

Aeroallergen-specific IgE changes in individuals with rapid human immunodeficiency virus disease progression

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Background: Progression of human immunodeficiency virus type 1 (HIV-1) infection to the acquired immunodeficiency syndrome (AIDS) is associated with elevated total IgE; however, previous cross-sectional studies have differed in their assessment of concurrent changes in allergic disease prevalence.

Objective: Assessment of changes in aeroallergen-specific IgE during progression from early to late HIV disease.

Methods: Total IgE, aeroallergen-specific IgE (rye grass, ragweed, *Alternaria*, dust mite, and cat), IFN- γ , IL-4, and soluble CD23 (sCD23) were measured in a longitudinal study of 20 subjects who had progressed from early-HIV infection (mean CD4 lymphocyte count of 650/mm³) to AIDS (mean CD4 lymphocyte count of 40/mm³) over an average of 4 years.

Results: Prevalence of positive aeroallergen specific-IgE assays in early HIV disease (11 subjects with 13 positives) decreased with progression to late disease (five subjects with nine positives, $P = .057$), while total IgE increased from a median of 69 to 116 IU/mL. IFN- γ and IL-4 were unchanged, while sCD23 decreased from a median of 72 to 9 U/mL ($P = .0005$) with disease progression in the full cohort. In contrast to other subjects, the subgroup of individuals with total IgE > 150 IU/mL in both early and late HIV disease demonstrated an increased frequency of aeroallergen-specific IgE.

Conclusions: The elevation of total IgE associated with rapid HIV-1 disease progression was unexplained by concurrent changes in aeroallergen-specific IgE, IL-4, IFN- γ , or sCD23. Overall, aeroallergen-specific IgE expression was less prevalent with HIV-1 progression, except in those individuals with elevated total IgE both before and after progression to AIDS.

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INTRODUCTION

The progressive immunodeficiency of the acquired immunodeficiency syndrome (AIDS) is associated with loss of CD4⁺ T cells, profound impairment of cellular immunity, and opportunistic infections. Even prior to significant decreases in CD4⁺ T cell numbers, early

manifestations of human immunodeficiency virus type 1 (HIV-1) infection result from immune activation and dysregulation. Polyclonal B-cell activation and hypergammaglobulinemia occur at all stages of HIV-1 infection,¹⁻³ with resultant production of autoantibodies and immune complexes, an increased frequency of B cell malignancies, and a high incidence of allergic and atopic disorders.⁴⁻⁶ Progression to late-stage HIV-1 infection and AIDS is associated with elevation of total IgE.⁷ Among the cytokines regulating the synthesis of IgE are IL-4, which can induce IgE synthesis in human B cells, and gamma interferon (IFN- γ) which suppresses its produc-

tion.⁸ One prior study has suggested that the production of IFN- γ is abnormally low in patients with AIDS.⁹ The balance, however, of IL-4 and IFN- γ in patients with AIDS has neither been fully investigated nor correlated with elevation of total IgE, with expression of aeroallergen-specific IgE, or with the soluble form of the low affinity receptor for IgE, ie, soluble CD23 (sCD23).

In this longitudinal, retrospective study of 20 subjects with HIV-1 infection, we investigated concurrent changes in total IgE, aeroallergen-specific IgE, IFN- γ , IL-4, and sCD23 with progression from early to late-stage disease.

METHODS AND MATERIALS

Subjects and Serum Samples

Serum samples had been collected prospectively from the cohort of HIV-1-infected subjects assessed at Wilford Hall Medical Center (WHMC) between 1986 and 1992. Twenty pairs of banked frozen sera were available that met the inclusion criteria: a decline in CD4⁺ lymphocyte counts from >450/mm³ to <100/mm³ over two or more follow-up visits at least 1 year apart. Serum samples had been collected with patient informed consent under a research protocol approved by the WHMC Institutional Review Committee. All samples had been stored in aliquots at -70 °C.

Serum samples were evaluated for the following: (1) total IgE by immunoassay; (2) rye grass, ragweed, *Alternaria*, dust mite (*Dermatophagoides pteronyssinus*), and cat specific-IgE by ELISA; and (3) IL-4, IFN- γ , and sCD23 by ELISA.

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Total IgE

Total serum IgE in each sample was measured according to method of RG Hamilton and NF Adkinson¹⁰ by a noncompetitive two-site immunoenzymetric assay. The detection range of the assay was 1 to 200 IU/mL.

Aeroallergen Extracts

Rye grass, giant ragweed, *Alternaria*, *D. pteronyssinus*, and cat hair and epithelium were purchased from Hollister-Stier Laboratories (Spokane, WA). Extracts were dialyzed, frozen, and then freeze-dried. The lyophilized extracts were stored at 4 °C. The protein concentration of each extract was determined by a modification of the Lowry technique.¹¹

Aeroallergen ELISA

IgE antibodies specific for each of the five aeroallergens were detected in each early and late-disease HIV-1 using an enzyme linked immunosorbent assay (ELISA). Pooled atopic sera specific for each allergen were used to construct a standard curve for each assay. Irrelevant atopic sera served as negative controls for each assay. ELISAs were accomplished as previously described.¹² In brief, wells of 96-well Immulon II plates were filled with 100 μ L of an extract solution in phosphate buffered saline (PBS) at previously optimized concentrations (rye grass = 200 μ g protein/mL, giant ragweed = 60 μ g protein/mL, *Alternaria* = 40 μ g protein/mL, *D. pteronyssinus* = 10 μ g protein/mL, and cat = 70 μ g protein/mL). Plates were incubated for one hour at 37 °C. All wells were evacuated, then refilled with 200 μ L of 0.1% human serum albumin (HSA, Sigma Chemical Company, St. Louis, MO) in PBS, and incubated for one hour at 37 °C. After evacuation and washing, wells were filled with 100 μ L of sera diluted 1:5 with 10% fetal bovine serum in PBS. All assays were performed in duplicate. After an overnight incubation at 4 °C, 100 μ L mouse monoclonal antibody against human IgE (Sigma) diluted 1:5000 with 10% fetal bovine serum was incubated in each well at

room temperature for three hours. The detection antibody was a peroxidase conjugated goat anti-mouse IgG (Boehringer Mannheim Biochemicals, Indianapolis, IN) diluted 1:5000 with 10% fetal bovine serum and incubated overnight at 4 °C. The peroxidase substrate for detection was a solution of citrate buffer (0.817% citric acid monohydrate and 0.896% Na_2HPO_4), 0.05% *o*-phenylenediamine (Sigma), and 0.04% hydrogen peroxide. After 30 minutes at room temperature, optical density of each well at 492 nm was measured with a spectrophotometer (Dynatech MR 5000, Guernsey Channel Islands, UK). Positive IgE ELISA tests were defined as those with optical densities on the standard curve, having an optical density of 0.020 or more and being at least 4 times greater than the atopic negative control.

IL-4, IFN- γ , and sCD23 ELISA

Commercial ELISA kits utilizing anti-human IL-4, IFN- γ , and sCD23 monoclonal antibodies were used according to the manufacturer's directions to measure serum levels of each protein. Samples were performed in duplicate. The minimal level of sensitivity of the IL-4 assay (InterTest-4TM, Genzyme Corp, Cambridge, MA) was 45 pg/mL. The minimal sensitivity of the IFN- γ assay (Research Diagnostics Inc, Flanders, NJ) was 5 pg/mL. The detection range of the sCD23 assay (Cell-freeTM CD23 Test Kit, T Cell Diagnostics, Cambridge, MA) was 15 to 800 U/mL.

Statistical Analysis

Statistical analyses were performed using the Kruskal-Wallis, Mann-Whitney U, and Wilcoxon signed-rank non-parametric tests. Parametric analysis for total IgE utilized the unpaired or paired *t* test. Two-tailed tests with significance level $\alpha = .05$ were used in all comparisons.

RESULTS

Subjects

Stored serum samples had been collected between 1986 and 1992. At the time of collection of the early-disease

serum sample the 20 subjects (19 men and 1 woman) were a mean of 27.4 years old (range 21 to 37 years). The mean time between early and late-disease serum samples was 47.7 ± 8.6 months (mean $\pm$ STD), with a range of 26 to 60 months. Thus, the cohort of 20 subjects constituted a group who rapidly progressed to AIDS. At the time of collection of the early-HIV disease samples 19 subjects were classified Walter Reed³ (WR) stage 1 or 2, while one subject was WR4. The group mean early CD4 lymphocyte count was $650 \pm 171/\text{mm}^3$ with a range of 451 to $995/\text{mm}^3$. At the time late-HIV disease sera were collected, 19 subjects were classified WR5 or WR6, with one subject classified WR4 (this individual having progressed from WR1 early to WR4 late). The late-disease group mean CD4 lymphocyte count was $40 \pm 25/\text{mm}^3$, range 0 to $99/\text{mm}^3$.

Early versus Late HIV Disease

Serologic results of all 20 subjects for total IgE, IL-4, IFN- γ , sCD23, and aeroallergen-specific IgE are shown in Table 1 for both early and late-HIV disease sera. Although total IgE (mean 280 IU/mL, range 21 to 1742 IU/mL early and mean 1339 IU/mL, range 25 to 9155 IU/mL late) rose from a median of 69 to 116 IU/mL between early and late-disease, the difference was not statistically significant. Median IL-4 and IFN- γ values for the study group remained essentially unchanged. Soluble-CD23, however, decreased significantly between early and late-disease from a median of 72 to 9 U/mL ($P = .0005$). Eleven of the initial 20 sera were positive for one or more of the specific-IgE allergen ELISA assays (a total of 13 positives). The number of sera demonstrating any positive specific IgE dropped to only five of the 20 late-disease HIV sera (a total of nine positive ELISAs) with close to statistical significance ($P = .057$). With progression from early to late-HIV disease, the net decrease of six individuals demonstrating specific IgE consisted of eight individuals who lost all positive aeroallergen specific-IgE, as well as two individuals who first dem-

Table 1. Early Versus Late-HIV Serologic Results (n = 20)

	Median					Number of Positive Specific-IgE ELISAs						Subjects Positive
	CD4, /mm ³	Total IgE, IU/mL	IL-4, pg/mL	IFN γ , pg/mL	sCD23, U/mL	Mite	Alternaria	Ragweed	Rye	Cat	Total	
Early	607	69	64	0	72*	1	1	2	1	8	13	11†
Late	38	116	68	0	9*	2	1	0	3	3	9	5†

* $P = .0005$.† $P = .057$.

onstrated aeroallergen specific IgE in late disease.

Grouping by Total IgE in Early and Late HIV Disease

Although the anticipated increase in group total IgE⁷ was evident with HIV-1 disease progression in the group of 20 subjects, the number of positive aeroallergen-specific IgE tests for the group actually decreased, as did the number of subjects exhibiting those positive specific IgE ELISA results. To investigate the relationship of changes in frequency of positive aeroallergen-specific IgE (rye grass, ragweed, Alternaria, dust mite, and cat) to changes in total IgE between early and late-HIV disease, we divided the 20 subjects into four groups for comparison (Table 2). Grouping was based upon early and late total IgE, and an expected normal total IgE < 150 IU/mL. The group with total IgE > 150 IU/mL early and > 150 IU/mL late contained four subjects (el-

evated total IgE in both early and late-HIV disease, group A). The second group with total IgE > 150 IU/mL early and < 150 IU/mL late included three subjects (elevated total IgE early but normal total IgE in late-HIV disease, group B). The third group with total IgE < 150 IU/mL early and > 150 IU/mL late contained three subjects (normal total IgE early but elevated total IgE in late-HIV disease, group C). The fourth and largest group with ten subjects demonstrated normal total IgE < 150 IU/mL in both early and late-HIV disease (group D). The mean time between early and late-disease serum collection for the four groups was similar (48.0, 48.7, 41.3, and 49.2 months, respectively).

The aeroallergen specific-IgE results for each of the four total IgE groups are shown in Table 2 for both early and late-HIV disease. While the small group sizes make statistical comparisons inappropriate, an inspection

of the changes among the four groups is notable. Two (50%) subjects in group A had at least one positive specific IgE aeroallergen ELISA during early-disease compared with three (100%), 1 (33%) and five (50%) subjects, respectively, in groups B through D. Comparison, however, of late-HIV disease sera demonstrated a differential change among groups with four (100%) of group A subjects (elevated total IgE both early and late) having at least one positive ELISA compared with one (33%) of group B and no subjects (0%) of groups C and D.

Only group A with total IgE > 150 IU/mL in both early and late-disease demonstrated an increase in the number of positive aeroallergen-specific IgE ELISAs (from four to eight) and number of subjects with positive specific-IgE values [from two (50%) to four (100%)] between early and late-HIV disease. All three remaining groups demonstrated decreases to one

Table 2. Early Versus Late-HIV Serologic Results*

	Median Total IgE, IU/mL	Number of Positive Specific-IgE ELISAs					Subjects Positive	
		Mite	Alternaria	Ragweed	Rye	Cat		Total
Group A. Early IgE > 150 and late IgE > 150 (n = 4)								
Early	800	0	1	0	1	2	4	2
Late	5538	1	1	0	3	3	8	4
Group B. Early IgE > 150 and late IgE < 150 (n = 3)								
Early	297	1	0	1	0	1	3	3
Late	79	1	0	0	0	0	1	1
Group C. Early IgE < 150 and late IgE > 150 (n = 3)								
Early	41	0	0	0	0	1	1	1
Late	1162	0	0	0	0	0	0	0
Group D. Early IgE < 150 and late IgE < 150 (n = 10)								
Early	37	0	0	1	0	4	5†	5†
Late	44	0	0	0	0	0	0†	0†

* Subjects grouped by total IgE.

† $P = .025$.

(group B) and none (groups C and D) in both categories. Group D was of adequate size for statistical comparison of early to late-disease, and the decreases (from five to zero subjects and positive aeroallergen specific-IgE ELISAs) were statistically significant ($P = .025$).

Grouping by Presence of Aeroallergen Specific-IgE ELISA

For further analysis of changes in IL-4, IFN- γ , and sCD23, patients were separated into two groups based upon their display of aeroallergen-specific IgE by ELISA (Table 3). Thirteen subjects demonstrated one or more positive specific-IgE ELISAs in early and/or late-HIV disease. Seven subjects exhibited no positive ELISA either early or late. Not unexpectedly, early-HIV disease total IgE was significantly less for the latter group compared with the subjects exhibiting positive specific IgE ($P = .007$). Only two subjects had late-disease positive ELISAs with no positive early-disease specific-IgE. Both these subjects had early and late total IgE > 150 IU/mL.

The positive aeroallergen-specific IgE group demonstrated a significant increase in IFN- γ ($P = .02$) and decrease in sCD23 ($P = .002$) in concert with the previously noted decrease in frequency of positive specific-IgE ELISAs between early and late-HIV disease. Concurrently, IL-4 did not significantly change.

The group with no positive aeroallergen-specific IgE demonstrated no

significant changes in IFN- γ , sCD23, or IL-4.

DISCUSSION

Recent studies have demonstrated that an elevated total IgE level in HIV-1 infected individuals is associated with progressive immunodeficiency, and appears to be an indicator of poor prognosis.^{4,7,13-17} In concert with these previous reports, we found that the mean total IgE of our full cohort of 20 subjects increased during progression from early-HIV disease to development of AIDS. This increase was the net result of seven individuals with an increased total IgE > 150 IU/mL after progression, and 13 individuals who either had decreased IgE < 150 IU/mL (three individuals) or IgE that remained below 150 IU/mL after progression (ten individuals, Table 2). As might be expected during early-HIV disease before development of AIDS, total IgE was significantly greater in the atopic subgroup with serologic evidence of specific IgE than in the subgroup without positive aeroallergen-specific IgE (Table 3). After development of AIDS, however, each subgroup had increased its mean total IgE and the difference between subgroups was no longer significant. This concurrent increase in total IgE, regardless of aeroallergen-specific IgE status, suggests that the elevation of total IgE with HIV-1 disease progression is not related to presence or absence of allergic disease, but is related

to other immunologic changes which accompany HIV-1 progression. Other studies have similarly concluded that there is no association with allergic disease and have suggested that the elevation of IgE is a nonspecific manifestation of the progressive immune dysregulation in advanced HIV-1 infection.^{13,17,23} This conclusion is further supported by our cohort's overall decrease in aeroallergen-specific IgE prevalence despite the concurrent increase in total IgE during HIV-1 disease progression.

While some researchers in previous cross-sectional studies have reported an increase in patient atopic disease with HIV-1 infection and disease progression,^{4,15} others have not,^{13,17} and still others have found an association of progressive HIV-1 disease and increased allergic disease only in those subjects with a prior history of atopy.^{6,14}

Consistent with our findings, both Israel-Biet et al¹⁴ and Parkin et al⁶ noted that historically pre-existent clinical atopic symptoms worsened in subjects with AIDS, while former nonatopics did not develop atopic symptoms after progressing to AIDS. In our longitudinal study, we found a decrease in both the prevalence of patients with serologic evidence of aeroallergen-specific IgE and their total number of positive specific IgE ELISAs during progression of our full cohort from early-HIV disease to AIDS (Table 1). This decrease in se-

Table 3. Early Versus Late-HIV Serologic Results*
Subjects grouped by presence of specific-IgE ELISA

	Positive ELISAs	Median				Mean ± SEM Total IgE, IU/mL	
		CD4, /mm ³	IL-4, pg/mL	IFNγ, pg/mL	sCD23, U/mL		Total IgE, IU/mL
One or more positive specific-IgE ELISAs (n = 13)							
Early	13	559	64	0†	87‡	175§	412 ± 138
Late	9	36	76	10†	8‡	120	1657 ± 839
No positive specific-IgE ELISAs (n = 7)							
Early	0	725	64	0	3	35§	35 ± 4
Late	0	43	60	0	10	43	749 ± 533

* Subjects grouped by presence of specific-IgE ELISA.
Early versus late (within group): † $P = .021$, ‡ $P = .002$.
Comparison between groups: § $P = .007$, || $P = .062$.

rologic evidence for allergic disease with HIV-1 progression (which closely approached statistical significance with $P = .057$) was better understood by subgrouping patients according to their change in total IgE during HIV-1 disease progression. Those individuals with IgE > 150 IU/mL both early and late actually demonstrated an increased prevalence of positive serologic evidence for allergy, while all other groups decreased in prevalence. These findings suggest that the presence of elevated total IgE both before and after HIV-1 disease progression to AIDS may distinguish those patients who are at risk of persistent and/or progressive expression of aeroallergen-specific IgE.

Previous studies evaluating the association of specific IgE responses with HIV-1 progression have primarily depended upon cross-sectional comparisons among patients in different stages of HIV-1 disease or comparisons of patients with noninfected controls. In contrast, our study utilized a longitudinal cohort design in which patients were identified retrospectively as having progressed from early-HIV infection (mean CD4 lymphocyte count of $650/\text{mm}^3$) to AIDS (mean CD4 lymphocyte count of $40/\text{mm}^3$) over an average duration of 4 years (range 26 to 60 months). Compared with a cross-sectional study, this longitudinal design allows more convincing conclusions to be drawn concerning changes in aeroallergen-specific IgE responses during HIV-1 progression. The major limitation of this retrospective, longitudinal study design is skewing of the patient recruitment toward subjects who progressed to AIDS more rapidly, ie, within the 7 years of serum collection, as opposed to individuals who progressed more slowly and would have required a longer duration of follow-up before their identification and inclusion in this study design. Whether our conclusion concerning changes in aeroallergen-specific IgE during HIV-1 disease progression applies to individuals who progress to AIDS more slowly will require further confirmation.

The immune dysregulation of IgE production, which is associated with HIV-1 disease progression and has been highlighted in this and previous studies, may be driven by changing cytokine and mediator profiles during disease progression. Among the cytokines regulating IgE production, IL-4 has been demonstrated to induce in vitro B-cell production of IgE, while IFN- γ suppresses production of IgE.⁸ Elevated serum levels of IL-4 have been reported in atopic individuals¹⁸ and elevated in vitro production of IL-4 has been demonstrated in asymptomatic HIV-infected individuals.¹⁹ In addition, AIDS has been associated with suppressed in vitro production of IFN- γ .⁹ Roles for IL-4 and IFN- γ in the HIV-1 dysregulation of IgE were not suggested by either our study or that of Vigano et al,¹⁷ in which they reported barely detectable levels of IL-4 and IFN- γ in both HIV-1-infected children and controls. While we found detectable levels of serum IL-4 in all our adult subjects, significant differences in IL-4 were found neither for the full cohort of 20 subject during HIV-1 disease progression (Table 1), nor between subjects with and without demonstrated aeroallergen specific-IgE in early or late-HIV disease (Table 3). Thus we find little current support for serum IL-4 playing a significant role in the immune dysregulation of IgE during HIV-1 disease progression.

While serum IFN- γ did not change significantly from early to late-HIV disease for either the entire cohort of 20 subjects or the subgroup with no aeroallergen-specific IgE, the subgroup with serologic evidence for allergic disease did have a significant increase in IFN- γ (Table 3). This increase in IFN- γ may have been responsible for the subgroup's concurrent decrease in prevalence of demonstrated aeroallergen-specific IgE. (This change in IFN- γ , however, is opposite to that expected if IFN- γ played a significant role in the elevation of total IgE with progression to AIDS.)

The soluble low affinity receptor for IgE, sCD23, has been shown to promote in vitro IgE production in periph-

eral blood mononuclear cells independently of IL-4²⁰ and is elevated in atopic sera compared with controls.¹⁸ As a potential mediator in the immune dysregulation of IgE in AIDS, sCD23 has shown little promise in previous studies. Bansal et al²¹ found no difference in sCD23 levels for control and HIV-1 infected patients, with or without AIDS. Similarly, Paganelli et al²² found no difference in sCD23 when comparing controls to atopic and nonatopic individuals with HIV-1 infection. In contrast to these previous studies, our current study found decreasing levels of sCD23 associated with increasing total IgE during progression to late-HIV disease. Soluble-CD23 decreased significantly from early to late-HIV disease for both the subgroup with serologic evidence for allergic disease and for the entire HIV-1 cohort, but not for the subgroup which did not demonstrate aeroallergen-specific IgE (Tables 1 and 3). This decrease in sCD23 is consistent with the observed decrease in prevalence of aeroallergen-specific IgE from early to late-HIV disease, but is opposite to that expected if sCD23 were mediating the changes in total IgE. We may speculate that sCD23 is a mediator of aeroallergen-specific IgE (but not total IgE) expression in HIV-infected atopic individuals.

In summary, we found that with rapid HIV-1 disease progression to AIDS over a mean of 4 years, elevation of serum total IgE in our cohort of subjects was not explained by any concurrent changes in serum levels of IL-4, IFN- γ , or sCD23. Total IgE elevation was unrelated to expression of aeroallergen-specific IgE, suggesting that aeroallergen-specific IgE regulation was different than that of total IgE during HIV-1 disease progression. Among all subjects, aeroallergen-specific IgE expression became less prevalent with HIV-1 disease progression. Those individuals with elevated total IgE both before and after progression to AIDS were a notable exception—they demonstrated an increased prevalence of aeroallergen specific-IgE with HIV-1 disease progression. Serum

IL-4 appeared to play no role; but in the subgroup of patients demonstrating aeroallergen-specific IgE, a significant increase in serum IFN- γ and decrease in sCD23 with HIV-1 disease progression were potential mediators in the overall decrease observed in aeroallergen-specific IgE prevalence during HIV-1 disease progression.

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