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-retinitis, We speculated like Stein3 indicating that after 8-17 months of ophthalmological examinations retinitis progression in all five. In fact, these findings mean. Uthayakumar correspondents speculate about what were the basis of our report. before. These objective observations prospective clinical trial a temporal much higher than previously reported initiation, and at a time when soon after HAART regimens were unusual cases of CMV retinitis who related opportunistic infections such 5 Stein DS, Drusano GL, Modeling of the combination antiretroviral therapy (also described as HAART) on the immune system and CD4 lymphocyte counts in patients with AIDS. J Infect Dis 1991; 164:486-95. 5 Stein DS, Drusano GL. Modeling of the change in CD4 lymphocyte counts in patients before and after administration of the human immunodeficiency virus protease inhibitor indinavir. Antimicrob Agents Chemother 1997; 41:495-53.

**Author's reply**

**Sir**—The effect of chronic potent combination antiretroviral therapy (also described as HAART) on the natural history of specific AIDS-related opportunistic infections such as CMV retinitis is largely undocumented. We reported five unusual cases of CMV retinitis who had in common clinical presentation soon after HAART regimens were initiated, and at a time when previously low absolute CD4 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. HAART was diagnosed 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 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. One would expect retinitis to occur in 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 monoclonal 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 266 between July, 1995, and August, 1996, four of 16 whose baseline absolute CD4 count was 50 cells/μL or greater had initiated protease inhibitor therapy 8-12 weeks before enrolment. Three of these 16 had initiated protease inhibitor therapy greater than 8 weeks before enrolment.

Mark A Jacobson
University of California San Francisco AIDS Program, San Francisco General Hospital, San Francisco, CA 94110, USA


Cold exposure and winter mortality in Europe

Sir—In the Eurowinter Group's (May 10, p 1341)1 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,2 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.4,4 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.4'5 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.3'5 Even underlying medical disorders were not relation between these variables evaluated in the Eurowinter study, the disorders. Since core temperature and core temperature should be taken into account in the analysis of cold-related disorders. Since core temperature and underlying medical disorders were not evaluated in the Eurowinter study, the relation between these variables and cold-related mortality remains uncertain.

Marius A MacKenzie
Department of Medicine, Division of Hematology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, Netherlands

1 The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. Lancet 1997; 349: 1341-46.


Sir—The Eurowinter Group's report on cold exposure and winter mortality,1 presents important findings, but the investigators draw inferences beyond the limits of the data and study design. First, in an ecological study of this sort individual risk factors are not related to individual outcomes; thus, causality cannot be proved. To demonstrate associations in an ecological study, it is essential that the populations used should be as similar as possible with respect to time and population characteristics. We assume that quota sampling was used to obtain the survey sample in this study, although the methods are not made explicit. This method is likely to have resulted in an unrepresentative population. For example, population groups unavailable at the time of survey, (eg, shift workers, and those without permanent residence) may not have been included. Such potential sources of bias have not been assessed in this study.

Second, the study is limited in its approach to the explanation of potential protective and risk factors for cold-related deaths. For example, it would have been helpful to take into account race, family history, diet, and other cultural factors. Genetic variation in both risk factors for cardiovascular disease and adaptation to cold may affect mortality outcomes. In addition, although the wearing of hats may be an important protective measure, it is likely that hat wearing is determined by other cultural factors as well as outdoor temperatures.

This is an important research study that has highlighted significant associations between mortality and cold exposure, but the data and study design do not support conclusions about causality. The logical next step should be prospective studies of the relation between cold exposure and mortality. Such studies could also examine the effects of climate on morbidity, which may be equally important.

Kath Mathar, Dave Cooper, Phil Janson, *Martin White
Department of Epidemiology and Public Health, School of Health Sciences, The Medical School, University of Newcastle, Newcastle upon tyne NE2 4HH, UK

1 The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. Lancet 1997; 349: 1341-46.

Sir—The report by the Eurowinter Group1 presents fascinating evidence that the association between low temperature and mortality is not constant across Europe. The finding that the slope of the association is steeper in countries with warmer winters may have implications for interpretations of studies of the association between daily mortality and air pollution. Although most of these studies found a positive association, even after statistically controlling for daily mean temperature, there are some inconsistencies with respect to the strength of the association. We suggest that part of this inconsistency between studies may be attributable to residual confounding by temperature. The argument is as follows: (1) daily temperature is inversely correlated with daily concentrations of sulphur dioxide and particulates; (2) temperature is inversely related to mortality; and (3) crude (bivariate) association between pollution and mortality is substantially attenuated by adjustment for temperature, suggesting a confounding role of temperature. It is plausible that the use of a single daily value of temperature may not be sufficient to remove entirely all the effect of temperature. Additionally, any residual confounding by temperature would be stronger in southern countries where

APHEA centre*  Average winter temperature (°C)

- Central Europe
- Wroclaw (Poland) 1-3
- Lodz (Poland) 1-7
- Poznan (Poland) 1-7
- Wroclaw (Poland) 1-3
- Bratislava (Slovakia) 0-9

- Western and southern Europe
- Barcelona (Spain) 11-3
- Athens (Greece) 17-4
- Cologne (Germany) 4-0
- Lyon (France) 3-3
- Paris (France) 5-1

* Only where mortality was studied. 1 Annual mean.

Average winter temperatures in various European countries

the slope of the association between temperature and mortality is steeper. As a consequence, the effects of pollution would seem stronger in countries with warmer winters.

This is the case in the APHEA project which analysed daily mortality and air pollution in several European countries. In this project, the effect of air pollution was apparent in centres in western and south Europe, but was weak or absent in central Europe.2 Explanation for this inconsistency is not clear. We speculate that the differences in the effects of pollution between the regions can be caused by differences in winter temperatures, since average winter temperatures in central Europe were substantially lower than in the west or south (table). Unfortunately, the effects of daily concentration of pollutants on deaths were not presented in identical units in the APHEA reports, and this speculation cannot be directly examined in published data. However, this is a testable suggestion that may also be relevant for studies outside Europe.

Martin Bobak
Department of Epidemiology and Public Health, University College London, London WC1C 8BT, UK

1 The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory mortality, and all causes in warm and cold regions of Europe. Lancet 1997; 349: 1341-46.


Authors' reply

Sir—Marius MacKenzie asks whether the large differences in winter mortality that we reported between different regions of western Europe were attributable to the concomitant differences that we reported in cold exposure. Our study did deal with the main alternative possibilities that he suggests. Variations in age structure were avoided

Vol 350 • August 23, 1997