Median HDL cholesterol concentrations (and ranges) (mmol/l) before and after treatment with cimetidine or ranitidine

	Before treatment	After treatment	Significance
HDL cholesterol:			
Cimetidine	1.24 (0.91-1.75)	1.39 (0.87-2.19)	NS
Ranitidine	1.08 (0.85-2.20)	1.07 (0.84-2.23)	NS
HDL ₂ cholesterol:			
Cimetidine	0.21 (0.04-0.57)	0.42 (0.11-0.85)	p < 0.01
Ranitidine	0.29 (0.06-1.24)	0.26 (0.12-1.34)	NS
HDL ₃ cholesterol:			
Cimetidine	0.97 (0.85-1.18)	0.90 (0.76-1.14)	NS
Ranitidine	0.81 (0.63-0.96)	0.83 (0.66-1.01)	NS

Conversion: SI to traditional units—Cholesterol: 1 mmol/l $\approx$ 38.6 mg/100 ml.

with ranitidine, and concentrations of HDL and HDL₃ cholesterol were not significantly different after treatment with cimetidine. HDL₂ cholesterol concentrations were significantly raised, however, after treatment with cimetidine ($p < 0.01$) (figure).

Discussion

An increase in HDL₂ cholesterol can be explained either by an increase in the secretion of new particles into this density

range or by changes in metabolism leading to accumulation of HDL₂ without the need for de novo synthesis. We suggest two possible mechanisms: firstly, cimetidine has antiandrogenic properties, and HDL is related to testosterone concentrations⁴; secondly, cimetidine might activate lipoprotein lipase or lecithin cholesterol acyltransferase, both of which play a part in converting HDL₃ to HDL₂. The true explanation for these changes remains unclear, but, in view of the widely reported inverse relation between HDL₂ concentrations and accelerated ischaemic heart disease, this finding is potentially useful. Further studies are being undertaken to examine the mechanism of this effect.

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Seroepidemiology of HTLV-III antibodies in a remote population of eastern Zaire

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Abstract

A human retrovirus—human T cell lymphotropic virus-III (HTLV-III)—has recently emerged as the probable cause of acquired immunodeficiency syndrome (AIDS). In May 1984, 250 outpatients at a hospital in a remote area of eastern Zaire were surveyed for AIDS type illnesses and the prevalence of antibodies against HTLV-III determined by an enzyme linked immunosorbent assay using disrupted whole HTLV-III virus as the antigen. No clinical cases of AIDS were diagnosed among these patients.

Overall, 31 (12.4%) had clearly positive ratios (≥ 5.0) and a further 30 (12.0%) had borderline ratios ($3.0 < 5.0$). Western blots of serum samples from subjects with antibodies yielded bands consistent with HTLV-III as found in American patients with AIDS and members of groups at risk of AIDS. The prevalence of antibody was highest in childhood ($p = 0.02$); among adults prevalence rose slightly with age. HTLV-III antibodies were more common among the uneducated ($p = 0.006$), agricultural workers ($p = 0.03$), and rural residents ($p = 0.06$), but the Western blot bands were generally weak in this group. By contrast, one urban resident had strong bands.

The relatively high prevalence of antibodies among the rural poor in this area of Zaire suggests that HTLV-III or a closely related, cross reactive virus may be endemic in the region. A different natural history of infection, perhaps in childhood, may also explain the findings.

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Introduction

Investigators have recently described a retrovirus that appears to be a causative for acquired immunodeficiency syndrome (AIDS).¹⁻⁴ This agent, a member of the human T cell lymphotropic virus (HTLV) family, has repeatedly been isolated from American and European patients with AIDS and subjects at risk of AIDS, most of whom also had detectable antibody against the agent.⁵⁻⁶ Prospective studies have confirmed that those with antibodies are more likely to develop AIDS.⁷⁻⁸ By contrast, fewer than 1% of healthy American blood donors have antibodies to the agent.^{5-8a}

AIDS has also been described in Africans⁹⁻¹³ and in Europeans who had a history of travel in Africa but no other risk

factors.^{14 15} Most of the African cases have come from central Africa,¹⁰ and among those recently described from urban areas of Kinshasa most of the patients were found to have antibody to the lymphadenopathy associated virus (LAV virus), an identical or closely related human retrovirus.¹⁶ Thus the virus is present in Africa, but no surveys of African populations have described the seroepidemiology of antibodies to this agent in an African population. In May 1984 we conducted a survey of an African population resident in eastern Zaire, a remote rural area with little exposure to international travellers, in order to document the presence of clinical AIDS and determine the prevalence of antibodies against HTLV-III and the factors related to seropositivity.

Methods

This survey was conducted at FOMULAC Hospital at Katana, Kivu District, in eastern Zaire. This hospital, of 700 beds, is staffed jointly by six to eight physicians from the Ministry of Health, government of Zaire, and the Medical Foundation of the University of Louvain for Central Africa. It is the primary medical facility for a population of 300 000 resident in this rural area. In addition, many people from Bukavu, the nearest city (30 km), attend hospital clinics. All patients attending the adult walk in clinic during the study period were interviewed and measured for height and weight. In order to diversify the study population, children (5-15 years) from the paediatric outpatient clinic and adults from the private (fee paying) service were similarly enrolled. Symptoms of illness were subsequently categorised as acute or non-acute on the basis of evaluation by a physician (RJB). These patients (or a responsible parent) were then asked to donate blood for our studies. Hospital wards were surveyed for clinical cases fitting the description of AIDS as recorded in Kigali (Rwanda)¹² and Kinshasa (Zaire)¹³ and the medical staff questioned about their experience of such cases. The design of the study was approved in advance by the director of the hospital, the director of the Institute of Tropical Medicine (Antwerp, Belgium), and the ethics committee of the National Cancer Institute (Bethesda, Maryland).

Serum from participants was stored at -20°C until departure (less than three weeks in all cases) and thereafter at -70°C . Testing was done using disrupted HTLV-III-H9 virus¹ as the antigen by an enzyme linked immunosorbent assay (ELISA).^{5 17} Antibody was considered to be present if the ratio between sample and background was 5.0 or greater and to be borderline if between 3.0 and 5.0. Western blots¹⁸ were performed under code on a sample of ELISA negative and positive sera. Detection was enhanced by using an unlabelled antibody-peroxidase procedure with sensitivity to immunoblots of HTLV-III antigens.¹⁹ Tests of significance (χ^2 unless indicated otherwise) were used to compare antibody positive with antibody negative subjects, excluding subjects with borderline ratios.

Results

During the month of the survey no patient with features suggesting AIDS was observed at the hospital. Although familiar with the reports of cases of AIDS from western Zaire, the hospital staff could not recall having seen any patient with AIDS like features. One case of cryptococcal meningitis had been diagnosed two years earlier at a neighbouring hospital, although the diagnosis of AIDS had not been considered; no follow up data were available on the patient.

Of 317 patients asked to donate blood, 258 (81.3%) agreed; in four cases, however, results were not available. Those not participating in the study were similar to participants in age and sex, education, occupation, location of residence, and category of symptoms. Four participants were Belgian residents attending the private service. They had lived in the region for one, seven, 13, and 34 years, and all were seronegative for HTLV-III antibody. They were excluded from further analysis.

The average age of the remaining 250 participants was 31.9 (SD 12.7) years, and the range 8-78 years; 140 (56%) were female. Of the 233 adults, 107 (45.9%) were in agricultural jobs, 87 (37.3%) were in other trades, 28 (12.0%) were students, and 11 (4.7%) were unemployed. Ninety six of the adults (41.2%) had no schooling. Two thirds of the subjects lived in small villages or in rural huts, and the rest came from Bukavu. Women were significantly more likely than men to be agricultural workers ($p=0.0001$) and uneducated ($p=0.01$) but

there was no significant difference in location of residence. The Shi people were the most numerous in the region and accounted for most (78.0%) of the study population.

Figure 1 shows the distribution of the ratios. Overall, 31 subjects (12.4%) had antibody against HTLV-III, 189 (75.6%) had no such antibody and 30 (12.0%) had ratios in the borderline range between 3.0 and 5.0. With the exclusion of those with borderline ratios, 12.6% of the adults and 35.6% of the children were seropositive ($p=0.02$). There was, however, a small increase with age after childhood (fig 2) and no significant trend by age overall. Prevalence of antibody did not differ significantly by sex. Of the adults with no schooling 17/84 (20.2%) were seropositive, compared with 9/113 (7.4%) of those with any schooling (average 7.4 years) ($p=0.006$). Agricultural workers were also significantly more likely to be seropositive (18/92 (19.6%) positive) than those in trade occupations and unemployed (7/85 (8.2%) positive; $p=0.03$). Rural residence was also weakly associated with seropositivity ($p=0.06$).

FIG 1—Distribution of ratio results for HTLV-III, as tested by ELISA method comparing sample sera with negative reference sera. Ratios ≥ 5.0 positive, $3.0 < 5.0$ borderline, < 3.0 negative on basis of comparisons with Western blot data.

FIG 2—Distribution of positive (ratio ≥ 5.0) and borderline (ratio ≥ 3.0) results of HTLV-III testing by age groups.

Prevalence of antibody also correlated with lower weight among adults. The average weight was 55.1 kg and the average height 159 cm. Weight did not differ significantly by sex, but men were an average of 8 cm taller than women ($p=0.0001$). After adjusting for age, sex, and height in a linear regression model lower weight was still an important variable in risk of seropositivity ($p=0.03$). With additional adjustment for agricultural employment and lack of education lower weight remained weakly associated with increased risk of seropositivity ($p=0.06$).

There was no correlation between symptoms of illness (acute versus non-acute or specific complaints leading to the outpatient visit) and presence of antibodies against HTLV-III. None of the outpatients had clinical conditions suggesting AIDS.

Western blots detected antibodies against HTLV-III viral components in eight out of eight subjects with ratios of greater than 10.0, four of six subjects with ratios of greater than 5.0, and one of nine subjects with ratios of less than 3.0. The subject with the highest ratio (21.5) was a 20 year old woman student from Bukavu who presented with acute onset gastroenteritis. In this patient the pattern of Western blotting was strongly positive for all the bands seen in patients with AIDS (p24, p41, p61). In the other subjects bands were relatively weak.

Discussion

The origins of a virus causing AIDS have been the subject of considerable speculation. Several investigators have suggested an African origin. Favouring this hypothesis are the reports of cases among Europeans with histories of travel to Africa well before the AIDS epidemic^{14 15} and the recognition of African cases with no admitted connection to groups at risk of the disease.⁹⁻¹³ Arguing that the AIDS agent is new in Africa was the sudden appearance of African cases in Europe only in 1980 and later,¹⁰ temporally coincident with the AIDS epidemic in the United States rather than earlier. Moreover, African cases in Africa appear to be increasing in a manner parallel to that of epidemic AIDS in America and Europe.^{12 13} Finally, a recent report suggested that Kaposi's sarcoma of the aggressive variety—a form often seen among homosexual men with AIDS in America and Europe—suddenly became epidemic in Zambia in 1983.²⁰ Kaposi's sarcoma is endemic in this region of Zaire,²¹ but no change in the incidence or type of Kaposi's sarcoma has been observed at FOMULAC Hospital, and the cases of Kaposi's sarcoma were not associated with HTLV-III.^{21a} None of the cases seen at FOMULAC Hospital showed features suggestive of the epidemic, aggressive cases of the type described in Zambia.²⁰

We found a high prevalence of antibodies against HTLV-III in this remote, rural population of eastern Zaire, which, if provoked by infection with HTLV-III, suggests that HTLV-III is unlikely to be new in this part of Africa. Factors influencing the likelihood of seropositivity were lack of education, agricultural employment, and rural residence, all suggesting that seropositivity is more common among the rural poor. In addition, people of lower weight appeared more likely to be seropositive, and if lower weight is a function of poverty in this environment it may be that the poorer of the poor are most at risk.

While antibodies against HTLV-III appear to be relatively common in this population, AIDS like illness has not been diagnosed. Recognition of AIDS among Africans may be limited, however, because of lack of experience with the range of clinical manifestations that this disease may have in areas with different opportunistic infections and in subjects infected at a young age. African cases have generally been in adults with the types of infection also seen among Europeans and Americans with AIDS. At FOMULAC Hospital no case of AIDS has ever been identified, although patients in two of the cases identified in Kinshasa were said to have come from Bukavu (de Feyter, personal information). Among the subjects with antibodies in this survey there was no correlation with any symptoms of illness or acute or non-acute health complaints, suggesting that these subjects were not ill with any of the AIDS related health problems described in current epidemics at the time of the survey. Thus if antibodies indicate prior exposure to HTLV-III, this population must have had and survived HTLV-III infection without lasting health problems.

There are several possible explanations. The greater prevalence of HTLV-III among children in this study might support a hypothesis in which the adult population has been exposed to HTLV-III infection in childhood, with some of the children who were infected being lost from the study population. An extension would be that the influx of an infected rural population (adapted biologically to the virus) into an urban area with a pool of susceptible, more affluent adults created new opportunities for the virus to cause illness in urban adults and the epidemic appearance of the disease in Africa. Many of the recognised cases have been in noticeably wealthy people, although this may well be a function of better access to medical facilities and diagnosis. In this regard the 20 year old student with strong bands on Western blots may be an example of a recently infected urban resident, whereas those with weaker bands, generally rural residents, may have had infection long before. In a setting

of high mortality in childhood, particularly from infectious diseases, cases of AIDS in children may well go unrecognised.

The possibility of non-specific results must be considered, since a high frequency of non-confirmed ELISA positivity against a related human retrovirus, HTLV-I, was found in subjects from Ghana, west Africa.²² Nevertheless, the correlation between Western blotting and ELISA results for HTLV-III in this study was excellent. The bands observed in these cases were generally weak, but they did correspond to proteins of the size and characteristics of the HTLV-III antigens precipitated by AIDS and seen in patients at risk of AIDS. This reactivity suggests that the provoking agent was HTLV-III or a highly cross reactive virus.

With regard to the latter possibility, the assay may be measuring responses to a similar and cross reactive virus that does not have the pathogenicity of the AIDS related HTLV-III. Such a virus might be the ancestor from which a new variant, pathogenic AIDS related HTLV-III, has recently mutated, or it might be another new member of the family of human retroviruses. Isolation and characterisation of the agent from healthy members of this population will be necessary to compare it with the virus causing AIDS.

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