REVIEW

Natural health product–HIV drug interactions: a systematic review

Edward Mills DPH MSc[1], **Victor Montori** MD MSc[2], **Dan Perri** MD[3],
Elizabeth Phillips MD[3,4] and **Gideon Koren** MD[4]

[1]*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton,
ON;* [2]*Department of Endocrinology, May Clinic College of Medicine, Rochester, MN;*
[3]*Department of Medicine, University of Toronto, Toronto, ON;* [4]*Department of Clinical
Pharmacology & Toxicology, Sick Children's Hospital, Toronto, ON, Canada*

Summary: The use of natural health products (NHPs) within the HIV community is high. Several NHPs have demonstrated interactions with HIV medications that could contribute to drug failure. We aimed to conduct a systematic review of clinical trials examining NHP–HIV drug interactions and their methodological characteristics. We searched electronic databases and unpublished resources independently, in duplicate. Nine studies were identified, eight clinical pharmacokinetics trials and one population-pharmacokinetics trial. Investigators studied four different herbal medicines (St John's wort, garlic, goldenseal and milk thistle) and one vitamin (vitamin C). Significant interactions were observed with St John's wort, garlic and vitamin C. However, methodological challenges exist to making the results directly generalizable to patients. This review finds that important drug level changes exist when NHPs are combined with HIV medications. Considering patient values and the implications of these studies, further research is urgently required to determine the extent of interactions with other commonly used NHPs.

Keywords: natural health products, complementary therapies, drug interactions, systematic review

Introduction

Complementary therapies for HIV have been defined as the 'scientific and non-scientific interventions that diverge from the accepted traditional treatment of HIV infection.'[1] Recent reports indicate that complementary and alternative medicine (CAM) use among North American HIV patients may be as high as 70%,[2-4] and that HIV patients do not communicate CAM usage to their physicians.[5] HIV patients in a recent qualitative study believed that complementary therapies would be synergistic with antiretrovirals or reduce HIV-related symptoms.[6]

Physicians treating HIV patients need to be aware of their patients' use of CAM and the potential for CAM therapies to influence the response to conventional treatments. Previous studies suggesting that natural health products (NHPs) could interact with HIV medications and lead to drug failure and resistance[7] have received widespread public health attention.[8,9]

To make causal inferences about NHP–drug interactions, it is important to conduct studies that control for time trends in drug metabolism (i.e., a concurrent control as in a controlled trial). Furthermore, investigators should carefully ascertain that the NHP dose contains the NHP dose intended and the placebo or inert controls are indeed inert. To particularize these causal inferences to patients, clinicians will need to know to what extent the conditions in the laboratory mimic those in clinical practice (i.e., the extent to which drug metabolism in healthy participants is similar to that of patients with HIV; the similarity between the dose and schedule of NHP that drug investigators chose, and the doses patients take usually), and the extent to which interactions in clinical pharmacology trials are clinically important.

In order to determine the current state of information on clinical trials of NHP–HIV drug interactions, we conducted a systematic review. The purposes of this review were to identify all clinical investigations examining NHP–drug interactions, to assess their methodological quality, and to summarize their findings .

Correspondence to: Dr E Mills, McMaster University, Faculty of Health Sciences, Clinical Epidemiology & Biostatistics, HSC-2C12, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada
Email: millsej@mcmaster.ca

Table 1 Study characteristics

Author and year	NHP	Drug	Design	HIV status	Participants	Outcomes	Results
Piscitelli (2000)[9]	St John's wort	Indinavir 800 mg four doses	Before-and-after	HIV−	n=8 (six men, two women, age range 29–50)	Plasma pharmacokinetics	AUC_{0-8} ↓ 54% (90% CI, −80 to 32%)
							C_{min} ↓ 81% (SD 16)
de Maat (2001)[22]	St John's wort	Nevirapine	Population pharmacokinetics	HIV+	Case n=5 (all men, aged 34–53); control n=171	Oral clearance	↑ Oral clearance of 35% (SE 15%)
Gallicano (2003)[20]	Garlic	Ritonavir 400 mg single dose	Before-and-after	HIV−	n=10 (five men, five women)	Plasma pharmacokinetics	$AUC_{0-\infty}$ ↓ 17% (90% CI, 0 to 31%)
							C_{max} ↓ 1% (90% CI, −25 to 31%)
Piscitelli (2002)[8]	Garlic	Saquinavir 1200 mg three times daily for 4 days	Three period one-way, crossover	HIV−	n=10 (four men, six women, age 38 SD 7.8)	Plasma pharmacokinetics	AUC_{0-8} ↓ 51% (90% CI, −84 to 12%)
							C_{min} ↓ 49% (90% CI, −82 to 33%)
							C_{max} ↓ 54% (90% CI, −88 to 30%)
Piscitelli (2002)[16]	Milk thistle	Indinavir 800 mg four doses	Three period one-way, crossover	HIV−	n=10 (six men, four women, age range 24–45)	Plasma pharmacokinetics	AUC_{0-8} ↓ 8% (−18 to 2%)
							C_{min} ↓ 25% (90% CI, −37 to −10%)
							C_{max} ↓ 9% (90 CI, −22 to 6%)
DiCenzo (2003)[18]	Milk thistle	Indinavir 800 mg four doses	Before-and-after	HIV−	n=10 (age range 18–55)	Plasma pharmacokinetics	AUC_{0-5} ↓ 7% (90% CI, −28 to 20%)
							C_{max} ↓ 11% (90% CI, −28 to 10%)
Sandhu (2003)[19]	Goldenseal	Indinavir 800 mg single dose	Before-and-after		n=11 (six men, five women); mean age 25.5 (21–47)	Plasma pharmacokinetics and oral clearance	C_{max} +2.6% (90% CI, 1.2 to 6.4%)
							Oral clearance ↓4.6% (−95% CI, −10.6 to 3.4%)
Mills (2003)[21]	Milk thistle	Indinavir 800 mg four doses	Three period RCT	HIV−	n=16 (all men, age range 22–36)	Plasma and urine pharmacokinetics	AUC_{0-8} ↑ 21% (90% CI, −13.6 to 71.5%)
							C_{max} ↑ 4.9% (90% CI, −24.5 to 45.6%)
							C_{min} ↑ 108% (90% CI, 16 to 273%)
							UR ↑ 53% (90% CI, 1 to 131%)
Slain (2003)	Vitamin C	Indinavir 800 mg four doses	Before-and-after	HIV−	n=7 (six men, one women, age range 18–55)	Plasma pharmacokinetics	AUC ↓ 14% (90% CI, −19 to 11)
							C_{max} ↓ 20% (90% CI, −29 to 14%)

Methods

Data sources

In consultation with an information specialist, we conducted a search of English and non-English language articles in the following databases: AMED (1985–February 2004), CINAHL (1982–February 2004), E-Psyche (1993–February 2004), Centralised Information Service for Complementary Medicine (CISCOM) (2000–February 2004), Cochrane Central Register of Controlled Trials (CENTRAL, May 2003), EMBASE (1985–February 2004) and MEDLINE (1966–February 2004). We supplemented this search by looking for unpublished trials on the National Research Register (UK) and *Clinicaltrials.gov* (USA). We used the search terms 'Drug Interactions' OR 'Food-Drug interactions', 'Medicine, Herbal', 'Complementary Therapies', 'Plant extracts/Pharmacology', 'Plant extracts/ adverse effects', 'Phytotherapy/adverse effects'. Additional searches were more specific, examining individual popular herbs and drugs, such as 'Hypericum/adverse effects' OR 'Garlic∗/adverse effects', 'Protease inhibitors/pharmacokinetics'. We searched the reference lists of included studies and of three other reviews.[10–13] We contacted authors in the field and the international NHP industry for unpublished reports.

Study selection

Two reviewers (EM, PW), working independently and in duplicate, searched the databases, identified relevant abstracts and decided on article eligibility after reading the full reports. To be included in the final review, a manuscript had to report the results of an original study examining the pharmacokinetic interaction between an NHP and an antiretroviral HIV drug in humans. Studies examining isolated chemical constituents and case reports were excluded. We resolved disputes on the inclusion criteria of either abstracts or final articles by consensus and, if necessary, by third-party arbitration (VM).

Data extraction and quality assessment

The same two reviewers (EM, PW) extracted data independently and in duplicate and evaluated the study quality. We resolved discrepancies by consensus. We extracted data about the characteristics of the population studied and of the NHP and HIV medication investigated (with dosage and duration of dosage).

To assess the quality of each study, we determined the study design, the duration of drug dosing and the inclusion of a control group. We also noted whether investigators justified their choice of sample size by reporting power calculations, and presented results using confidence intervals (CIs). In addition, we determined whether the trial used healthy participants, and whether it studied the NHPs at doses commensurate with real-life levels. We also determined if the investigators verified whether the NHP used in the trial contained the active herbal ingredients.[14]

Data analyses

We measured chance-adjusted interrater agreement for inclusion of studies using the κ statistic. We determined differences in the area under the curve (AUC) of the regulated medication before and after challenge with the NHP. These differences indicate the magnitude of the interaction. We expressed those differences as percentage of the AUC at baseline and derived the 95% CI around this difference from reported measures of variance.[15] We did not conduct a pooled meta-analysis due to heterogeneity of study design, probe drugs and NHPs.

We display the results using a forest plot with studies ordered by NHP, generated using StatsDirect software (StatsDirect Ltd, 2003).

Results

Figure 1 details the yield of the searches and study selection. κ for initial decisions on the inclusion of studies was 0.8 (95% CI: 0.56–0.98), suggesting substantial agreement. The included studies were from the three countries (USA,[8,9,16–19] Canada[20,21] and Netherlands[22]), all were reported in English, and were published between 2000 and November 2003; two studies remain unpublished.[17,21]

Of the nine included studies (Table 1),[8,9,16–22] only one studied HIV+ participants.[22] The eight pharmacokinetic clinical trials included studied an average of 10 participants (SD, 3), and one population-pharmacokinetic study used five cases and 176 controls.[22] Investigators studied four different herbal medicines (St John's wort,[9,22] garlic,[8,20] Goldenseal[19] and milk thistle[16,18,21]) and one vitamin[17] (Vitamin C). Two trials (one of garlic[8] and one of St John's Wort[9]) did not report validating the NHP constituents. Investigators studied the protease inhibitors (PIs) indinavir,[9,16–19,21] ritonavir[20] and saquinavir,[8] and the non-nucleoside reverse transcriptase inhibitor, nevirapine.[22]

All clinical trials investigated short dosing of PIs in steady-state pharmacokinetics. All PIs used in these studies are metabolized primarily through the CYP 3A4 cytochrome. The mean duration of NHP dosing for steady-state studies was 15.2 days (95% CI, 8.8–21.6). On clinic days, NHPs were administered concurrently with the study drug in two studies.[20,21]

Investigators assayed the serum concentration of the regulated medication for a mean of 10.0 h (95% CI, 3.1–16.8, range 0–30) to generate a concentration
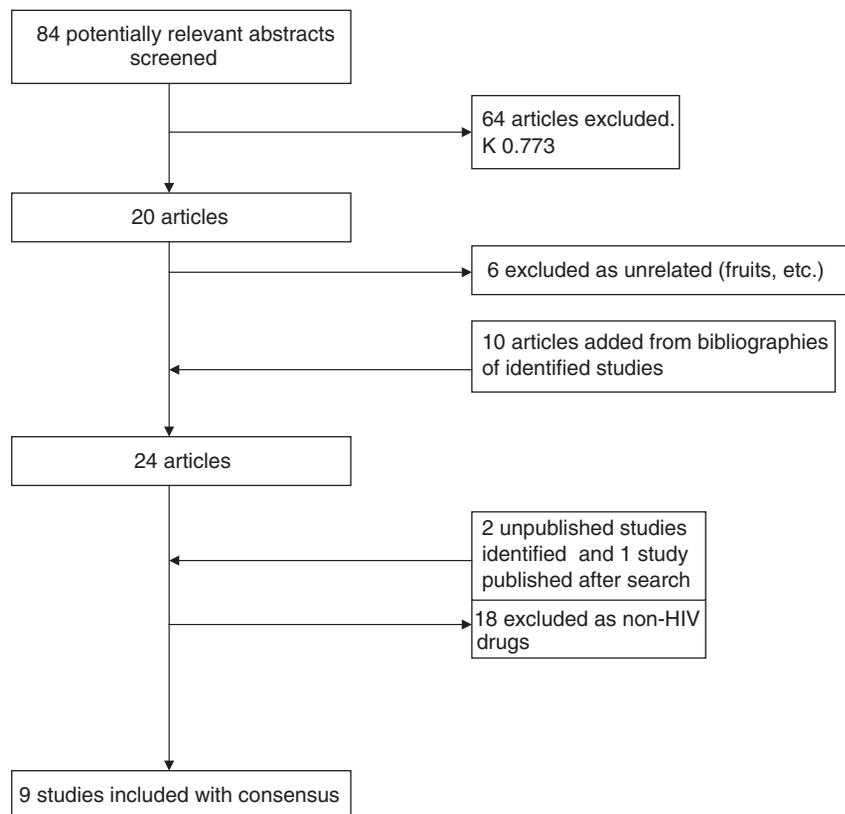
```
┌─────────────────────────────┐
│ 84 potentially relevant     │
│ abstracts screened          │
└─────────────────────────────┘
              │
              │          ┌──────────────────────────┐
              ├─────────▶│ 64 articles excluded.    │
              │          │ K 0.773                  │
              ▼          └──────────────────────────┘
┌─────────────────────────────┐
│ 20 articles                 │
└─────────────────────────────┘
              │
              │          ┌──────────────────────────┐
              ├─────────▶│ 6 excluded as unrelated  │
              │          │ (fruits, etc.)           │
              │          └──────────────────────────┘
              │          ┌──────────────────────────┐
              │◀─────────│ 10 articles added from   │
              │          │ bibliographies of        │
              ▼          │ identified studies       │
┌─────────────────────────────┐└──────────────────────────┘
│ 24 articles                 │
└─────────────────────────────┘
              │          ┌──────────────────────────┐
              │◀─────────│ 2 unpublished studies    │
              │          │ identified and 1 study   │
              │          │ published after search   │
              │          └──────────────────────────┘
              │          ┌──────────────────────────┐
              ├─────────▶│ 18 excluded as non-HIV   │
              │          │ drugs                    │
              │          └──────────────────────────┘
              ▼
┌─────────────────────────────┐
│ 9 studies included with     │
│ consensus                   │
└─────────────────────────────┘
```

Figure 1 Flow diagram of search results

time curve and the AUC. Three indinavir trials extrapolated the findings of shorter periods of sampling to full 8 h AUC periods.[9,17,18]

Designs

Seven studies used a before-and-after design,[8,9,16–20] two of which evaluated rebound after a washout period.[8,16] One study used a randomized controlled design with a rebound washout period;[21] and the other used a population-pharmacokinetics design.[22]

Interactions

Figure 2 displays the AUC profiles of the drugs in a forest plot. We did not pool the results due to the large heterogeneity between studies. St John's wort significantly decreased the plasma levels of indinavir.[9] This was also observed in the population-pharmacokinetics study of nevirapine.[22] Garlic supplements significantly decreased plasma levels of saquinavir,[8] but did not affect ritonavir levels.[20] Investigators did not identify significant interactions between goldenseal and indinavir[19] or milk thistle and indinavir.[16,18,21] Vitamin C caused a small but statistically significant reduction in the AUC_{0-8} of indinavir levels in one study.[17]

Discussion

We found only nine reports of the interactions of NHPs and HIV medications in the literature. Investigators have only reported on interactions between five NHPs and HIV medications. We found evidence of no interaction between goldenseal or milk thistle and indinavir, important interaction between garlic and PIs, important interaction between St John's wort and indinavir, and insufficient clinically important evidence about vitamin C and indinavir. Most studies used a before–after design, enrolled healthy participants, and studied one antiretroviral agent and one NHP at a time.

There are several limitations to consider in our study. No quality standards and no standards for appraising the quality of pharmacokinetics trials exist. We cannot determine the extent to which publication bias affects this review. We would like to draw the following strengths of our work to readers' attention. To the best of our knowledge, this is the first systematic review of NHP–HIV drug interactions. We used explicit methods to decrease bias in the inclusion, data extraction, and quality assessment of the studies, did not exclude studies on the basis of their language of publication, and decreased the possibility of publication bias by searching extensively, contacting all authors, and by seeking (and finding) unpublished research.
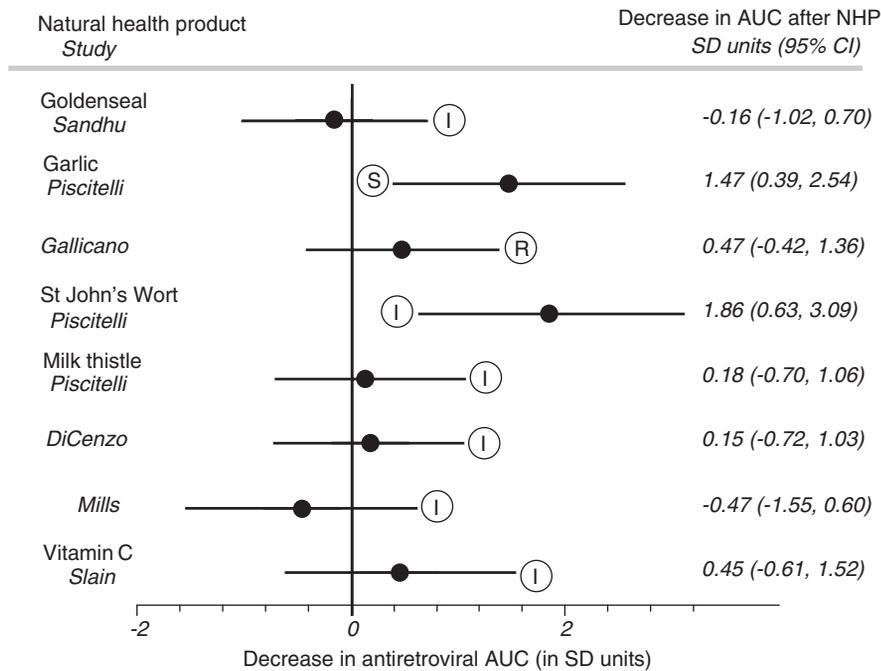
Figure 2 Forest plot of eight clinical trials. I=indinavir, S=saquinavir, R=ritonavir, CI=confidence interval

The clinical trials examined in our study are proof-of-concept studies. That is, the choice of CYP 3A4 metabolized medication is arbitrary. As such, studies using non-HIV drugs also metabolized through the CYP 3A4 isoform, such as midazolam, are relevant to HIV patients, and the results of non-HIV trials should be interpreted for relevance.

There are several important considerations from the results of our study. All of the clinical trials found were conducted in healthy volunteers. However, it is known that HIV+ individuals metabolize at a rate up to 50% slower than HIV− individuals,[23] due to disease state, co-medications and other unknown factors. In addition, due to ethical considerations of toxic exposure or the potential for drug resistance with some HIV drugs, the healthy participants are exposed to short-term dosing of the PIs, dissimilar from the treatment of HIV+ individuals. It is possible that dosing with PIs affects the manner with which they would be metabolized again by activation of the pregnane X receptor, the effect of which would not be apparent after the first dose, possibly explaining the reduction in the control group in the study by Mills *et al.*

A further concern is the heterogeneity of the study populations. Most studies include men and women of varying ages and races, in keeping with recommendations made by the National Institutes of Health.[24] However, this may introduce variability and substantially reduces the ratio of signal to noise, thus reducing the likelihood of identifying significant interactions with few and heterogeneous participants. Drug metabolism and drug transporter genotype and function may vary significantly with race and gender. When studies show no average effect, they should present CIs for readers to assess the likelihood that important effects are also excluded. In our review, CIs were presented in five studies.[8,16,18–21] In addition, authors of the studies we reviewed did not report the magnitude of change in AUC that readers should consider the smallest meaningful interaction between NHP and conventional medication. Without this knowledge, readers cannot judge whether studies reporting no interaction were large enough to exclude the smallest interaction that is of clinical significance.

The available evidence cannot conclusively ascertain what is the effect of using NHPs on the efficacy of current antiretroviral therapy. A substantial limitation to generalizability is that all of the clinical trials included in this review used single PIs, uncommonly prescribed to patients in current clinical practice. Considering the effects of polypharmacy with triple therapy, the effects of NHPs on patient drug levels cannot be determined. In addition, a constraint of these trials in healthy participants is the inability to examine for P-glycoprotein effects in order to determine if ingestion of the NHP may affect drug disposition to remote areas of the body. Clinical trials using HIV+ individuals in a population-pharmacokinetic manner, such as those performed by de Maat *et al.*,[22] may yield generalizable results.

The methodological quality of the included studies was variable. Most studies used a before-and-after design which lacks contemporary controls, in particular to control for time-dependent metabolic variability and co-ingestions.[25] The use of a control group in the study by Mills *et al.* had a

reduction in indinavir levels that reached significance from baseline, suggesting that variables other than the NHP may affect pharmacokinetics. Further research is required to determine the necessity of control groups in pharmacokinetic studies. Two trials (one of garlic[8] and one of St John's Wort[9]) did not report validating the NHP constituents. Due to the potential variability of NHP products on the shelves, investigators should validate the NHP constituents.[14]

In conclusion, despite the heightened awareness for herb–HIV drug interactions in the media and scientific journals, the number of investigations is limited in scope and methodological quality. Clinicians and the public do not have high-quality information to guide their decisions to use NHPs. Additional research into both pharmacokinetic methodology and NHP–HIV drug interactions is warranted.

References

1 Elion RA, Cohen C. Complementary medicine and HIV infection. *Prim Care* 1997;**24**:905–19
2 Fairfield KM, Eisenberg DM, Davis RB, Libman H, Phillips RS. Patterns of use, expenditures, and perceived efficacy of complementary and alternative therapies in HIV-infected patients. *Arch Intern Med* 1998;**158**:2257–64
3 Duggan J, Peterson WS, Schutz M, Khuder S, Charkraborty J. Use of complementary and alternative therapies in HIV-infected patients. *AIDS Pat Care STDS* 2001;**15**:159–67
4 Furler MD, Einarson TR, Walmsley S, Millson M, Bendayan R. Use of complementary and alternative medicine by HIV-infected outpatients in Ontario, Canada. *AIDS Pat Care STDS* 2003;**17**:155–68
5 Wynia MK, Eisenberg DM, Wilson IB. Physician–patient communication about complementary and alternative medical therapies: a survey of physicians caring for patients with human immunodeficiency virus infection. *J Altern Complement Med* 1999;**5**:447–56
6 Mills EJ, Leonard BL, Huff H, Merryweather B. Knowledge and safety and drug interactions amongst HIV+ individuals: a focus group study. *Ontario HIV Treatment Network Research Day*. Toronto: November 2003
7 Van de Vijver D. *CATCH Study*. 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris, France: Oral Presentation, 2003
8 Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis* 2002;**34**:234–8
9 Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. *Lancet* 2000;**355**:547–8
10 Fugh-Berman A, Ernst E. Herb–drug interactions: review and assessment of report reliability. *Br J Clin Pharmacol* 2001;**52**:587–95
11 Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* 2001;**61**:2163–75
12 Mills EJ, Montori VM, Wu P, Gallicano K, Guyatt G, Clarke M. Herb–Drug Interactions: A Systematic Review and Meta-analysis. *10th International Symposium on Complementary Medicine Research* London, UK, 2003 (abstract)
13 Brazier NC, Levine MA. Drug-herb interaction among commonly used conventional medicines: a compendium for health care professionals. *Am J Ther* 2003;**10**:163–9
14 Straus SE. Herbal medicines – what's in the bottle? *N Engl J Med* 2002;**347**:1997–8
15 Altman DG, Gardner MJ. Means and their differences In: Altman DG, Bryant TN, Gardner MJ, eds. *Statistics with Confidence*. 2nd edn. Bristol: BMJ Publishing, 2000;28–35
16 Piscitelli SC, Formentini E, Burstein AH, Alfaro R, Jagannatha S, Falloon J. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. *Pharmacotherapy* 2002;**22**:551–6
17 Slain D, Amsden JR, Khakoo RA. Effect of High-dose Vitamin C on the Steady-state Pharmacokinetics of the Protease Inhibitor Indinavir in Healthy Volunteers. *43rd Interscience Conference on Antimicrobial Agents and Chemotherapy,* 14–17 September 2003, Chicago, IL (abstract A-1610)
18 DiCenzo R, Shelton M, Jordan K, *et al.* Coadministration of milk thistle and indinavir in healthy subjects. *Pharmacotherapy* 2003;**23**:866–70
19 Sandhu RS, Prescilla RP, Simonelli TM, Edwards DJ. Influence of goldenseal root on the pharmacokinetics of indinavir. *J Clin Pharmacol* 2003;**43**:1283–8
20 Gallicano K, Foster B, Choudhri S. Effect of short-term administration of garlic supplements on single-dose ritonavir pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 2003;**55**:199–202
21 Mills EJ, Wilson K, Foser BC, *et al. Milk Thistle and Indinavir: A Randomized Controlled Trial*. Toronto: OHTN Conference Proceedings, 2003
22 de Maat MM, Hoetelmans RM, Math t RA, *et al.* Drug interaction between St John's wort and nevirapine. *AIDS* 2001;**15**:420–1
23 Perry CM, Noble S. Saquinavir soft-gel capsule formulation. A review of its use in patients with HIV infection. *Drugs* 1998;**55**:461–86
24 NIH. *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Updated 1 August 2000* Office of Extramural Research, 2000 [www.grants.nih.gov/grants/funding/women_min/guidelines_update.htm] (accessed 25 May 2003)
25 Altman DG, Bland JM. Statistics notes. Treatment allocation in controlled trials: why randomise? *BMJ* 1999;**318**:1209