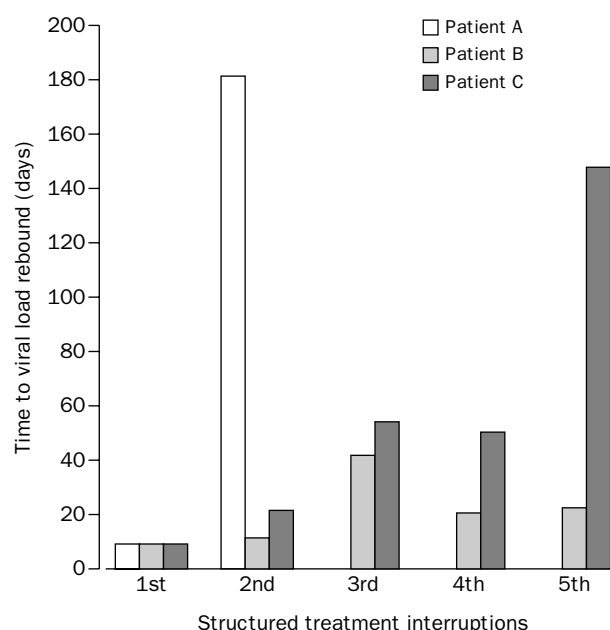




Time to viraemia rebound

Number of days with viral load consecutively below 5000 copies/mL during sequential structured treatment interruptions.

264/μL, and 880/μL). Patients were scheduled to be treated for 3 weeks followed by 1 week's structured treatment interruption to mimic the case of the Berlin patient.⁴ Subsequently, patients were treated in consecutive cycles of about 3 months treatment followed by structured treatment interruption. Viral load was monitored weekly when treatment was withheld. After the second treatment interruption, treatment was scheduled to be restarted when viral load rose above the threshold of 5000 copies/mL. Patient A maintained a load of around 2000 copies/mL (about 1 log lower than baseline) for 6 months during the second treatment interruption (figure). The load then rebounded above 5000 copies/mL and the patient restarted treatment. The time to rebound increased in patient B between the second and the third interruptions but not during the fourth and fifth interruptions. In patient C, the time to rebound increased during subsequent interruptions, and viral load remained below 5000 copies/mL (2 to 3 logs lower than baseline values) as long as 5 months during the fifth structured treatment interruption. The rates of HIV-1 RNA rebound (table) showed different patterns in each patient. In patient A, an exceptionally low rate was recorded at the second structured treatment interruption. The rate was about 1 log lower than previously reported after

interruption of HAART.² The rate of rebound in patients B and C during the second treatment interruption was similar to that of patients interrupting HAART.² The rate did not change in patient B during the subsequent treatment interruptions. In contrast, in patient C, the rate of rebound progressively decreased from the second to the fifth treatment interruption to values as low as those seen in patient A. Importantly, antiretroviral treatment rapidly reduced viraemia below the limit of detection after each restart. The CD4-cell counts at the end of the follow-up were 690/μL, 435/μL, and 630/μL, respectively.

These results suggest that hydroxycarbamide-based combinations can be interrupted and successfully restarted several times. HIV-1 could be controlled after each treatment restart, suggesting that no drug resistance emerged after as many as five consecutive treatment discontinuations. A lower viral load set point was induced and maintained for several months in two of three patients. Changes in HIV-1 kinetics and immune responses could account for the results. One patient, however, did not show persistent control of HIV-1 in the absence of treatment. Thus, control of HIV-1 infection may require several structured treatment interruptions in some patients and may not be successful in others.

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Paclitaxel hypersensitivity reactions related to bee-sting allergy

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Patients with a history of bee-sting allergy may have a higher risk of a hypersensitivity reaction with paclitaxel treatment. We suggest careful screening of patients for allergies.

Severe acute hypersensitivity reactions to paclitaxel, such as respiratory distress, bronchospasm, hypotension, diaphoresis, and angio-oedema, were initially seen in 2–8% of patients receiving the drug.^{1,2} Most reactions occur within minutes and are due to IgE and other vasoactive substances stimulated by paclitaxel (and not the substance in which it is suspended).³

One of our clinical nurse specialists observed that patients who reacted to paclitaxel also tended to report an allergy to bee stings. Therefore, we did a retrospective

	Rebound rate (log/day)	Change in viral load (copies/mL)*	Change in CD4-cell count (/μL)*
Patient A			
2nd interruption	0.027	6870	182
Patient B			
2nd interruption	0.118	1098†	96
3rd interruption	0.127	11 637	–78
4th interruption	0.267	13 926	36
5th interruption	0.233	8124	–225
Patient C			
2nd interruption	0.264	5605	–97
3rd interruption	0.097	8199	21
4th interruption	0.070	9907	–42
5th interruption	0.036	5831	30

*Value minus value after rebound above 5000 copies/mL before interruption.

†Treatment restarted at patient's request.

HIV kinetics during sequential structured treatment interruptions

Allergy	Cases (n=19)	Controls (n=38)	p
Any	15	20	0.054
None	4	18	0.054
Bee sting	7	0	0.001
Animal	3	0	0.012
Plant	4	2	0.07
Drug	12	20	0.35

Allergy histories

case-controlled chart review of patients given paclitaxel between 1995 and 1998 at the University of Wisconsin Hospital and Clinics. 19 patients with a documented anaphylactic reaction to paclitaxel and 38 controls were chosen. Allergy history was also obtained from chart review. Controls were matched for age and year of treatment. Proportions of patients and controls with allergies (to bee sting or to any substance), were compared by the χ^2 test.

There was a highly significant difference between patients and controls in history of bee-sting allergy and a significant difference in animal allergies, but not for other plant or drug allergies (table). The mean dose of paclitaxel administered before anaphylactic reaction was 4.26 mg (range 0.62–9.10). Patients had been pretreated in the usual way with dexamethasone, diphenhydramine, and cimetidine.⁴ Those who had experienced hypersensitivity reactions were admitted for observation and treatment. Six of the 19 patients had been successfully retreated with paclitaxel after 24 h of intravenous steroid dosing.

The consequences of a hypersensitivity reaction to paclitaxel include: the cost of drug wastage US\$2900–4900 per cycle; extra hospital admissions; and psychological trauma. Before treatment with paclitaxel, patients should be asked in detail about previous allergies. A test dose of paclitaxel should be given to patients with a history of allergy, especially to bee stings. If the patient reacts to the test dose, we would recommend premedication with oral dexamethasone for 48–72 h.

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Neuroleptic malignant syndrome after venlafaxine

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A patient developed neuroleptic malignant syndrome after a single dose of venlafaxine with trifluoperazine treatment. A dopamine-inhibition effect induced by one dose of venlafaxine may have augmented dopamine-receptor inhibition by trifluoperazine.

A 44-year-old man with depressive symptoms was prescribed venlafaxine, 75 mg once a day, in addition

to trifluoperazine 1 mg, three times a day, prescribed 10 years previously as a anxiolytic. 12 h after the first dose of venlafaxine he presented with profound anxiety and malaise. The patient was sweating profusely and showed tremor and rigidity. His blood pressure fluctuated between 130/80 mm Hg and 165/100 mm Hg, with a pulse of 163 beats per min, temperature 38.3°C, and a respiratory rate of 25 breaths per min. Haemoglobin, platelets, urea and electrolytes, results of liver function test, blood sugar, midstream urine, blood culture, and urine myoglobins were within normal limits. However, the patient's creatine phosphokinase concentration was high (11 320 IU/L) and his white-cell count was $23.5 \times 10^9/L$ ($20.8 \times 10^9/L$ neutrophils).

Neuroleptic malignant syndrome (NMS) was diagnosed. A single dose of 70 mg dantrolene was given, and 15 mg bromocriptine twice daily was prescribed for 48 h. All psychotropic medication was discontinued. 24 h after admission the patient's vital signs had returned to normal and he recovered completely. Trifluoperazine was reintroduced uneventfully.

The characteristic features of NMS may be mimicked by the serotonin syndrome (caused by drugs that increase serotonin activity) with changes in cognition, behaviour, function of the autonomic nervous system, and neuromuscular activity.¹ However, in this patient the pyrexia, muscular rigidity, tremor, labile blood pressure, raised creatine phosphokinase, and neutrophilia were indicative of NMS. A possible explanation is a pharmacokinetic interaction in which venlafaxine inhibited the metabolism of trifluoperazine by inhibition of CYP2D6. However, this mechanism is unlikely because venlafaxine is a weak inhibitor of CYP2D6.² We had no serum from our patient to test this idea. A direct effect of venlafaxine on dopamine neurotransmission is unlikely because long-term venlafaxine administration increases dopamine-receptor responsiveness,³ the opposite effect to that causing NMS. Conversely, increased dopamine concentrations found in experimental hepatic encephalopathy in rats were abrogated by a single dose of venlafaxine, which suggested that an initial decrease in dopamine had occurred.⁴ Therefore, the NMS in this patient may have developed because of the pharmacodynamic interaction of a dopamine-inhibition effect induced by one dose of venlafaxine, which augmented dopamine-receptor inhibition by trifluoperazine.

Extrapyramidal side-effects including NMS have been reported with selective serotonin-receptor inhibitors (SSRIs); these side-effects may involve serotonin's inhibitory action on dopamine activity.⁵ Venlafaxine (not an SSRI) selectively inhibits the presynaptic reuptake of serotonin as SSRIs do. However, an adverse reaction by this mechanism is unlikely because extrapyramidal signs have not been reported after venlafaxine overdose.

A small number of cases of NMS have been reported to Wyeth Laboratories (personal communication) after the introduction of venlafaxine to concurrent antipsychotic medication (risperidone, olanzapine, and molindone).

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