doxycycline again presented with an infiltrate at the same location and similar symptoms after 35 months of follow-up, but refused further diagnostic or therapeutic attempts. Another four patients experienced local infectious complications probably related to the former actinomycosis at 4, 25, 27 and 30 months after the end of treatment, respectively. Treatment duration in 5 of these 6 patients had a length of <3 months and was significantly shorter than that of the 35 patients with an uneventful follow-up \((P=0.001,\) two-sided Mann–Whitney \(U\)-test).

According to reviews, the recommended treatment length consists of several weeks of intravenous therapy followed by 6–12 months of oral treatment.\(^1,2\) Recently, the concept of shorter treatment courses has been introduced, especially for cervicofacial actinomycosis. Case series involving patients with pulmonary actinomycosis, treated exclusively medically with short course regimens, are sparse: a few series with a maximum number of 15 patients showed treatment successes after antibiotic regimens shortened to a median duration of 4–20 weeks; however, follow-up data were often missing or incomplete.\(^3–6\) In our series, 24 patients (56\%) were treated for <6 months without prior surgical debulking and with a clinical cure rate of 100\%. On the other hand, 10 of 13 patients with evidence of abscess formation or chest wall involvement were treated for >6–14 months because of slow resolution of the radiographic lesions. Six of 41 patients (15\%) with complete follow-up data developed either documented or possible recurrence or local complications. These patients received significantly shorter antibiotic courses when compared with the other patients, and duration was below 3 months in five of them. We suggest that antibiotic treatment duration should be individualized, and termination of treatment can probably be considered 1 or 2 months after complete clinical and radiological disease resolution in most patients. However, treatment durations below 3 months in medically treated patients without prior surgical debulking should probably be avoided, as they might be associated with an increased risk of complications.

The main limitations of our study are those generally inherent in retrospective analyses. We were not able to calculate the diagnostic accuracy of the applied procedures in detail, and we cannot provide a prospective comparison between different antibiotics and treatment durations. However, due to the sporadic occurrence of actinomycosis, prospective trials might be nearly impossible to perform, and our case series represents the largest report on pulmonary actinomycosis in the recent literature.

We conclude that (i) surgical diagnostic procedures can be avoided in the majority of patients by performing transbronchial catheter biopsies and/or transthoracic needle aspiration, (ii) antibiotic treatment with penicillin and alternatively doxycycline is associated with an excellent clinical cure rate despite high rates of penicillin intolerance, and (iii) individual treatment duration can be shortened below the recommended 6–12 months; however, treatment below 3 months in exclusively medically treated patients might be associated with complications during follow-up.

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Association of high T allele frequency of CYP2B6 G516T polymorphism among ethnic south Indian HIV-infected patients with elevated plasma efavirenz and nevirapine

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Sir,

Plasma concentrations of the non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine are known to exhibit a high degree of inter-patient variability.\(^1\) A comprehensive analysis of the existing literature on the pharmacogenetic
determinants of antiretroviral drug exposure, toxicity and activity has been undertaken.\textsuperscript{1} Plasma concentrations of efavirenz and nevirapine are known to be influenced by a G to T change at codon 516 of \textit{CYP2B6}.\textsuperscript{1} The frequency of the T allele varies widely across populations.\textsuperscript{2} We report the prevalence of the 516 G>T polymorphism of the \textit{CYP2B6} gene and its influence on steady-state plasma efavirenz and nevirapine concentrations in HIV-infected patients in south India.

The study participants were HIV-1-infected individuals receiving antiretroviral treatment with either efavirenz (600 mg once daily)- or nevirapine (200 mg twice daily)-based highly active antiretroviral therapy (‘HAART’) regimens for a minimum period of 15 days from the Government Hospital of Thoracic Medicine, Chennai, south India. These patients were not receiving any concomitant medications known to alter the blood levels of efavirenz or nevirapine. The study was approved by the Institutional Ethics Committee, and all patients gave written informed consent.

A single timepoint blood collection at 12 and 2 h post-dose for efavirenz and nevirapine, respectively, was done. Genomic DNA was extracted from whole blood, and the \textit{CYP2B6} amplicon was directly sequenced using a 3100 Avant Genetic Analyzer.\textsuperscript{3} Plasma concentrations of efavirenz and nevirapine were quantified using HPLC.\textsuperscript{4,5}

Analysis of data was performed using SPSS, version 14. Shapiro’s test was done to confirm normal distribution of the data. Groupwise comparison of plasma concentrations was done using Tukey’s multiple comparison test. A \( P \) value of <0.05 was considered to be statistically significant. Deviation of genotype frequencies from Hardy–Weinberg equilibrium expectations was evaluated using the \( \chi^2 \) test. Allelic frequency was estimated by dividing total copies of individual alleles by all alleles in the population.

A total of 135 HIV-1-infected persons were studied; their mean (range) age and body weight were 35 years (20–59) and 49 kg (26–91), respectively, and 90 were males. Patient adherence to treatment was satisfactory as assessed by regularity of hospital visits to collect drugs and also by the treating physician. The proportions of GG, GT and TT genotypes were 47 (35%), 58 (43%) and 30 (22%), respectively. The G and T allele frequencies in this population were 0.56 and 0.44, respectively; the \( \chi^2 \) test showed no deviation from Hardy–Weinberg equilibrium.

Among the 135 patients, 69 and 66 were receiving treatment with efavirenz- and nevirapine-containing regimens, respectively. The mean 12 h plasma efavirenz and 2 h plasma nevirapine concentrations for the GG, GT and TT genotypes are shown in Table 1. The TT genotypes had significantly higher plasma efavirenz and nevirapine concentrations than the GG and GT genotypes (\( P<0.001 \)). Drug levels did not significantly differ between GG and GT genotypes.

The study data showed that \textit{CYP2B6} G516T polymorphism significantly influences blood levels of efavirenz and nevirapine in the south Indian population: a finding similar to that reported by others.\textsuperscript{1} High inter-individual variability in plasma efavirenz and nevirapine levels is largely due to genetic variations in the \textit{CYP2B6} gene.\textsuperscript{3}

We obtained a T allele frequency of 0.44, which is higher than that reported in Koreans (0.14), Japanese (0.16), Caucasians (0.25), White Americans (0.25) and African-Americans (0.28), but similar to that of West Africans (0.42), Chinese (0.43) and Hispanics (0.43).\textsuperscript{2} This implies that differences in pharmacogenetic and pharmacokinetic characteristics appear to be associated with ethnicity. Validated pharmacogenetic and pharmacokinetic analyses should be used to help predict likely patterns of antiretroviral treatment response among different populations worldwide. Plasma exposure to efavirenz may be higher among ethnic south Indians than among other populations. Hence, clinical trials using lower doses of these drugs are required. In fact, the feasibility of genotype-based efavirenz dose reduction in \textit{CYP2B6} G516T allelic carriers was studied and the dose reduction was found to relieve patients of efavirenz-associated CNS symptoms.\textsuperscript{6}

Such studies are important, because they would have cost-saving implications, particularly for developing countries. \textit{CYP2B6} G516T genotyping at baseline may allow clinicians to optimize antiretroviral therapy in patients who initiate an efavirenz- or nevirapine-based regimen.

The clinical implications of altered plasma efavirenz and nevirapine levels, as observed in this study, are not clear. Although an association between \textit{CYP2B6} G516T polymorphism and increased adverse events in the CNS during the first week of efavirenz therapy has been previously reported, this association was not apparent during subsequent weeks, despite persistently elevated efavirenz concentrations.\textsuperscript{1} This is in agreement with our observation that, in spite of TT genotypes having mean plasma efavirenz concentrations at 12 h as high as 10.59 \( \mu \)g/mL (peak levels could be still higher), none of the patients had persistent CNS effects or complaints of efavirenz toxicity. However, ours was a cross-sectional assessment without long-term follow-up. Prospective studies are required to definitively relate blood levels of efavirenz and nevirapine to the occurrence of adverse reactions as well as to determine whether dose modifications are effective and safe.

### Table 1. Plasma concentrations of efavirenz (EFV) and nevirapine (NVP) for the different genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Mean (95% confidence interval) (( \mu )g/mL)</th>
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<tbody>
<tr>
<td></td>
<td>12 h EFV (( n = 69 ))</td>
</tr>
<tr>
<td>GG</td>
<td>2.16 (1.73–2.59) (( n = 28 ))</td>
</tr>
<tr>
<td>GT</td>
<td>2.78 (2.28–3.29) (( n = 28 ))</td>
</tr>
<tr>
<td>TT</td>
<td>10.59\textsuperscript{a} (7.43–13.74) (( n = 13 ))</td>
</tr>
</tbody>
</table>

\textsuperscript{a}\( P<0.05 \) versus GG and GT.
Research letters

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Methodological issues regarding safety evaluation in randomized controlled trials of the effectiveness of antibiotic prophylaxis for the prevention of post-operative wound infection: systematic review

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Keywords: clinical trials, safety data reporting, hernia surgery, breast surgery, laparoscopic cholecystectomy, RCTs

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Sir,

The effectiveness of antibiotic prophylaxis in low-risk patients remains a matter of investigation, since it is well known that antibiotic prophylaxis can be associated with adverse drug events1 (e.g. haemolytic anaemia after proper administration of just one dose of cephalosporin prophylaxis’).

Randomized controlled trials (RCTs) are widely accepted to be the most reliable method for determining the efficacy of an intervention; however, methodological limitations have been expressed in terms of safety assessment. The aim of this systematic review was to describe the methodology of safety evaluation in RCTs concerning antibiotic prophylaxis in hernia and breast surgeries and in laparoscopic cholecystectomy (LC).

PubMed, Scopus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Science Citation Index Expanded and Google Scholar were searched in order to identify articles assessing the effectiveness of systemic antibiotic prophylaxis versus placebo in hernia surgery, breast surgery and LC. An electronic search was performed from 1995 up to and including February 2008. The electronic literature search was performed with the search terms laparoscopic cholecystectomy, hernia surgery, breast surgery, antibiotics, chemotherapy and antibiotic prophylaxis. There was no language restriction. The reference list of all the identified trials was checked for more relevant trials. Contact with pharmaceutical companies or researchers for identifying unpublished studies or additional data for retrieved studies was not attempted.

The titles and abstracts of the identified articles were evaluated by the reviewer. Any article deemed appropriate or possibly meeting the inclusion criteria from the title or abstract was retrieved. The following criteria were used for study selection:

(i) The study had to be an RCT comparing pre-operative antibiotic prophylaxis versus placebo. The type of antibiotic was not specified a priori. Post-operative prophylactic antibiotics were included.
(ii) The population had to be adults over 18 years old undergoing hernia surgery or breast surgery for benign or malignant disease and low-risk patients undergoing elective LC.
(iii) The intervention had to be pre-operative antibiotic prophylaxis versus placebo (at least two treatment arms with one arm taking antibiotic prophylaxis and the other arm taking placebo or no treatment).

Only full publications were included. Case series, uncontrolled studies, articles published only as abstracts, editorials, and news and correspondence articles were excluded. For duplicate publications, the most complete report was selected.

The main outcomes were methodological differences in the definition, assessment, analysis and reporting of adverse event data in these trials. Information retrieved included the name of the first author, year of publication, population characteristics, type and dosage of antibiotic, route of administration and duration of follow-up, as well as any mention of adverse events in the abstract, methods, results or discussion section or inclusion of adverse