provide no information on the effect of these drugs in pregnancy.

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Prevention of nevirapine-associated rash

Sir—Andrew Carr and David Cooper (Oct 21, p 1423)[1] report on adverse effects of antiretroviral therapy. Hypersensitivity reactions can occur within the first 6 weeks of treatment with abacavir, amprenavir, or any non-nucleoside analogue. Skin reactions complicate nevirapine prescription in nearly 20% of patients, causing drug discontinuation in half of them. Carr and Cooper state that corticosteroids are not preventive, antihistaminics provide no proven benefit, and desensitisation might be risky, since nevirapine-resistant viruses can be selected quickly under subtherapeutic drug concentrations.

We have done a 2-year prospective trial of 459 individuals to compare the incidence of nevirapine rash after use of recommended standard doses (200 mg once daily for 2 weeks and 200 mg twice daily thereafter) or three alternative strategies: addition of loratadine 10 mg twice daily for the first 2 weeks; addition of prednisone 50 mg on alternate days during the first 2 weeks; and use of a slower escalating dose regimen, starting at 100 mg once daily for the first week, and increasing the dose by 100 mg weekly to the full daily dose of 200 mg twice daily at the fourth week. The incidence of rash and drug discontinuation in each group is shown in the table.

All the alternative regimens were more effective than the standard escalating dosing for reducing the frequency of nevirapine-associated rash. Moreover, the desensitisation strategy was pharmacokinetically safe since the induced metabolism of nevirapine by cytochrome is delayed after introducing the drug at lower doses.[2] Preliminary data from other trials show that nevirapine rash might not be reduced at all by corticosteroids,[3,4] although these studies recruited small numbers of individuals or did not record accurately mild skin rashes. Since protease-inhibitor-sparing regimens have become popular for the treatment of HIV infection, the appropriate management of rash, which is the leading reason for nevirapine discontinuation, is warranted.

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Sir—Andrew Carr and David Cooper[1] omit an important adverse effect of antiretroviral therapy: sexual dysfunction.[2,3]

In a survey, done by anonymous questionnaire distributed among 904 people receiving antiretroviral therapy in ten European countries, a decrease in sexual interest was significantly more frequently reported by men and women using protease inhibitors containing highly active antiretroviral treatment (HAART) than by those using regimens not containing protease inhibitors (40 *vs* 16%).[3] In the same survey, 34% of protease-inhibitor-experienced men reported a decrease in sexual potency compared with 12% of protease-inhibitor-naïve men.

Between September and November, 2000, at the outpatient HIV clinic of the Institute of Tropical Medicine, Antwerp, Belgium, we interviewed 17 consecutive men—15 (88%) homosexual and two (12%) heterosexual men—who developed sexual dysfunction after starting a protease inhibitor regimen containing HAART and who had switched at least 1 month previously to a regimen not containing a protease inhibitor. We excluded men with an obvious reason for sexual dysfunction, such as psychological factors, difficulties with the sexual partner, and so on. The mean age of participants was 46·5 years, the mean duration of protease-inhibitor treatment 30·2 months. In all patients, the protease inhibitors were switched to nevirapine and the median duration on nevirapine was 6·25 months.

16 (91·1%) participants had developed a decrease in sexual interest during protease-inhibitor treatment and 14 (82·4%) had developed difficulties in achieving an erection. 13 (81·3%) reported that their sexual interest increased after the switch (in eight [50%], sexual interest increased but did not normalise, in five [31·3%] sexual interest returned to a normal). In 11 (85%) the increase in sexual interest occurred within 1 month of the switch. 12 (86%) reported that their erectile function improved after their switch (in seven [50%] the ability to get an erection returned to normal). In nine (75%) men, this improvement was noted in the first month after the switch.

The fact that sexual dysfunction develops more often in people during protease-inhibitor treatment compared with those not taking protease inhibitors, and that sexual dysfunction in most individuals regresses or disappears after a switch in regimen, strongly suggests an association between protease inhibitors and sexual dysfunction. The reason for this effect is unknown. We propose that in clinical trials, quality-of-life questionnaires should include questions about sexual dysfunction and that in daily practice physicians

	Standard (n=166)	Antihistaminics (n=93)	p	Prednisone (n=93)	p	Desensitisation (n=107)	p
Rash	18·7%	8·8%	0·03	8·6%	0·02	11·2%	0·09
Withdrawal	8·5%	5·3%	0·3	4·3%	0·2	4·7%	0·2

Incidence of nevirapine rash with different interventions

should pay attention to this side-effect of HAART.

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Fibre supplementation

Sir—We are concerned that people will erroneously conclude that fibre supplementation increases the recurrence rate of colon polyps, as reported by Claire Bonithon-Kopp and colleagues (Oct 14, p 1300).[1] They measured adherence to fibre supplementation by self-reporting, assessed every 6 months by a standard interview validated in France, but not in the other nine countries, and by counting the number of unused fibre sachets returned.

Self-reporting, especially after counselling, generally yields unreliable information by over-reporting. Simple and inexpensive recording of weight and cholesterol were not done. A higher fibre diet would lower both. Finally, the 1999 Colon Cancer Prevention Program Project[2] concludes that the typical diet in more-developed countries, which provides about 10 g of fibre daily, plus a daily wheat bran supplement of 13·5 g decreases the recurrence rate of colon polyps. So even if participants in Bonithon-Kopp and colleagues' study took 3·5 g supplemental fibre daily, which is unlikely, the total fibre is still much less than that reported to be beneficial.

To support their conclusion, Bonithon-Kopp and colleagues reference two studies that also used self-reporting. People in the first study were asked to consume 13·5 g fibre supplements daily. No weight or cholesterol was recorded. Similarly, compliance, after counselling, was measured by the number of filled supplement boxes returned.[3] Participants in the second study were asked to eat a 20% fat, 18 g fibre diet daily that should have, but did not, change their weight and cholesterol.[4]

The US National Cancer Institute suggests that development of colorectal cancer takes decades and that an intervention of a few years is not long enough; nutritional factors influence critical events at molecular, cellular, or tissue levels in colorectal-cancer formation, well before polyps are formed; and recurrent polyps are generally small—dietary changes might affect only the growth of small polyps into large polyps or large polyps into invasive cancers (http://rex.nci.nih.gov/massmedia/pressreleases/polyp_prev_diet.html).

The conclusions of Bonithon-Kopp and colleagues are suspect because there is no objective evidence of adherence. Motivation of people to adhere to a low-fat, high-fibre diet is difficult especially when the media report erroneous conclusions.[1,3,4] On the basis of hundreds of clinical studies, international governmental agencies and seven international Consensus statements, there is little doubt that a high-fibre diet lowers the risk of colorectal cancer.[5]

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Authors' reply

Sir—The main conclusion of our randomised intervention trial was that supplementation with ispaghula husk (a mucilaginous fibre) in patients with resected colorectal adenomas is associated with a significant increase in the risk of adenoma recurrence. By contrast, calcium supplementation showed a slight non-significant, beneficial effect on adenoma recurrence. Whichever way of assessing treatment adherence was used, our results would have been biased towards the null hypothesis of a lack of treatment effect on adenoma recurrence. Thus, poor adherence could explain the small beneficial effects of calcium treatment. It cannot explain the significant adverse effects of ispaghula husk supplementation. Consequently, the lack of objective measurement of compliance with fibre supplementation cannot be considered as a valid argument for refuting our results.

Weight and cholesterol measurements might be useful indicators of adherence in intervention studies based on dietary changes. In our study, these measurements would have been of little interest. Ispaghula husk does not lower weight and blood cholesterol and recruited patients received no dietary counselling. The objective assessment of calcium adherence (1-year faecal calcium concentrations) included in our trial was in good agreement with self-reported adherence. This finding suggests that compliance assessment, based on self-reporting and counting unused sachets, provides fairly reliable information.

We used an amount of ispaghula husk that was recommended to obtain stool bulking without major side-effects likely to affect treatment adherence. Because of large differences in their nature and chemical composition, a much larger amount of wheat bran is needed to obtain similar effects on stool bulking. Given the adverse effects seen with 3·5 g ispaghula husk, it would be somewhat paradoxical to expect beneficial effects with larger amounts.

Charles Simone and colleagues' reference 2, cited in support of his opinion, is erroneous. In fact, this reference relates to a progress report of the Arizona Study, which has concluded that a dietary supplement of 13·5 g of wheat bran fibre did not protect against colorectal adenomas.[1] Our results cannot be interpreted as evidence that a high-fibre diet leads to a high risk of colorectal cancer, as has been suggested by some influential media. The only firm conclusion that could be drawn from our trial is that ispaghula husk supplementation increases the risk of small adenoma recurrence in patients who have a history of adenomas. We cannot exclude a beneficial effect of other types of fibre. Furthermore, as noted by Simone and colleagues, colorectal carcinogenesis is a long multistep process. Fibre supplementation might have to last longer to have beneficial effects on carcinogenesis. An alternative, as we mention, is that fibre may be effective only on the later stages of