

# Serum IgE and human immunodeficiency virus (HIV) infection

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*Human immunodeficiency virus infection is characterized by a progressive depletion of helper T-lymphocytes and, like allergic diseases, is associated with altered T cell regulation. Total serum IgE was measured in 67 infected male subjects, 27 uninfected heterosexual male subjects, and 18 uninfected homosexual male subjects. The mean IgE level (132 IU/ml) of infected subjects with a helper T-lymphocyte number  $\leq 200/\text{mm}^3$  was significantly greater than mean IgE levels of the uninfected heterosexual (38 IU/ml) and homosexual (35 IU/ml) groups. IgE levels were inversely related to both helper T cell and suppressor/cytotoxic T cell numbers but not to IgG or IgA levels. The increase in IgE was not a reflection of an increased prevalence of atopic disease (allergic asthma, allergic rhinitis, or atopic dermatitis) in the infected subjects. The elevation of IgE may be related to a difference among the groups in T cell production of IgE regulatory lymphokines. (J ALLERGY CLIN IMMUNOL 1990;85:445-52.)*

A high incidence of clinical manifestations suggestive of IgE-mediated allergic disease occurs in individuals infected with the HIV.<sup>1,2</sup> Nasal congestion and sinusitis are reported problems among patients with advanced HIV infection, as are skin eruptions consistent with AD.<sup>1,3</sup> Wheezing and chest tightness suggestive of asthma have also been described in patients with AIDS.<sup>4</sup> The mechanisms of these expressions of HIV infection are believed to involve the immune dysregulation that occurs with infection.<sup>5,6</sup>

A primary target of HIV infection is the CD4. Infection results in a selective CD4 depletion and an impairment of T cell regulation.<sup>1</sup> Patients infected with the HIV also have an associated polyclonal B cell activation manifested by increased serum levels of IgG, IgA, and IgM.<sup>7,8</sup> The cause of this phenomenon is unclear. The Epstein-Barr virus and cytomegalovirus, as well as the HIV and its subunits, are believed to be involved as polyclonal B cell activators.<sup>6,9</sup>

The regulation of IgE synthesis is independent of that of the other immunoglobulin isotypes. CD4

## Abbreviations used

|                  |                                                                                |
|------------------|--------------------------------------------------------------------------------|
| HIV:             | Human immunodeficiency virus                                                   |
| AIDS:            | Acquired immunodeficiency syndrome                                             |
| CD4:             | Helper T-lymphocyte                                                            |
| CD8:             | Suppressor/cytotoxic T-lymphocyte                                              |
| CDC:             | Centers for Disease Control                                                    |
| CD4 $\leq 200$ : | HIV-infected subjects with a helper T-lymphocyte number $\leq 200/\text{mm}^3$ |
| CD4 $> 200$ :    | HIV-infected subjects with a helper T-lymphocyte $> 200/\text{mm}^3$           |
| AR:              | Allergic rhinitis                                                              |
| AS:              | Allergic asthma                                                                |
| AD:              | Atopic dermatitis                                                              |
| IL-4:            | Interleukin-4                                                                  |

cells modulate IgE production through the lymphokines IL-4 and gamma interferon.<sup>10,11</sup> Various disorders of T cell regulation are associated with elevated IgE levels, such as atopic disease (AS, AR, and AD), autoimmune disease, the hyper-IgE syndrome, and acute graft-versus-host disease after allogeneic bone marrow transplantation.<sup>10</sup> Conflicting data exist as to whether IgE levels are elevated in HIV infection.<sup>6,12-15</sup>

Total serum IgE levels in HIV-infected male subjects with and without atopic disease were determined and compared to corresponding uninfected male heterosexuals and homosexuals in the present study. Serum IgG and IgA levels were also determined and compared with IgE levels as indicators of the poly-

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TABLE I. Age, racial, smoking, and atopic histories of the study and control groups

| Group                      | n  | Mean age | No. of black subjects (%) | No. of smokers (%) | No. with atopic disease (%)                                                                                                      |
|----------------------------|----|----------|---------------------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------|
| HIV-infected               | 67 | 33       | 8 (12)                    | 42 (63)            | 19 (28) <ul style="list-style-type: none"> <li>/ 12 (18) AR</li> <li>— 5 (7) AR and AS</li> <li>\ 2 (3) AS only</li> </ul>       |
| CD4 $\leq$ 200             | 29 | 32       | 5 (17)                    | 16 (55)            | 8 (28) <ul style="list-style-type: none"> <li>— 7 (24) AR</li> <li>\ 1 (3) AR and AS</li> </ul>                                  |
| CD4 > 200                  | 38 | 33       | 3 (8)                     | 26 (68)            | 11 (29) <ul style="list-style-type: none"> <li>/ 5 (13) AR</li> <li>— 4 (11) AR and AS</li> <li>\ 2 (5) AS only</li> </ul>       |
| HIV-negative Heterosexuals | 27 | 32       | 0                         | 3 (11)             | 9 (33) <ul style="list-style-type: none"> <li>/ 4 (15) AR and AS</li> <li>— 4 (15) AR</li> <li>\ 1 (4) AR, AS, and AD</li> </ul> |
| Homosexuals                | 18 | 36       | 0                         | 10 (56)            | 6 (33) <ul style="list-style-type: none"> <li>/ 4 (22) AR</li> <li>— 1 (6) AR and AS</li> <li>\ 1 (6) AS only</li> </ul>         |

clonal hypergammaglobulinemia associated with HIV infection. Significant differences in immunoglobulin levels were observed for which explanations are proposed.

## MATERIAL AND METHODS

### Study population

The study population consisted of 67 consecutively evaluated HIV-infected male subjects, 17 to 63 years of age. The subjects were treated by the Division of Allergy and Immunology at the University of South Florida College of Medicine Immunodeficiency Clinic between August 1, 1986, and July 6, 1989. All subjects were HIV antibody positive as confirmed by Western blot analysis. Sera were obtained from these subjects, with consent, during the course of treatment.

The HIV-infected subjects were divided by CD4 number into two groups: subjects with a CD4 number  $\leq 200/\text{mm}^3$  (CD4  $\leq 200$ ) and subjects with a CD4 number  $> 200/\text{mm}^3$  (CD4 > 200). Subjects were classified according to the criteria of the CDC for HIV infection.<sup>16</sup>

The CD4  $\leq 200$  subject group consisted of 29 HIV-infected male subjects, aged 17 to 49 years (mean, 32 years) (Table I). Twenty-six of the subjects were homosexual or bisexual (two subjects also had a history of intravenous drug abuse), one subject was infected via a blood transfusion, one subject became HIV-infected after clotting factor treatment of his hemophilia, and one subject had no known or stated risk factors for HIV infection.

Three of the 29 subjects had persistent generalized lymphadenopathy (CDC group III), and 10 subjects had a history of a minor opportunistic infection (CDC group IVC2), nine with oral candidiasis and one subject with oral hairy leukoplakia. Eleven of the 29 subjects had a history of a major opportunistic infection (CDC group IVC1), 10 of these subjects with *Pneumocystis carinii* pneumonia and one subject

with esophageal candidiasis. Five subjects had a history of a HIV-associated neoplasm (CDC group IVD), four with Kaposi's sarcoma, and one subject with a central nervous system lymphoma. Nineteen of the 29 subjects were receiving azidothymidine. Five subjects had seborrheic dermatitis, three had folliculitis, and one subject had psoriasis.

The CD4 > 200 study group consisted of 38 HIV-infected male subjects, aged 19 to 63 years (mean, 33 years). Thirty-six of the subjects were homosexual or bisexual (with three subjects having a history of intravenous drug use), one subject was infected via blood transfusion, and one became HIV-infected after clotting factor treatment of his hemophilia.

Thirteen of the 38 subjects were asymptomatic (CDC group II); four HIV-infected subjects were in the CDC group III. Six of the 38 subjects had constitutional symptoms of fever and/or weight loss of  $> 10\%$  of baseline (CDC group IVA). Ten of the 38 subjects were included in the CDC group IVC2, eight of these subjects had oral candidiasis, one subject had oral hairy leukoplakia, and one subject had herpes zoster infection. Two of the 38 subjects had previous *Pneumocystis carinii* pneumonia (CDC group IVC1), and three subjects had Kaposi's sarcoma (CDC group IVD). One of the subjects with Kaposi's sarcoma was receiving azidothymidine. One of the 38 subjects had an undefined medium-size vessel vasculitis, for which he started receiving prednisone (after phlebotomy). One of the 38 subjects had signs and symptoms consistent with Reiter's syndrome.

Control subjects were 18 uninfected white homosexual male subjects, aged 25 to 61 years (mean, 36 years) and 27 uninfected heterosexual white male subjects, aged 26 to 42 years (mean, 32 years). The uninfected homosexual subjects were volunteers who consented to anonymous HIV-antibody testing; all subjects were HIV-antibody negative by ELISA (described later). The uninfected heterosexuals were house staff and faculty of the University of South Florida College

of Medicine who had no history or risk factors of HIV infection (homosexuality, intravenous drug abuse, past blood or blood product transfusion, or promiscuity) by anonymous questionnaire; these subjects were not tested for HIV infection and considered to be HIV-antibody negative. Sera were obtained from these subjects with consent.

Study and control subjects provided detailed smoking, allergic, and sexual histories through interview and/or questionnaire. A subject was considered to have atopic disease if he had symptoms and/or signs consistent with AR, AS, or AD.

AR was defined as a history of seasonal or perennial nasal congestion, rhinorrhea, postnasal drip, itching, sneezing, and a history of nasal eosinophilia or aeroallergen skin test positivity. AS was defined as episodic wheezing and dyspnea or coughing that was seasonal or perennial with a familial history of atopic disease and/or a history of aeroallergen skin test positivity. Individuals with asthma not triggered by aeroallergens were not classified as having atopic disease. AD was defined as persistent dermatitis in the antecubital and/or popliteal fossae with or without involvement of other skin regions associated with AR and AS.

Eight of the 29 subjects (28%) of the CD4  $\leq$ 200 HIV-infected group had atopic disease (seven with AR and one subject with AR and AS; Table I). Two of the nonatopic subjects in this group had a history of sulfa allergy. Eleven of the 29 subjects (38%) experienced symptoms and/or signs suggestive of sinusitis (i.e., facial pain, purulent nasal and/or postnasal secretions, and irritated oropharynx), four of these subjects (14%) had maxillary sinus abnormalities on occipitomental sinus x-ray (Water's view), and one had sphenoid sinus opacification on computerized tomographic scan.

Eleven of the 38 subjects (29%) of the CD4 >200 HIV-infected group had atopic disease (five with AR, four with AR and asthma, and two subjects with AS; Table I). One of the subjects with AS had a recent history of rhinitis, but a single nasal smear did not reveal eosinophils. Two of the subjects with AR had received immunotherapy before the study. Two of the subjects without atopic disease had a history of penicillin-related urticaria, and one other nonatopic subject had a history of aspirin sensitivity (urticaria/angioedema type). One other nonatopic subject had a history of a systemic allergic reaction (bronchospasm) to imported fire ant sting. Thirteen of these 38 subjects (34%) experienced sinusitis symptoms (see above); five subjects (13%) had maxillary sinus abnormalities on occipitomental sinus x-ray, and two subjects without atopic disease had a history of recurrent otitis media.

The predominant atopic diseases among the 27 heterosexual-group subjects were AR and AS, present in five of the nine atopic subjects (Table I). The other four subjects had AR. Four of the nine subjects had received immunotherapy (two with AR and AS, one with AR, AS, and AD, and one subject with AR) in the past.

Six of the 18 HIV-negative homosexuals (33%) had atopic disease (four with AR, one with AR and AS, and one subject with AS). Four atopic subjects (three with AR

and one subject with AR and AS) had received immunotherapy in the past. One of these subjects without atopic disease had penicillin hypersensitivity.

All study and control subjects with diarrhea (regardless of etiology) or a history suggestive of parasitic (especially helminthic) infection were excluded from the study. CDC group IV A subjects with chronic diarrhea ascribed to HIV infection were not included in the study. All subjects who were not natives of the United States, Canada or Western Europe were also excluded.

### HIV antibody assay

An ELISA (Abbott Laboratories, North Chicago, Ill.) was used to screen subjects for the presence of IgG directed against HIV. Positive results were confirmed by Western blot; criteria for a positive test were IgG specific for the p24 and p41 proteins.<sup>17</sup> Testing was performed at the Department of Health and Rehabilitative Services Laboratory in Tampa, Fla., or at a private laboratory (SmithKline Laboratories, Tampa, Fla.).

### IgE assay

Total IgE measurements were determined by the fluoroallergosorbent test (FAST; 3M, Santa Clara, Calif.).<sup>18</sup>

### IgG and IgA determinations

IgG and IgA levels were determined by radial immunodiffusion (Nor-Partigen, Behring Diagnostics, LaJolla, Calif.). Plates were read at 48 hours, and the IgA and IgG values were derived from linear plots constructed from the appropriate standards.<sup>19</sup>

### T-lymphocyte enumeration

T cell subpopulations were determined by direct immunofluorescence either manually with a fluorescence microscope or with the EPICS automated flow cytometer (Coulter Diagnostics, Hialeah, Fla.). For the manual counting, heparinized blood was obtained and peripheral blood mononuclear cells were isolated within 8 hours of bleeding by Ficoll-Hypaque density-gradient centrifugation, according to the method of Boyum.<sup>20</sup> Fluorescein-labeled monoclonal antibody (OKT4 or OKT8; Ortho Diagnostics, Raritan, N.J.) was added to the peripheral blood mononuclear cells according to the technique of Hoffman et al.,<sup>21</sup> and the cells were washed. One hundred peripheral blood mononuclear cells were counted manually or automated analysis was performed with the flow cytometer.<sup>22</sup> Absolute lymphocyte counts were derived from leukocyte differential counts and used to calculate the numbers of each lymphocyte population.

### Data analysis

Chi-square analysis with Yates' correction was used for percentile analysis.<sup>23</sup> A two-tailed *p* value of <0.05 was regarded as statistically significant.

IgE, IgG, and IgA data were expressed as geometric means  $\pm$  SEM. These data were treated as nonparametric and compared by the two-tailed Mann-Whitney U test.

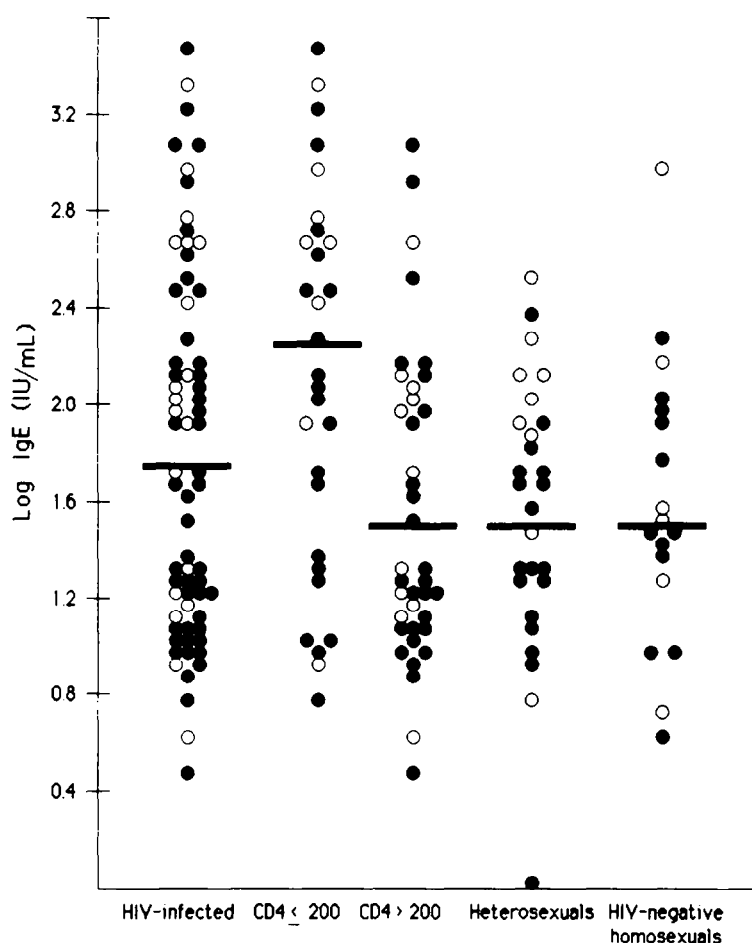


**FIG. 1.** IgE data on the HIV-infected and HIV-negative heterosexual and homosexual subjects. (Open circles represent atopic and blackened circles represent nonatopic subjects). The bars represent the geometric mean of each subject group.

Ranks were  $z$  transformed to give the exact  $p$  levels.<sup>23</sup> With a two-tailed level of significance of 5%, the test had an 86% ability to distinguish a 100 IU/ml difference in mean IgE between the HIV-negative heterosexual group and both HIV-infected groups. There was a 48% ability to distinguish such a difference in mean IgE between the HIV-negative homosexual group and the subjects of the two HIV-infected groups with a similar amount of significance.<sup>24</sup>

Spearman's rank-correlation coefficients were calculated with the use of the Statview 512 Plus program (Brainpower, Inc., Calabasas, Calif.) for the Macintosh SE computer (Apple Computer, Inc., Cupertino, Calif.) and were  $z$  transformed to determine statistical significance. A two-tailed  $p$  value of  $<0.05$  was regarded as statistically significant. The Spearman's rank-correlation coefficients were transformed into Pearson product-moment correlation coefficients,<sup>23</sup> which are represented in the text as  $r$ .

## RESULTS

The mean ages of the entire group of HIV-infected subjects, the HIV-negative heterosexuals and the

HIV-negative homosexuals, were all similar (Table I). Eight HIV-infected subjects were black, whereas none of the HIV-negative heterosexuals or homosexuals were black, but these differences were not statistically significant. The entire HIV-infected group and the HIV-negative homosexual group had significantly more subjects with smoking histories than the HIV-negative heterosexual group ( $X^2 = 18.5$ ,  $p < 0.001$ ; and  $X^2 = 8.6$ ,  $p < 0.01$ , respectively). The prevalence of atopic disease in the entire group of HIV-infected subjects was not significantly different from prevalences in the HIV-negative heterosexuals and homosexuals.

The entire group of HIV-infected subjects had a mean CD4 number ( $\pm$ SEM) of  $191 \pm 32/\text{mm}^3$ , a mean CD8 number of  $534 \pm 51/\text{mm}^3$ , and a mean CD4/CD8 ratio of  $0.36 \pm 0.05$ . The mean CD4 numbers of the CD4  $\leq 200$  and CD4  $> 200$  infected groups were  $59 \pm 11$  and  $465 \pm 32/\text{mm}^3$ , respectively; the respective mean CD8 numbers were  $353 \pm 54$  and  $732 \pm 69/\text{mm}^3$ , and the re-

**TABLE II.** IgE data of the study and control groups (expressed as the geometric mean  $\pm$  SEM)

| Group          | n  | No. with IgE<br>> 100 IU/ml<br>(%) | Mean IgE<br>(IU/ml) | Mean IgE                   |                                            |
|----------------|----|------------------------------------|---------------------|----------------------------|--------------------------------------------|
|                |    |                                    |                     | Atopic subjects<br>(IU/ml) | Subjects without atopic<br>disease (IU/ml) |
| HIV-infected   | 67 | 27 (40)                            | 62 $\pm$ 63         | 97 $\pm$ 126               | 53 $\pm$ 13                                |
| CD4 $\leq$ 200 | 29 | 17 (59)*                           | 132 $\pm$ 129*      | 295 $\pm$ 260†             | 97 $\pm$ 148†                              |
| CD4 > 200      | 38 | 10 (26)                            | 35 $\pm$ 39         | 43 $\pm$ 41                | 34 $\pm$ 34                                |
| HIV-negative   |    |                                    |                     |                            |                                            |
| Heterosexuals  | 27 | 6 (22)                             | 38 $\pm$ 15         | 81 $\pm$ 32                | 26 $\pm$ 12                                |
| Homosexuals    | 18 | 4 (22)                             | 35 $\pm$ 49         | 50 $\pm$ 144               | 33 $\pm$ 16                                |

\*Significantly greater than the HIV-negative heterosexual and homosexual groups and the CD4 &gt; 200 infected group.

†Significantly greater than the HIV-negative heterosexual and CD4 &gt; 200 infected groups.

**TABLE III.** IgG and IgA data (expressed as the geometric mean  $\pm$  SEM)

| Group          | n  | IgG (mg/dl)     | n  | IgA (mg/dl)    |
|----------------|----|-----------------|----|----------------|
| HIV-infected   | 67 | 2317 $\pm$ 191* | 53 | 400 $\pm$ 228* |
| CD4 $\leq$ 200 | 29 | 2558 $\pm$ 307* | 25 | 484 $\pm$ 48*  |
| CD4 > 200      | 38 | 2149 $\pm$ 242* | 28 | 337 $\pm$ 37*  |
| HIV-negative   |    |                 |    |                |
| Heterosexuals  | 27 | 985 $\pm$ 152   | 26 | 152 $\pm$ 27   |
| Homosexuals    | 18 | 1925 $\pm$ 193* | 16 | 201 $\pm$ 46   |

\*Significantly greater than the HIV-negative heterosexual group.

spective CD4/CD8 ratios were  $0.17 \pm 0.03$  and  $0.64 \pm 0.07$ .

Forty percent of all the HIV-infected subjects had an IgE level >100 IU/ml (Table II; Fig. 1); this finding was not significantly different from the percentages in the HIV-negative heterosexual and homosexual groups. However, the CD4  $\leq$ 200 infected group had significantly more subjects with an IgE level >100 IU/ml than the HIV-negative heterosexual and homosexual groups ( $X^2 = 6.2$ ,  $p < 0.025$ ;  $X^2 = 4.6$ ,  $p < 0.05$ , respectively) and the CD4 >200 infected group ( $X^2 = 5.9$ ;  $p < 0.025$ ). The mean IgE levels of the entire HIV-infected group, the HIV-negative heterosexual group, and the HIV-negative homosexual group were not significantly different. However, the mean IgE level of the CD4  $\leq$ 200 infected group subjects was significantly greater than that of the HIV-negative heterosexuals ( $p = 0.011$ ) and homosexuals ( $p = 0.023$ ). The mean IgE level of the CD4  $\leq$ 200 infected subjects was also significantly greater than that of the CD4 >200 group subjects ( $p = 0.006$ ).

The difference in mean IgE in each group between subjects with atopic disease and without such disease was not statistically significant except for the HIV-negative heterosexuals; that is, the mean level of the

atopic heterosexuals was significantly greater than that of the nonatopic heterosexuals ( $p = 0.013$ ). The mean IgE of the atopic CD4  $\leq$ 200 subjects was significantly greater than that of the atopic HIV-negative heterosexuals ( $p = 0.043$ ) and the atopic CD4 >200 subjects ( $p = 0.026$ ) but not that of the atopic HIV-negative homosexuals ( $p = 0.093$ ). Likewise, the mean IgE level of the CD4  $\leq$ 200 infected subjects without atopic disease was significantly greater than those of the nonatopic subjects of the HIV-negative heterosexual and CD4 >200 groups ( $p = 0.029$  and  $0.049$ , respectively), but not that of the nonatopic HIV-negative homosexuals ( $p = 0.091$ ).

The mean IgG levels of the entire HIV-infected group and the HIV-negative homosexual group were significantly greater than that of the HIV-negative heterosexual group ( $p < 0.001$  and  $p = 0.008$ , respectively; Table III). The mean IgG level of the CD4  $\leq$ 200 infected group was significantly greater than that of the HIV-negative homosexuals ( $p = 0.047$ ), but not that of the CD4 >200 infected group.

The mean IgA level of all of the HIV-infected subjects was significantly greater than that of the HIV-negative heterosexuals ( $p < 0.001$ ) and homosexuals ( $p = 0.003$ ). The mean IgA level of the CD4  $\leq$ 200 infected group was significantly greater than that of

the CD4 >200 group ( $p = 0.024$ ); the mean IgA level of the latter infected group was significantly greater than that of the HIV-negative homosexuals ( $p = 0.038$ ). No significant difference in mean IgA level was found between the HIV-negative heterosexuals and homosexuals.

IgE level in the HIV-infected subjects was inversely correlated with both CD4 ( $r = -0.34$ ;  $p = 0.008$ ) and CD8 ( $r = -0.33$ ;  $p = 0.011$ ) numbers, but not with CD4/CD8 ratio ( $r = -0.21$ ;  $p = 0.097$ ). Statistical significance in the HIV-infected subjects was not found in the correlations between IgE and IgG ( $r = -0.015$ ) and IgE and IgA ( $r = -0.019$ ) levels.

## DISCUSSION

Fifty-nine percent of the HIV-infected male subjects with a CD4 number  $\leq 200/\text{mm}^3$  had a serum IgE level  $>100$  IU/ml. The mean IgE level of this group (132 IU/ml) was significantly greater than levels of the HIV-negative heterosexuals and homosexuals and the infected subjects with a CD4 number  $>200/\text{mm}^3$ . The mean IgE of all of the HIV-infected subjects was 62 IU/ml; 40% had an IgE level  $>100$  IU/ml.

Five previous studies have measured serum IgE levels in HIV-infected subjects. In the first study,<sup>12</sup> serum IgE levels were measured in healthy homosexuals and HIV-infected subjects with persistent generalized lymphadenopathy (CDC group III) or Kaposi's sarcoma (CDC group IVD). The mean IgE level of the CDC group III subjects was significantly greater than the level of the heterosexual control subjects. The second study<sup>13</sup> compared the median serum levels of IgE of HIV-negative homosexuals to asymptomatic and symptomatic HIV-infected subjects. The median IgE level of the uninfected homosexual group was significantly greater than IgE levels of the infected groups. A third study<sup>14</sup> found a mean IgE level of 166 IU/ml for 21 subjects with AIDS-related complex (CDC group IVA) and AIDS. In the fourth study,<sup>15</sup> HIV-infected subjects were subdivided by CD4 number; subjects with lower CD4 numbers were found to have IgE levels higher than normal control subjects, but the statistical significance was not stated. Fifty-percent of HIV-infected subjects in a fifth study<sup>2</sup> had elevated IgE levels, but a normal range of IgE and a mean IgE level were not included.

The increase in mean IgE found in this study in HIV-infected subjects with a CD4 number  $\leq 200/\text{mm}^3$  cannot be ascribed to an increased prevalence of atopic disease. Furthermore, no difference in mean IgE was found between the atopic and nonatopic subjects of both of the HIV-infected groups. This is in agreement with two other studies.<sup>3, 14</sup> HIV infection has been

documented to exacerbate atopic disease in both children and adults<sup>3, 25</sup>; from this study, it can be concluded that a total serum IgE is useless to diagnose these diseases in HIV-infected adults with a CD4 number  $\leq 200/\text{mm}^3$ .

The mean IgE levels of the atopic and nonatopic HIV-infected subjects with a CD4 number  $\leq 200/\text{mm}^3$  were significantly greater than the IgE levels of the corresponding subjects of the HIV-negative heterosexual group and the infected group with a CD4 number  $>200/\text{mm}^3$ . However, no such differences were noted in comparison with the levels of the atopic and nonatopic HIV-negative homosexuals, probably because of the small numbers of homosexual subjects.

CD4 and CD8 numbers were both inversely correlated with IgE level. In one other study a statistically significant CD4 and IgE relationship was noted.<sup>15</sup>

The mean IgG levels of the entire HIV-infected group and the HIV-negative homosexual group were significantly greater than the level of the HIV-negative heterosexual group. The mean IgA of the HIV-infected subjects as a whole was greater than the mean levels of the HIV-negative heterosexuals and homosexuals. Similar increases in IgG have been reported,<sup>8, 26, 27</sup> whereas IgA has been reported to be significantly greater than levels in control subjects in HIV-infected subjects with advanced disease and/or a CD4 number  $<400/\text{mm}^3$ .<sup>12, 28, 29</sup>

No correlation was found between IgE level and either IgG or IgA levels. This is in agreement with other studies.<sup>14, 15</sup> One of these studies found no significant difference in mean IgE in subjects with or without the hypergammaglobulinemia associated with HIV infection.<sup>14</sup> Thus, the factors causing increased IgG and IgA in HIV infection may not be involved in the elevation of IgE.

Serum IgE levels are increased in certain populations with a high incidence of parasitic infection.<sup>30-33</sup> Male homosexuals and Third World inhabitants are known to have a high rate of helminthic infection.<sup>34-36</sup> It is possible that these infestations are related to the elevated IgE levels found in this study. However, subjects with diarrhea or a history suggestive of parasitic infection were excluded from the study, as were subjects not native to the United States, Canada, or western Europe.

The elevation of IgE found in the HIV-infected subjects with a CD4 number  $\leq 200/\text{mm}^3$  relative to the HIV-negative heterosexuals and homosexuals may be related to differences in T cell production of IgE regulatory lymphokines in these groups. One such factor is gamma interferon that suppresses IgE synthesis by normal B cells.<sup>10, 11</sup> HIV-infected subjects have been found to have impaired production of this

lymphokine in response to antigen stimulation.<sup>37-39</sup> One study of treatment with recombinant gamma interferon has demonstrated improvement of the atopic symptoms of two HIV-infected subjects after treatment.<sup>1</sup> Two classes of helper T-lymphocytes have been identified in mice that secrete different lymphokines; the cells of one class (T<sub>H1</sub>) secrete gamma interferon.<sup>40</sup> It can be postulated that HIV infection in humans preferentially depletes or causes dysfunction of CD4 cells analogous to T<sub>H1</sub> cells leading to deficient gamma interferon production.

IgE-binding factors are other lymphokines that modulate IgE synthesis. The mononuclear cells of many HIV-infected subjects have been found to spontaneously produce these factors, whereas mononuclear cells from normal individuals do not.<sup>5</sup> Gamma interferon and IL-4 had no effect on factor production. Most of the HIV-infected subjects that produced gamma interferon and IL-4 had AIDS, and one quarter had elevated IgE levels.<sup>5</sup>

This study demonstrates that advanced HIV infection, as manifested by CD4 numbers  $\leq 200/\text{mm}^3$ , is associated with increased IgE levels. Thus, total IgE levels are not useful in the diagnosis of atopic disease in such subjects. The degree of IgE elevation is inversely related to both CD4 and CD8 T-lymphocyte numbers. Abnormal T cell regulation of IgE synthesis may be involved in this phenomenon. Further study is needed to elucidate the relationship between HIV infection and T cell regulation of IgE synthesis and IgE control mechanisms not involving T cells.

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