, the gathering of clinical endpoints for all new drugs and drug combinations is impracticable. Thus, when is the use of surrogate markers in clinical trials in HIV-1 justified?

Surrogate endpoints should be used in screening for promising new therapies and for evaluation of biological activity in phase I/II trials. Results of these trials will inform discussion about whether the treatment should be used in large-scale or long-term clinical trials. Clinical efficacy can be claimed only when the regimen has been evaluated with clinical endpoints. One suggestion is that only drug regimens that are expected to suppress HIV-1 replication to undetectable levels should be studied in phase III clinical trials[14] or adopted in clinical practice, and that the use of any form of suboptimum therapy is unacceptable in all phases of drug development. However, the Cameron trial has shown that clinical benefit can be obtained in advanced disease despite the poor virological results. It is also argued that when optimum viral suppression is not achieved in a patient in a phase III trial, alternative therapy should be offered. Such a practice would make it difficult to do clinical-endpoint trials that might identify clear treatment effects in patients whose virological response is poor. Nevertheless, the need for long-term clinical efficacy and safety data and treatment-strategy studies must be recognised, especially since more and more patients who have taken sequential combinations of therapy are showing poor virological responses.

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## Cardiac troponins: IT upgrade for the heart

The outlook for patients who present with an acute coronary syndrome (unstable angina or acute myocardial infarction) is widely variable, but the degree of myocardial cell necrosis determines risk of death or (re)infarction, or need for revascularisation, in the short to medium term. The provision of individualised treatment to such a heterogeneous population requires sensitive diagnostic and prognostic information at the time when important clinical decisions are being made. The electrocardiogram and conventional serum markers of myocardial damage (eg, creatine kinase-MB [CK-MB]) are useful but imperfect tools for making an early diagnosis and for identifying high-risk patients who merit further investigation, including coronary angiography. For instance, in 50% of patients with acute myocardial infarction the electrocardiogram recorded on admission is not diagnostic, and, among those who present with unstable angina or non-Q-wave myocardial infarction, minor increases in CK-MB are of limited value in identifying the subset of patients (10–20%) who experience serious cardiac events (death or non-fatal acute myocardial infarction) within 6 months of diagnosis.[1]

As cardiac myocytes become necrotic, intracellular proteins (table) leak into the interstitial space and enter the systemic circulation via local microvascular and lymphatic drainage. The concentration-time profile for these markers in peripheral blood depends on their

| Marker* | Times to initial increase (range) | Time to peak† (mean) | Time to return to normal range | Typical sampling schedule after onset of chest pain |
|---|---|---|---|---|
| Myoglobin (17·8) | 1–4 h | 6–7 h | 24 h | Frequent; 1–2 hourly |
| MLC (19·27) | 6–12 h | 2–4 days | 6–12 days | Once >12 h |
| cTN-I (23·5) | 3–12 h | 24 h | 5–10 days | Once >12 h |
| cTN-T (37) | 3–12 h | 12 h–2 days | 5–14 days | Once >12 h |
| CK-MB (86) | 3–12 h | 24 h | 48–72 h | 12 hourly×3 |
| Enolase (90) | 6–10 h | 24 h | 48 h | 12 hourly×3 |
| LDH (135) | 10 h | 24–48 h | 10–14 h | Once >24 h |
| MCH (400) | 48 h | 5–6 days | 14 days | Once >2 days |

*Molecular weight in kDa given in parentheses. MLC=myosin light chain; cTn-I=cardiac troponin I; cTN-T=cardiac troponin T; CK-MB= creatine kinase MB isoenzyme; LDH=lactate dehydrogenase; MHC=myosin heavy chain; †In absence of thrombolytic therapy.

molecular weight, where they are located within the cell and their release characteristics, and their rates of vascular or lymphatic drainage and systemic clearance. Small cytosolic proteins such as myoglobin are detectable within 1–2 h after tissue injury, whereas large enzymes such as lactate dehydrogenase diffuse much more slowly. The troponin (Tn) complex (subunits I, T, and C) on the actin filament regulates the force and velocity of muscle contraction. Troponin-T (Tn-T) anchors the Tn complex to tropomyosin; troponin-C (Tn-C) binds calcium ions and initiates the contractile response; and troponin-I (Tn-I) inhibits actin-myosin cross-linking. Because separate genes code for the cardiac and skeletal muscle forms of Tn-T and Tn-I, cardiac Tn-T (cTn-T, 37 kDa) and cardiac Tn-I (cTn-I, 23·5 kDa) have unique aminoacid sequences that bind to specific monoclonal antibodies. cTn-T and cTn-I are highly sensitive and specific markers of myocardial necrosis in patients with acute myocardial infarction.[2] Like CK-MB they are detectable within 3–12 h of onset of symptoms but troponin concentrations remain raised for four times longer than CK-MB concentrations because of sustained release of structurally-bound protein from disintegrating myofibrils.

Several important findings have emerged from recent studies of cTn-T in patients with suspected acute myocardial infarction:

- In the GUSTO-IIa substudy, which enrolled patients of all ages within 12 h of onset of chest pain, including those with ST-elevation and ST-depression on the electrocardiogram, 36% had raised cTn-T concentrations (>0·1 ng/mL) on admission, and increased cTn-T was a powerful independent predictor of 30-day mortality in all electrocardiographic subgroups.[3]
- Among patients in whom acute myocardial infarction was ruled out according to standard criteria, increased concentrations of cTn-T identified a subgroup (25%) with minor myocardial damage but whose cardiac event rate during follow-up was the same as for those with confirmed acute myocardial infarction.[4]
- One cTn-T measurement less than 0·1 ng/mL 12 h after onset of chest pain effectively excluded acute myocardial infarction and should facilitate early transfer out of the coronary-care unit and a shorter hospital stay;[5] and finally
- In patients who had ST-elevation and thrombolytic therapy in GUSTO-IIa, none of 32% with raised cTn-T on admission had complete reperfusion (TIMI III flow) at 90 min and their 30-day mortality was three times higher than that for patients with ST-elevation and cTn-T of less than 0·1 ng/mL.[3] Other papers have also shown that troponin measurements can be useful for triage of patients with chest pain in the emergency room[5] (although myoglobin may be even better) and for assessment of coronary reperfusion after thrombolytic therapy.[6]

The use of troponin values for risk stratification in unstable angina is an important advance. A quantitative relation between cTn-T measured in the first 24 h after admission and long-term outcome was described in 976 patients in the FRISC trial.[1] Discriminatory values of cTn-T less than 0·06, 0·06–0·18, and more than 0·18 ng/mL separated patients with unstable angina into groups at low, intermediate, and high risk, with cardiac-event rates (death or acute myocardial infarction) during 5 months of follow-up of 4·3%, 10·5%, and 16·1%, respectively. Within each band of cTn-T, there were no differences in outcome between patients with unstable angina and those with non-Q-wave myocardial infarction. Similar prognostic information was reported in a prospective study of 183 patients, with a higher cut-off of cTn-T of more than 0·2 ng/mL.[7] Among patients with unstable angina negative for CK-MB, the 6-month risk of a cardiac event is 3·9 times higher in those with increased cTn-T,[8] but combination of troponin data with results of symptom-limited predischarge exercise tests improves the risk stratification even further. By use of both tests, patients can be categorised into low, intermediate, and high risk groups corresponding to 1%, 7%, and 20% risk of death or acute myocardial infarction within 5 months.[9]

cTn-I is a similar but independent prognostic marker.[10] cTn-I concentrations of more than 0·4 ng/mL were identified in 41% of patients with unstable angina in the TIMI-IIIB trial;[11] mortality at 42 days was significantly higher among those positive for cTn-I (3·7% *vs* 1·0%), and each 1 ng/mL increment in cTn-I concentration at admission was associated with a significant increase in the risk ratio for death and acute myocardial infarction. Surprisingly, there were no significant differences in angiographic scoring between those with and without a rise in cTn-I.[11] A smaller study has suggested that troponin concentrations correlate with severity of coronary artery disease,[12] but further work is necessary to relate cTn-T and cTn-I values to angiographic data. Nevertheless, the subgroup of patients with unstable angina and increased cTn-T or cTn-I concentrations represent a high-risk population suitable for randomised controlled clinical trials to assess specific interventions. For example, a retrospective analysis of the FRISC data has suggested that troponin-positive patients with

unstable angina benefit from a long course of antithrombotic therapy with heparin.[13]

The quantitative cTn-T assay takes 90 min to complete and requires a dedicated instrument using expensive reagents, but newer qualitative assays designed for bedside use provide a result in 20 min and require only 150 μL of whole blood. False-positive results in patients with chronic renal impairment have raised doubts about the cardiac specificity of cTn-T, so cTn-I—for which assays are less well developed—may become the preferred marker in future studies. Troponin measurements have also been used to detect perioperative myocardial injury during cardiac and non-cardiac surgical procedures. Uncomplicated percutaneous transluminal coronary angioplasty does not increase cTn-T levels,[14] but the sensitivity of troponin measurements has highlighted the susceptibility to myocardial damage among children undergoing routine cardiac surgery. Other areas of current interest include polymorphisms in the cTn-T and cTn-I genes, which have been linked with hypertrophic cardiomyopathy, and the functional and prognostic significance of upregulation of a fetal isoform of cTn-T in patients with cardiac failure.

How quickly troponin measurements become incorporated into routine clinical practice will depend on the costs and simplicity of cTn-T and cTn-I assays, but the major impetus could be the demonstration, by randomised controlled trials, that the outcome for patients with raised troponin concentrations can be improved with changes to current practice.

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## Human laryngeal allograft: shift of emphasis in transplantation

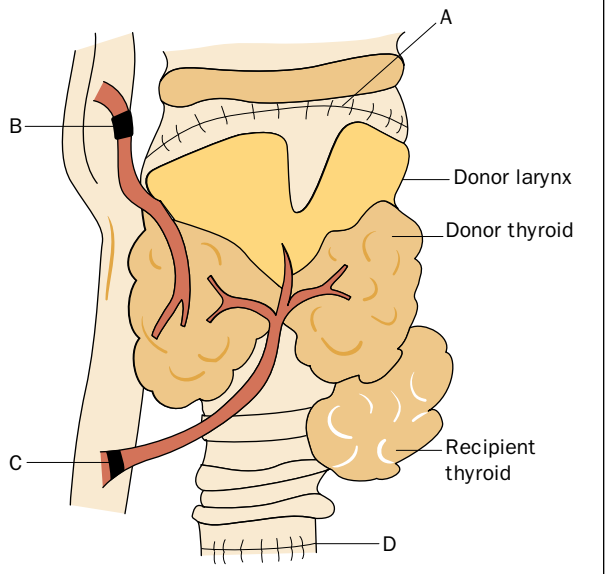
On Jan 4, 1998, Marshall Strome of the Cleveland Clinic, Philadelphia, USA, carried out the world's first true human laryngeal transplant. The patient, aged 40, whose larynx had been irreversibly damaged by a motorcycle accident, received a revascularised allograft, and on the third postoperative day was able to say his first word in 19 years: "hello".[1] The graft consisted of the larynx, thyroid, parathyroids, three tracheal rings, and 70% of the pharynx. So far there has been no biopsy sign of rejection and the patient can now say whole sentences (Strome M, personal communication).

The response of otolaryngologists to news of this operation was mixed but, whatever the eventual outcome, this event represents an important milestone in transplantation history. This transplantation of a "non-essential" organ indicates the dawn of an era of transplantation not just for saving life, but also for improving quality of life.

Loss of a functioning larynx, whether by laryngectomy or trauma, undoubtedly has a devastating impact on quality of life. Preservation of the airway requires a tracheostome, with the concurrent problems of crusting, poor healing, recurrent infection, and cosmetic treatment. Loss of an upper-airway sphincter leads to obvious difficulties with bathing, swimming, and heavy lifting. Decreased efficacy of the nasal airway severely impairs taste and smell, and dysphagia may further reduce the pleasure of eating. Devices for replacing phonation, such as external electronic larynxes and tracheo-oesophageal valves,[2] have been only partly successful.

Although this case has shown that human laryngeal transplantation is now technically possible, several issues

**Anastomoses in a human laryngeal transplant**




A = hypopharynx and tongue base, B = superior thyroid artery end-to-end, C = inferior thyroid vein end-to-side to internal jugular vein, D = trachea. In addition, the recurrent laryngeal nerves may be repaired directly or by use of ansa cervicalis.

have to be resolved before the operation can be introduced into routine clinical practice. For a start, making severed laryngeal nerves work again has proved elusive.[3] Also, little has been published on the major potential causes of mucosal loss after laryngeal transplantation—reperfusion injury, immunological rejection,[4] and infection. Finally, the precise indications for the operation need to be made clear. Loss of a larynx because of trauma is rare.[5] Most people who would merit a laryngeal transplant would have a present or past history of laryngeal carcinoma. Transplanting organs because of cancer can lead to rapid tumour recurrence,[6] unless sufficient time has elapsed to be confident that the patient is "cured". If a patient who has undergone a laryngectomy for cancer can be assumed to be cured after 5 years without recurrence of the disease, there would be a substantial pool of candidates—about 1000 in the UK.—although many of these may be deemed unfit for a transplant for several reasons.

There are potential solutions in sight for each of these issues, especially with the development of a suitable pre-clinical model.[7] Even if tight criteria for transplantation reduce the number of candidates substantially, the ability to transplant larynxes with a high degree of success would be of enormous benefit to the quality of life of patients.

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## Scleroderma: chimerism, the blind man, and the scientist

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Scleroderma is a rare but usually fatal disease, for which there is no cure. Nor has there been any great advance in general treatment in recent years, although some subsets of the disease are now well controlled. If, as the paper in today's *Lancet* by Lee Nelson and colleagues gently implies, scleroderma can be caused by circulation of fetal cells, then a whole series of new treatments—for example, with monoclonal antibodies directed at mismatched MHC— would be feasible. Exactly the same mechanism (ie, a form of graft-versus-host reaction) has been put forward as an explanation for the development of scleroderma in some patients.[1] The evidence offered, based on fetal-maternal HLA compatibility, is also similar to that provided by Nelson and colleagues but chimerism was not examined.

Scleroderma resembles the proverbial elephant which, when examined by six blind men, was perceived to be a distinct and different structure by each depending on the part of the elephant examined.[2] Scientists examining masked tissue samples from the mythical chimera might also have concluded that the samples were from distinct and different animals depending on the part of the chimera examined. When one knows the broader picture, the blind men were obviously wrong. Were the scientists wrong too?

If the chimerism is assumed to be true, can the possibility that a form of graft-versus-host disease induces scleroderma be taken as confirmed? Not unexpectedly, the answer is no. The existence of over 1000 papers on the topic reinforces the fact that chimerism has been very fully investigated in both solid-organ and bone-marrow transplants, for example, over many years.[3-5] Although there are peripheral similarities between scleroderma and graft-versus-host disease, there is no proof that any transplant recipient has developed scleroderma. Many individuals, myself included, have been injected repeatedly with live lymphocytes in attempts to raise specific responses to HLA. Invariably these injections have been of cells whose HLA types were almost identical to those of the recipient. To my knowledge none of us has developed scleroderma even though many did not produce measurable responses to the injections. Similarly, what of all the recipients of blood transfusions over the years? Clearly, therefore, whether there is recipient immunosuppression or not, scleroderma is not an apparent risk after allogeneic cell transfer.

In murine models autoimmune syndromes have been reported after induction of tolerance[6,7] and proven chimerism but, although a wide range of autoantibodies—for example, to single-stranded DNA, platelets, and IgG (rheumatoid factor)—are reported, the scleroderma-characteristic antibodies to topoisomerase, RNA polymerases, and centromere are absent.

Do the arguments given above mean that Nelson and colleagues have incorrectly defined chimerism? Certainly the very sensitive techniques needed to detect male cells in females through amplification of HY sequences (male-specific gene sequences) can give false-positive results because of HY-like sequences elsewhere in the genome. However, Nelson and colleagues state that their analysis was blinded and that the false-positive rates, if any, would be similar in controls and patients. There is more danger associated with the nested approach that Nelson and colleagues also used for the determination of class II chimerism since certain amplicons will be incorrectly assigned as alleles because of sequence homology with self alleles or pseudo gene sequences. Unless samples are run from the recipient before the transplant/transfusion, all nested PCR data have to be viewed with some scepticism. The ability of nested PCR to amplify sequences not amplified by conventional PCR is as legion as the chimera is legendary, and the scientist is wrong probably up to 80% of the time. However, there are many studies that have proven chimerism.

Even if the molecular biology is not convincing, there are two papers agreeing that HLA sharing between mother and child is associated with scleroderma. If chimerism is not present, is there an alternative mechanism that would operate in an HLA-compatible pregnancy but not through HLA-compatible transfusion or transplantation? If chimerism is accepted, is there a form of chimerism that would operate sometimes in pregnancy but not through HLA-compatible transfusion or transplantation? Unfortunately, the answer to both questions is no. Nevertheless, the HLA-share finding does

in itself suggest new and worthwhile areas of scleroderma research. For other autoimmune disorders such as systemic lupus erythematosus, thrombocytopenia, and rheumatoid arthritis, where chimerism in the mouse has been shown to induce autoantibodies of the types found in human beings,[6,7] there is even more encouragement to follow and consolidate this line of research.

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## Oral antifungal agents for onychomycosis

Onychomycosis affects about 7–8% of the North American population.[1] It is commonly more than a cosmetic issue since it can cause pain or discomfort and affect mobility as well as other activities of daily living.[2] An important advance in its management is the development of oral antifungal agents and methods of their administration.

Griseofulvin, the first promising oral antifungal agent for the treatment of onychomycosis and other dermatomycoses,[3] was introduced 40 years ago. Surprisingly, the pharmacokinetics of griseofulvin in the nail have not been studied in detail. Griseofulvin has a low affinity for keratin, with drug concentrations in keratin declining in parallel with those in plasma.[4,5] A study[4] has shown that in many patients no drug was detectable in the stratum corneum within 48–72 h of stopping griseofulvin 500 mg twice a day for 25 days; however, drug remained in the plasma for about 6 days. Griseofulvin is thought to enter the nail via the nail matrix, and it needs to be given for as long as the diseased nail is growing out. Because of the slow rate at which toenails grow out (0·5–1·0 mm/month), for onychomycosis of the toes griseofulvin usually has to be given for 12–24 months. Meta-analysis shows a mycological cure rate of 24·5% (SE 6·7), with a relapse rate of 40% 3–12 months after end of therapy.[6] Hence griseofulvin has been superseded by the newer oral antifungal agents for the treatment of onychomycosis, particularly of the toes.

Introduced in 1980, ketoconazole was the first important azole for the treatment of onychomycosis.[3,7] It is an imidazole with a high affinity for nail keratin. Ketoconazole has been detected in the distal nail within 11 days of the start of therapy,[5] which suggests that it enters the nail plate via both the nail matrix and the nail bed. It is no longer preferred for the treatment of onychomycosis of the toes because, in the rare case, it has been associated with idiosyncratic, sometimes fatal, hepatotoxicity.[3]

The newer generation of oral antifungal agents for the treatment of onychomycosis are terbinafine,[8] itraconazole, and fluconazole. Itraconazole, a triazole, was first approved for the treatment of onychomycosis as a continuous regimen in Mexico in 1989.[9] The concept of pulse therapy was soon introduced, because itraconazole reaches the distal end of the toenail within 2 weeks of starting therapy and persists in the nail plate for about 9–12 months from the start of therapy, even though it is present at low to negligible concentrations in the plasma within 7–14 days after the end of a week of treatment.[9,10] Itraconazole pulse therapy was first approved for onychomycosis in 1993, in Finland. Fluconazole, the latest of the newer antifungal agents for the treatment of onychomycosis is also a triazole.

Terbinafine, itraconazole, and fluconazole enter the nail plate via both the nail matrix and nail bed. Like itraconazole,terbinafine and fluconazole can be found at the distal end of the nail plate within a few weeks of start of therapy and persist in the nail for several months after withdrawal of therapy.[11-13] They are also eliminated from the plasma within weeks of the end of treatment. This difference is associated with a high benefit to risk ratio. The persistence of drug in the nail plate may explain why the mycological cure rates (60–80%) for the newer agents are higher than that of griseofulvin.[6] The pharmacokinetics of these newer agents has enabled shortening of treatment duration, which increases compliance. Another advantage is that, unlike griseofulvin, which has activity against dermatophytes only, the newer agents are also active in vivo against *Candida* species and some non-dermatophyte moulds. Pharmacoeconomic analyses of griseofulvin, terbinafine, and itraconazole (continuous or pulse) in the treatment of onychomycosis of the toes indicate that terbinafine and pulse therapy with itraconazole are the two most cost-effective treatments, with no significant difference between them.[6]

For terbinafine the recommended treatment regimen for onychomycosis of the toes is 250 mg/day for 12 weeks. In a double-blind trial 6 weeks of treatment was compared with 12 weeks in patients in whom the proximal part of the toenails was not affected.[14] Among the patients who completed the study, the mycological cure rate at 48 weeks after the start of therapy in the 6-week group was 56% (34/61), compared with 82% (46/56) for the 12-week group. Responders did not differ from non-responders in age, weight, or degree of nail involvement. A trend towards better response was observed in those with a short duration of disease and with infection of toenails other than the big (first) toenail. Positive mycology at week 24 predicted therapeutic failure or relapse in 68% (25/37) patients. The investigators[14] suggest that one management approach would be to check mycological status 6 months after the start of therapy and then to repeat treatment for those with positive results.

With itraconazole, despite the popularity of pulse therapy, there has been only one study that has compared pulse (200 mg twice daily for 1 week a month for 3 months) against continuous therapy (200 mg daily for 3 months). At month 12 after the start of therapy, mycological cure rates were 69% for pulse therapy

(n=59) and 66% for continuous therapy (n=62). In patients with less than 75% nail-plate involvement, the mycological cure rates at month 12 were 75% for pulse therapy and 79% for continuous therapy. When more than 75% of the nail plate was affected, the corresponding figures were 66% and 60%, respectively.[15] Although there were no significant differences, the investigators found a trend for superiority of the pulse over the continuous regimen. Furthermore, for onychomycosis of the toes, itraconazole pulse therapy requires exactly half the drug needed for the continuous regimen, thus making the former more cost-effective.

The newer oral antifungal agents used alone, or in some cases in conjunction with topical antifungals or surgery, are providing the basis for effective treatment of onychomycosis of the toes in a large proportion of affected individuals. Efficacy can be improved if those unikely to respond to therapy can be identified, and efforts to do so and to find the most cost-effective manner of treating pedal onychomycosis are under way. Recurrence of disease still occurs in a high proportion of patients. It can be due to inadequate eradication of onychomycosis or reinfection. Hence once cure has been obtained it is prudent to counsel the patient about measures that will reduce the likelihood of reinfection.[16] Some strategies include avoidance of facilities with a high level of dermatophyte contamination (communal swimming pools, showers, changing facilities) discarding old shoes that may have a high density of fungal spores, and the judicious use of topical antifungal agents.

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## Fast-track publication at *The Lancet*

In April, 1997, *The Lancet* began offering to authors of selected research papers publication within 28 calendar days.[1] That time includes full peer-review by clinicians and statisticians, and authors' revisions in response to external review. By the end of the year, seven papers[2-8] had been accepted and published under the fast-track programme, within a mean of 27·7 days (range 21–36).

110 requests have been made for fast-track publication. In telephone conversations with an editor 18 authors were discouraged from proceeding further. 92 manuscripts were scrutinised by the editorial team as serious contenders, but only 14 were selected for peer-review. From that 14, seven were accepted, two were rejected, and five were put through the normal review process.

All that activity shows that the 4-week review and publication schedule is popular with researchers. To our delight, fast-tracking also proved popular with peer-reviewers. They are asked to report within 48 h of receiving the manuscript, and we had little difficulty in finding suitable advisers. We thank all those clinicians, scientists, and statisticians who have helped *The Lancet* in our fast-track programme for their rapid turnarounds. They and all the other reviewers who helped the journal in 1997 processing articles and research letters are listed on our website (http://www.thelancet.com).

Also on our website are further details about fast-track publication at *The Lancet*, including how to ask about a specific manuscript entering the system. A new development for 1998 is the extension of the fast-track system to Research Letters. For openers, we present a fast-tracked letter on p 567.

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