vitritis in two of the five cases and the hypothesis given the presence of HAART does allow widespread availability of the potent undocumented. We reported five natural history of specific AIDS-related opportunistic infections such as CMV retinitis who had in common clinical presentation soon after HAART regimens were initiated, and at a time when previously undetectable CMV lymphocyte counts had risen (in response to HAART) to values of 200 cells/μL or greater. These values are much higher than previously reported in patients with this AIDS-related complication. We also noted in a prospective clinical trial a temporal trend toward higher absolute CD4 counts occurring in patients with CMV retinitis diagnosed after the widespread availability of the potent HIV protease inhibitors indinavir and ritonavir that was not seen before. These objective observations were the basis of our report.

We, in our report, and your correspondents speculate about what these findings mean. Uthayakumar and colleagues and Stein and colleagues provide additional observations to support the hypothesis that HAART does allow reconstitution of protective CMV-specific immunity. Certainly, our observations are consistent with this hypothesis, given the presence of vitritis in two of the five cases and the subsequent prolonged time without retinitis progression in all five. In fact, since publication of our report, ophthalmological examinations indicate that after 8–17 months of treatment, none of these five patients have yet to show progression of retinitis. We speculated, like Stein, that these cases could have had subclinical CMV retinal infection that was unmasked by a HAART-induced immune inflammatory response. At scientific meetings, others have also reported CMV retinitis developing in the first 2 months after the institution of HAART, but not in subsequent months.1 One would expect retinitis to occur at an increasing rather than decreasing frequency after HAART-induced absolute CD4 count rises if these increases did not represent improved functional immunity. On the other hand, Mitchell and colleagues’ hypothesis that functional CMV immunity takes several months to be restored and that of Carr and Cooper that improved CMV immunity may be anatomically restricted and not penetrate into the eye are equally plausible.

However, to put these speculations in perspective, we note that neither we nor any of your correspondents have any direct evidence proving that HAART does or does not allow reconstitution of clinically meaningful CMV-specific protective immunity in vivo. Searching for such direct evidence should now be a high priority objective of clinical research.

In response to specific questions raised, first, none of the patients described were receiving anti-CMV monoclone antibody at the time that CMV retinitis was diagnosed. Second, routine ophthalmological monitoring began only after retinitis was diagnosed. Third, the nadir CD4 counts reported, ranging from 14 to 82 cells/μL, were obtained 1–17 weeks before HAART was initiated. And last, of the patients enrolled in ACTG protocol 266 between July, 1995, and August, 1996, four of 16 whose baseline absolute CD4 count was 50 cells/μL or greater had initiated ritonavir at 8 weeks before enrolment and three of these 16 had initiated protease inhibitor therapy greater than 8 weeks before enrolment.

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COLD EXPOSURE AND WINTER MORTALITY IN EUROPE

Sir—In the Eurowinter Group’s (May 10, p 1341) report on cold-related mortality in warm and cold regions of Europe, the increase in mortality with given fall of temperature in regions with warmer winters are associated with cooler homes, less appropriate clothing, and decreased activity outdoors. However, as Amy Sperber and Simon Weitzman state in their commentary,1 the causal and temporal relation between observed risk factors (eg, living-room temperature) and cold-related mortality remains controversial and many questions remain to be elucidated. The mean percentage increase in mortality with each 1°C fall from 18°C was the lowest in Finland and highest in Athens; however, the striking differences in mortality with given fall of temperature between regions with virtually identical mean winter temperature (London 7·6°C and north Italy 7·7°C; 1·37 and 0·51% mortality increase, respectively), indicate a more complex relation.

A single recording of living-room temperature during the interview is not representative for the average indoor temperature during winter and does not reflect circadian fluctuations in ambient temperature. Were additional cold-protective measures during the night (eg, use of an electric blanket) or differences in insulation of housing units investigated? The observed differences in indoor heating conditions, clothing, and outdoor physical activity during cold exposure between residents of cold and warm regions can partly account for the lower mortality in the former group. On the basis of differences in shivering and sweating in the cold, more adequate acclimatisation to cold exposure probably contributed to the lower mortality in colder regions.

The Eurowinter Group analysed several risk factors for cold-related mortality, and emphasised the importance of adequate modulation of clothing and environmental conditions. Other relevant factors that affect the ability to withstand cold stress and its complications include adequate intake of (warm) food and drinks, subcutaneous fat content, nutritional state, musculature, extremes of age, physical fitness, cold awareness, underlying medical diseases, use of drugs and alcohol, as well as wind velocity and air humidity.4,5 Furthermore, both individual and clinical experience with cold-related disorders can greatly affect survival outcome.

Efficient thermoregulatory behaviour is pivotal to survival in cold regions and to reduction of cold-related morbidity.
and mortality, particularly in patients with impaired autonomic thermoregulation. Depending on environmental conditions and other risk factors, failure of autonomic or behavioural thermoregulation can cause fluctuations of core temperature or overt hypothermia or hyperthermia with potentially lethal consequences. Even small decreases in core temperature can induce striking changes in cardiovascular, (neuro)physiological, and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; therefore, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and immunological responses; hence, core temperature should be taken into account in the analysis of cold-related disorders. Since...