Published in final edited form as:
J Infect Dis. 2008 January 15; 197(2): 319–327. doi:10.1086/524848.

Associations of Insulin-Like Growth Factor (IGF)–I and IGF-Binding Protein–3 with HIV Disease Progression in Women

Howard D. Strickler[1], **Melissa Fazzari**[1], **Andrea Kovacs**[3], **Carmen Isasi**[1], **Laura A. Napolitano**[4], **Howard Minkoff**[2], **Stephen Gange**[5], **Mary Young**[7], **Gerald B. Sharp**[6], **Robert C. Kaplan**[1], **Mardge Cohen**[8], **Marc J. Gunter**[1], **Tiffany G. Harris**[1], **Herbert Yu**[9], **Ellie Schoenbaum**[1], **Alan L. Landay**[8], and **Kathryn Anastos**[1]

[1] Albert Einstein College of Medicine, Bronx [2] Maimonides Medical Center, Brooklyn, New York [3] University of Southern California, Los Angeles [4] Gladstone Institute of Virology and Immunology, University of California, San Francisco [5] Johns Hopkins University, Baltimore [6] Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [7] Georgetown University, Washington, DC [8] John H. Stroger Hospital of Cook County and Rush University Medical Center, Chicago, Illinois [9] Yale University, New Haven, Connecticut

Abstract

Background—The insulin-like growth factor (IGF) axis has been hypothesized to influence the rate of human immunodeficiency virus (HIV) disease progression. This premise is based largely on laboratory models showing that IGF-I stimulates thymic growth and increases lymphocyte numbers and that IGF-binding protein (IGFBP)–3 has an opposing effect, inhibiting hematopoietic stem cell development.

Methods—We studied 1422 HIV-infected women enrolled in a large cohort that entailed semiannual follow-up (initiated in 1994). Baseline serum samples were tested for IGF-I and IGFBP-3 to determine their associations with incident clinical acquired immunodeficiency syndrome (AIDS) and $CD4^+$ T cell count decline prior to April 1996 (before the era of highly active antiretroviral therapy [HAART]).

Results—Low IGF-I levels (P_{trend} = .02) and high IGFBP-3 levels (P_{trend} = .02) were associated with rapid $CD4^+$ T cell count decline. Only IGFBP-3, however, was significantly associated with AIDS incidence (hazard ratio for highest vs. lowest quartile, 2.65 [95% confidence interval, 1.30–5.42]; P_{trend} = .02) in multivariable models.

Conclusions—These findings suggest that serum levels of IGFBP-3 (and possibly IGF-I) are associated with the rate of HIV disease progression in women and, more broadly, that interindividual heterogeneity in the IGF axis may influence HIV pathogenesis. If correct, the IGF axis could be a target for interventions to slow HIV disease progression and extend the time before use of HAART becomes necessary.

The insulin-like growth factor (IGF) axis is thought to play a role in host immunity, prompting speculation that it might also affect the host immune response to HIV and influence the rate of HIV disease progression [1–4]. IGF-I, a peptide hormone with strong mitogenic and antiapoptotic activity, mediates many of the effects of growth hormone (GH),

Reprints or correspondence: Dr. Howard D. Strickler, Dept. of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Ave., Belfer 1308-B, Bronx, NY 10461 (strickle@aecom.yu.edu).

Potential conflicts of interest: none reported.

and most cells, including human thymocytes, express the IGF-I receptor [1]. IGF-I can inhibit the apoptosis of hematopoietic progenitor cells [5], and, in animal models, IGF-I administration has been shown to stimulate thymic growth, increase lymphocyte numbers, and partially reverse age-related thymic atrophy [1]. Moreover, the administration of recombinant human IGF-I to cats with feline immunodeficiency virus infection was found to induce thymic cortical regeneration [6].

IGF-binding proteins (IGFBPs) may also play a role in HIV-disease progression. Although IGFBPs were originally considered to be passive circulating transport molecules, they are now understood to play a variety of roles in circulation and within cells [7, 8]. IGFBP-3 is the most abundant IGFBP in serum [7] and has IGF-independent effects that are largely opposite those of IGF-I; that is, IGFBP-3 is proapoptotic [7, 9–17] and has direct antiproliferative effects on the cell cycle [16, 18–22]. IGFBP-3 is expressed by immune cells as well as related stromal cells [1], and, in bone marrow models, IGFBP-3 (but no other IGFBP) was found to inhibit hematopoietic stem cell development [8]. It is reasonable, therefore, to hypothesize that high IGFBP-3 levels might limit the capacity of HIV-infected patients to replace depleted immune cells, including $CD4^+$ T cells.

No studies, however, have actually addressed the fundamental question of whether circulating endogenous levels of IGF-I and IGFBP-3 are associated with HIV disease progression. Observational studies have to date focused mainly on the associations between IGF-I and metabolic disorders in HIV-infected patients, such as lipodystrophy and AIDS wasting [23]. Although these studies contributed useful information on HIV-related metabolic conditions, they were typically small ($n < 100$) and cross-sectional and cannot be used to address the pathogenesis of HIV/AIDS. One observational study of 76 HIV-infected patients that focused on stage of HIV disease found that higher $CD4^+$ T cell count was cross-sectionally associated with higher IGF-I level, higher IGFBP-3 protease activity, and lower total IGFBP-2 level [3]. The prospective predictors of HIV disease progression could not be studied, however. Furthermore, coinfection with hepatitis C virus (HCV) was generally not assessed in prior studies, despite evidence that it is an important potential confounder; that is, HCV has been reported to affect HIV disease progression [24] as well as IGF-I and IGFBP-3 production by the liver [25].

Several small clinical trials, principally pilot studies, have been conducted to evaluate the effects of administering IGF-I, GH, and GH-releasing hormone to HIV-infected patients, but, as with the prior observational studies, most of these trials focused on lipodystrophy and AIDS wasting [23, 26]. One study of 5 HIV-infected adults that focused on HIV pathogenesis found that administration of GH for 6–12 months increased thymic mass and circulating naive $CD4^+$ T cell counts [27], whereas another small pilot study with a shorter follow-up found no effect of GH and/or IGF-I level on $CD4^+$ T cell count [28]. Notably, the impact of these interventions on IGFBP-3 levels and how this might have influenced treatment outcomes were not addressed, even though IGF-I and GH administration increase IGFBP-3 levels.

The present investigation is the first large prospective investigation of the associations of circulating endogenous levels of IGF-I and IGFBP-3 with the risk of incident clinical AIDS. To best understand these biological relationships, we wished to study HIV disease progression unaffected by the use of highly active antiretroviral therapy (HAART); therefore, only specimens and data obtained before the HAART era were used. If an association of IGF-I and/or IGFBP-3 level with incident AIDS was observed, not only would it provide insight into HIV pathogenesis, it would raise the possibility that the IGF axis could be a target for interventions to slow HIV disease (e.g., to extend the time before use of HAART becomes necessary).

METHODS

Subjects and specimens

The Women's Interagency HIV Study (WIHS) is a large multi-institutional prospective cohort investigation of the natural history and pathogenesis of HIV/AIDS in women. As reported in detail elsewhere [29], between October 1994 and November 1995 the WIHS enrolled 2058 HIV-infected and 568 HIV-uninfected women ≥13 years of age from similar clinical and outreach sources at sites in Brooklyn and the Bronx, NY; Chicago, IL; Los Angeles and San Francisco, CA; and Washington, DC. On an ongoing semiannual basis, WIHS subjects undergo an interview and physical examination, during which a blood sample is collected. The WIHS protocol was approved by each local institutional review board, and all participants provided written informed consent. For the present investigation, we selected a random sample of 1450 HIV-infected and 150 HIV-uninfected women. Subjects who missed sequential visits during the first 2 years of follow-up were excluded. Of those selected, 1422 HIV-infected and 146 HIV-uninfected women had enrollment serum specimens available for testing. The HIV-uninfected women were tested solely as a convenient means for establishing IGF-I and IGFBP-3 strata (see below). Follow-up in this substudy was limited to the pre-HAART era (i.e., before April 1996, when HAART use began to involve ≥5% subjects). This restriction was made to optimally assess the biological associations of HIV pathogenesis with endogenous IGF-I and IGFBP-3 levels, given that HAART could potentially alter IGF-I or IGFBP-3 levels and/or perturb their relationship with HIV disease. Notably, had we instead censored women at HAART initiation, it might have introduced confounding by indication, because patients who start treatment are on average less healthy than those who do not (even after controlling for $CD4^+$ T cell counts and HIV RNA levels) [30].

Laboratory measurements

T cell subsets were determined by flow cytometry [31]. Plasma HIV RNA levels were measured with a nucleic acid sequence–based amplification technique that had 4000 copies/mL as its lower threshold of detection (Organon Teknika). HCV serological analysis was performed at baseline using the Abbott HCV EIA 2.0 or 3.0 (Abbott Laboratories). Levels of aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), and albumin, used as measures of liver function, were measured in fresh specimens by standard methodology in Clinical Laboratory Improvement Amendments–certified facilities, as were hemoglobin levels.

All serum specimens were stored at −70°C until tested. Concentrations of total IGF-I and IGFBP-3 were determined using commercially available ELISAs from Diagnostic Systems Laboratories (Webster; kits 10–2800 and 10–6600, respectively), in accordance with the manufacturer's recommendations. In previous testing in our laboratory, the coefficient of variation within and between batches, respectively, was 3.6% and 4.9% for total IGF-I level and 4.2% and 5.5% for IGFBP-3 level, on the basis of masked specimens tested in 45 separate batches (data not shown).

Statistical analysis

IGF-I and IGFBP-3 data were a priori divided into strata, in keeping with what has commonly been done in epidemiological studies of IGFs and cancer [32]. Specifically, we used quartile values of total IGF-I and IGFBP-3 levels in the representative subsample of 146 HIV-uninfected WIHS subjects (i.e., levels unaffected by HIV disease) as a convenient basis for defining the IGF-I and IGFBP-3 strata serocutoffs in our analyses. HIV-uninfected subjects did not otherwise contribute to this study of incident clinical AIDS. In preliminary data analysis, using linear regression, we studied the cross-sectional univariate associations

of total IGF-I and IGFBP-3 levels with selected patient characteristics at baseline, including $CD4^+$T cell count, plasma HIV RNA level, clinical AIDS, history of injection drug use (IDU), HCV serostatus, alcohol consumption, AST level, ALT level, albumin level, hemoglobin level, cigarette smoking, body mass index (BMI), and race/ethnicity. Multivariate linear regression was then used to determine which factors were independently associated with IGF-I and IGFBP-3 quartile—factors that might confound our main analyses of incident clinical AIDS and its associations with IGF-I and IGFBP-3 levels (see below). Age, $CD4^+$ T cell count, and HIV RNA level were included in all models because of their perceived biological importance, as were other variables that were significant in univariate analysis.

Clinical AIDS was defined as a self-report of any of the 26 clinical AIDS surveillance definitions specified in the 1993 Centers for Disease Control revision [33]. Multivariable Cox models were then used to study the association of incident clinical AIDS (among women free of clinical AIDS at baseline) with IGF-I and IGFBP-3 quartile, adjusted for age and other potential confounders. As a first step, we assessed an a priori model, defined before beginning preliminary data analysis, which included baseline $CD4^+$ T cell count, HCV serostatus, age, IGF-I level, and IGFBP-3 level. Plasma HIV RNA level and other potential covariates defined at baseline were evaluated in subsequent models. Specifically, all-subset selection [34, 35] was used to exhaustively evaluate all potential covariates (parameters) and all possible combinations of these potential covariates. In accordance with the approach described by Miller [36] and others [34, 35], any variables that were found to consistently contribute to informative and high-ranking models—as assessed using the overall score statistic at each level of complexity (i.e., the number of parameters in the model)—were subsequently examined in models that incorporated age, IGF-I level, and IGFBP-3 level. A major advantage to this approach (e.g., compared with commonly employed stepwise procedures) is that all-subset selection is more likely to appropriately include covariates in the final model that are noted to be confounders of the variable(s) of interest only when the model contains other pertinent covariates. For completeness, we also assessed whether any covariates found to be significantly associated with IGF-I or IGFBP-3 level or any predictors of incident clinical AIDS in “univariate” models (adjusted only for age) meaningfully altered the effect estimates for IGF-I and IGFBP-3 levels.

Although incident clinical AIDS was our major end point, we also studied the associations of IGF-I and IGFBP-3 with changes in $CD4^+$ T cell count and HIV RNA level. The short follow-up time, though, limited our ability to accurately estimate slopes, because these levels are known to have substantial intraindividual variability [37, 38]—for example, with short follow-up there can be large increases followed by large decreases in the $CD4^+$T cell count (or vice versa), data that can not be meaningfully summarized by a single slope. To address this issue, we limited analysis to women who had a clear pattern to their findings through the first 3 visits. Specifically, for $CD4^+$T cell count, case patients were women with >50 $CD4^+$ T cells/mm^3 at baseline who had a rapid and persisting $CD4^+$ T cell count decline, defined as follows: compared with baseline, the $CD4^+$ T cell counts at both the second and third visit either (1) fell into a lower $CD4^+$ T cell stratum (based on 4 strata, namely, >500, 200–500, 50–<200, and <50 $CD4^+$ T cells/mm^3) or (2) had a ≥50% reduction in count (within the same stratum). In a second analysis, we used a more-moderate ≥20% reduction in $CD4^+$ T cell count in the definition. The comparison group was women whose $CD4^+$T cell count remained at ≥95% of the baseline value through the first 3 visits. A similar approach was used for HIV RNA. Case patients were women with an HIV RNA level >4000 copies/mL at baseline who had a rapid and persisting increase in HIV RNA level, defined as follows: compared with baseline, the HIV RNA level at the second and third visit either (1) fell into a higher HIV RNA stratum (i.e., 4000–<20,000, 20,000–<100,000, and ≥100,000 copies/mL) or (2) doubled in level. The comparison group was

women whose HIV RNA level remained ≤105% of baseline through the first 3 visits. Multivariate logistic regression was then used to study the association of total IGF-I and IGFBP-3 levels with the case-control status for each end point.

RESULTS

Table 1 shows selected baseline characteristics of the 1422 HIV-infected subjects included in this study and the cross-sectional associations of IGF-I and IGFPB-3 levels with these characteristics. A low IGF-I level was significantly associated with a low $CD4^+$ T cell count and a high HIV RNA level, albeit not with clinical AIDS. A number of other factors were also associated with IGF-I levels, and, in the final multivariate model, the level of IGF-I was associated with the $CD4^+$T cell count, HIV RNA level, age, race/ethnicity, HCV serostatus, BMI, and the level of IGFBP-3. For IGFBP-3 levels, we observed cross-sectional associations with the level of HIV RNA but not with $CD4^+$ T cell count or clinical AIDS, and, in the final multivariate model, IGFBP-3 levels were significantly associated with HIV RNA levels, age, race/ethnicity, HCV serostatus, and IGF-I levels.

Incident clinical AIDS occurred in 101 of the 1010 women without AIDS at baseline (before April 1996). Cox proportional hazards models were used to assess the associations of circulating IGF-I and IGFBP-3 levels with the risk (hazard ratio [HR]) of AIDS as well as to identify relevant cofactors. Preliminary Cox models that adjusted only for age are shown in table 2. Having a low $CD4^+$T cell count, high HIV RNA level, use of azidothymidine, low BMI, low hemoglobin level, HCV seropositivity, and high AST level were each significant predictors of incident clinical AIDS. IGF-I and IGFBP-3 levels were not significantly associated with the incidence of clinical AIDS in these initial models.

However, in multivariable Cox analysis, the level of IGFBP-3 was highly significant and, as hypothesized, was positively associated with the risk of incident AIDS (table 3). In our a priori model, the hazard ratio contrasting the highest and lowest IGFBP-3 quartiles [$HR_{q4\text{-}q1}$] was 2.65 (95% confidence interval [CI], 1.30–5.42) with adjustment for age, $CD4^+$ T cell count, HCV seropositivity, and the level of IGF-I. Examination of other models containing the level of IGFBP-3 provided similar inferences. For example, IGFBP-3 levels remained significantly associated with the risk of incident clinical AIDS ($HR_{q4\text{-}q1}$, 2.50 [95% CI, 1.20–5.22]) in a model that adjusted for the $CD4^+$ T cell count, HIV RNA level, HCV seropositivity, smoking status, hemoglobin level, age, and the level of IGF-I. A low BMI (<18.5 kg/m^2) and abnormal liver function test results were also highly significant predictors of incident clinical AIDS in multivariable models, but inclusion of these predictors did not meaningfully alter the relationship between IGFBP-3 levels and the end point or its statistical significance. The level of IGF-I was not significantly associated with AIDS (although the relationship was in the predicted direction), nor was age, but both were retained in the final model because of their perceived biological relevance to the study of IGFBP-3 and AIDS. The trend in HRs across IGFBP-3 quartiles showed that there was a gradient of increasing risk of incident clinical AIDS with increasing IGFBP-3 level (P_{trend} = .02).

Table 4 shows the associations IGF-I and IGFBP-3 levels with risk of a rapid and persistent decline in $CD4^+$T cell count. There were 83 women who had complete data for the first 3 visits and met our strict case definition—that is, a $CD4^+$ T cell count that (1) at the second and third visits fell into a lower $CD4^+$ T cell stratum than at baseline or (2) remained in the same stratum but was ≥50% lower. The comparison group was 190 women with complete data and a stable or increasing $CD4^+$ T cell count. In multivariable logistic regression, we observed contrasting associations of IGF-I level (odds ratio $[OR]_{q4\text{-}q1}$, 0.32 [95% CI, 0.12–0.83]; P_{trend} = .02) and IGFBP-3 levels ($OR_{q4\text{-}q1}$, 2.40 [95% CI, 0.95–6.09]; P_{trend} = .02)

with the risk of rapid and persistent $CD4^+$ T cell count decline, after adjusting for the starting $CD4^+$ T cell stratum, age, and HCV seropositivity. A similar but non-significant association with IGF-I levels ($OR_{q4\text{-}q1}$, 0.55 [95% CI, 0.25–1.18]; P_{trend} = .13) was observed using a more moderate decline of ≥20% (instead of ≥50%) in the case definition (*n* = 124 cases), whereas the association with IGFBP-3 levels remained significant ($OR_{q4\text{-}q1}$, 2.12 [95% CI, 0.97–5.01]; P_{trend} = .01). The findings for a rapid and persisting elevation in HIV RNA level were nonsignificant but showed a similar pattern; that is, the risk of rapid and persisting elevation in HIV RNA levels had a nonsignificant inverse association with the level of IGF-I ($OR_{q4\text{-}q1}$, 0.53 [95% CI, 0.23–1.23]) and a nonsignificant positive association with IGFBP-3 levels ($OR_{q4\text{-}q1}$, 1.72 [95% CI, 0.74–4.04]), after adjusting for starting $CD4^+$ T cell stratum, age, and HCV seropositivity. Inclusion of additional covariates in our multivariable models of $CD4^+$ T cell count or HIV RNA level did not meaningfully alter the above findings (data not shown).

DISCUSSION

This prospective cohort study of >1400 HIV-infected women found a strong positive association between the risk of incident clinical AIDS and high levels of serum IGFBP-3, the main IGFBP in circulation. Specifically, there was a 2.65-fold increase in the risk of incident clinical AIDS among women in the highest compared with those in the lowest IGBFP-3 strata, an effect that was similar in magnitude to that observed for a low versus a high $CD4^+$ T cell count. The effects of IGFBP-3 level on incident clinical AIDS were estimated using statistical models that controlled for $CD4^+$T cell count and HCV serostatus, 2 strong predictors of AIDS in the WIHS cohort, and other likely confounders did not significantly contribute to the results. Therefore, our data suggest that serum IGFBP-3 levels may be an independent predictor of HIV disease progression.

Consistent with these findings, we observed that a high IGFBP-3 level was associated with increased risk of a rapid and persisting $CD4^+$ T cell decline during follow-up. We had additionally predicted that the effects of IGF-I would be opposite those of IGFBP-3, and indeed IGF-I had an inverse association with the development of rapid and persisting declines in $CD4^+$T cell count in prospective analysis. Similarly, in cross-sectional analysis, having poor immune status at enrollment (i.e., a low $CD4^+$T cell count and high HIV RNA level) was associated with a low IGF-I and a high IGFBP-3 level, although the association between IGFBP-3 levels and $CD4^+$ T cell count was not as clear cross-sectionally as it was prospectively (see above). The surprising finding was that the IGF-I level, despite its strong relationship with $CD4^+$ T cell count, was not statistically significantly associated with the risk of incident clinical AIDS; nonetheless, this relationship was in the expected (inverse) direction.

As a whole, these findings provide evidence that interindividual heterogeneity in the IGF axis may be an important host factor in HIV pathogenesis and for the first time indicate that high circulating IGFBP-3 levels may increase the rate of progression to incident clinical AIDS. Although there has been considerable speculation that high circulating IGF-I levels in HIV-infected patients might help preserve thymic mass and function as well as $CD4^+$ T cell count [4, 27]—with the latter supported by the data in the present study—there has been little similar discussion regarding IGFBP-3. IGFBP-3 could play a biological role in HIV pathogenesis either through its effects on IGF-I (binding and sequestering IGF-I in circulation) or independent of IGF-I. IGFBP-3 has been shown to bind cellular targets in the cytoplasm and can localize to the nucleus, where it binds proteins involved in the cell cycle (including Rpb3), suggesting a direct role for IGFBP-3 in the modulation of gene transcription [39]. Cell culture and animal studies show that IGFBP-3 has IGF-independent effects that are largely opposite those of IGF-I; that is, IGFBP-3 is proapoptotic [7, 9–17]

and has direct anti-proliferative effects on the cell cycle [16, 18–22]. Furthermore, IGFBP-3 is expressed by immune cells as well as related stromal cells [1], and, in bone marrow models IGFBP-3 (but no other IGFBP) was observed to inhibit hematopoietic precursor cell development [8]. We cannot, however, distinguish between the IGF-I–dependent and IGF-I–independent effects of IGFBP-3 in this study; nor can we entirely exclude the possibility that serum IGFBP-3 levels are simply a biomarker for an unidentified risk factor that is strongly associated with incident clinical AIDS.

In the future, prospective studies will need to examine the IGF axis more comprehensively, measuring not only total IGF-I and IGFBP-3 levels but also levels of fragmented IGFBP-3, other IGFBPs, free (unbound) IGF-I, and IGF-II (a related growth factor). Indeed, the incomplete assessment of the IGF axis is one possible reason that we may not have observed a statistically significant association between IGF-I levels and the risk of incident clinical AIDS in this study. The present investigation was also limited in having measured total IGF-I and IGFBP-3 levels only at baseline. Although IGF-I and IGFBP-3 levels are reported to be stable for several years in HIV-uninfected subjects, repeated observations and much longer follow-up of HIV-infected patients will be needed to more accurately measure the association between the IGF axis and the risk of incident AIDS. Furthermore, our study did not address whether serum IGF-I and IGFBP-3 levels are associated with the effectiveness of HAART use, which will be very important to determine in future studies; nor did we study men or children and adolescents. Separate studies of men are necessary because there is extensive biological cross talk between the sex hormone and IGF axes, and there are known sex-related differences in the progression of HIV disease [40]. Separate studies of children will be important because serum levels of IGF-I, IGFBP-3, and other IGF axis components vary considerably during development, and there are known age-related differences in HIV disease progression [41].

The results of the present investigation await confirmation. If correct, our findings indicate that serum IGFBP-3, and possibly IGF-I, may be involved in HIV disease progression; evidence that interindividual heterogeneity in the IGF axis may be an important host factor in HIV pathogenesis. From a clinical perspective, these data suggest that the IGF axis might be a target for interventions to slow HIV disease progression (and possibly forestall the need to initiate HAART). Such interventions will be of increasing importance as the HAART era continues. As recently stated, “despite declines in morbidity and mortality with the use of combination antiretroviral therapy, its effectiveness is limited by adverse events, problems with adherence, and resistance of HIV” [42]. Further efforts are, therefore, warranted to more comprehensively assess the effects of the IGF axis on HIV disease progression and to determine whether these effects might be exploited to treat patients with HIV infection both before and possibly during the use of HAART.

Acknowledgments

Financial support: Center for AIDS Research at the Albert Einstein College of Medicine and the Montefiore Medical Center, funded by the National Institutes of Health (grant AI-51519). Data in this manuscript were collected by the Women’s Interagency HIV Study (WIHS) Collaborative Study Group with centers (principal investigators) at the New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); the Washington, DC, Metropolitan Consortium (Mary Young); the Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); the Los Angeles County/Southern California Consortium (Alexandra Levine); the Chicago Consortium (Mardge Cohen); and the Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases, with supplemental funding from the National Cancer Institute and the National Institute on Drug Abuse (grants UO1-AI-35004, UO1-AI-31834, UO1-AI-34994, UO1-AI-34989, UO1-AI-34993, and UO1-AI-42590). Funding was also provided by the National Institute of Child Health and Human Development (grant UO1-HD-32632) and the National Center for Research Resources (grants MO1-RR-00071, MO1-RR-00079, and MO1-RR-00083).

References

1. Clark R. The somatogenic hormones and insulin-like growth factor-1: stimulators of lymphopoiesis and immune function. Endocr Rev. 1997; 18:157–79. [PubMed: 9101135]
2. Chappel S. Growth hormone in immune reconstitution. J Acquir Immune Defic Syndr Hum Retrovirol. 1999; 20:423–31. [PubMed: 10225223]
3. Helle SI, Ueland T, Ekse D, et al. The insulin-like growth factor system in human immunodeficiency virus infection: relations to immunological parameters, disease progression, and antiretroviral therapy. J Clin Endocrinol Metab. 2001; 86:227–33. [PubMed: 11232005]
4. van den Brink MR, Alpdogan O, Boyd RL. Strategies to enhance T-cell reconstitution in immunocompromised patients. Nat Rev Immunol. 2004; 4:856–67. [PubMed: 15516965]
5. Kelley KW, Meier WA, Minshall C, et al. Insulin growth factor-I inhibits apoptosis in hematopoietic progenitor cells. Implications in thymic aging. Ann NY Acad Sci. 1998; 840:518–24. [PubMed: 9629278]
6. Woo JC, Dean GA, Lavoy A, Clark R, Moore PF. Investigation of recombinant human insulin-like growth factor type I in thymus regeneration in the acute stage of experimental FIV infection in juvenile cats. AIDS Res Hum Retroviruses. 1999; 15:1377–88. [PubMed: 10515153]
7. Firth SM, Baxter RC. Cellular actions of the insulin-like growth factor binding proteins. Endocr Rev. 2002; 23:824–54. [PubMed: 12466191]
8. Taguchi T, Takenouchi H, Matsui J, et al. Involvement of insulin-like growth factor-I and insulin-like growth factor binding proteins in proB-cell development. Exp Hematol. 2006; 34:508–18. [PubMed: 16569597]
9. Rajah R, Katz L, Nunn S, Solberg P, Beers T, Cohen P. Insulin-like growth factor binding protein (IGFBP) proteases: functional regulators of cell growth. Prog Growth Factor Res. 1995; 6:273–84. [PubMed: 8817670]
10. Rajah R, Khare A, Lee PD, Cohen P. Insulin-like growth factor-binding protein-3 is partially responsible for high-serum-induced apoptosis in PC-3 prostate cancer cells. J Endocrinol. 1999; 163:487–94. [PubMed: 10588822]
11. Rajah R, Lee KW, Cohen P. Insulin-like growth factor binding protein-3 mediates tumor necrosis factor-alpha-induced apoptosis: role of Bcl-2 phosphorylation. Cell Growth Differ. 2002; 13:163–71. [PubMed: 11971816]
12. Rajah R, Valentinis B, Cohen P. Insulin-like growth factor (IGF)-binding protein-3 induces apoptosis and mediates the effects of transforming growth factor-beta1 on programmed cell death through a p53-and IGF-independent mechanism. J Biol Chem. 1997; 272:12181–8. [PubMed: 9115291]
13. Cobb LJ, Liu B, Lee KW, Cohen P. Phosphorylation by DNA-dependent protein kinase is critical for apoptosis induction by insulin-like growth factor binding protein-3. Cancer Res. 2006; 66:10878–84. [PubMed: 17108124]
14. Lee KW, Ma L, Yan X, Liu B, Zhang XK, Cohen P. Rapid apoptosis induction by IGFBP-3 involves an insulin-like growth factor-independent nucleomitochondrial translocation of RXRalpha/Nur77. J Biol Chem. 2005; 280:16942–8. [PubMed: 15731112]
15. Butt AJ, Fraley KA, Firth SM, Baxter RC. IGF-binding protein-3-induced growth inhibition and apoptosis do not require cell surface binding and nuclear translocation in human breast cancer cells. Endocrinology. 2002; 143:2693–9. [PubMed: 12072403]
16. Hong J, Zhang G, Dong F, Rechler MM. Insulin-like growth factor (IGF)-binding protein-3 mutants that do not bind IGF-I or IGF-II stimulate apoptosis in human prostate cancer cells. J Biol Chem. 2002; 277:10489–97. [PubMed: 11784719]
17. Bhattacharyya N, Pechhold K, Shahjee H, et al. Nonsecreted insulin-like growth factor binding protein-3 (IGFBP-3) can induce apoptosis in human prostate cancer cells by IGF-independent mechanisms without being concentrated in the nucleus. J Biol Chem. 2006; 281:24588–601. [PubMed: 16793770]
18. Hochscheid R, Jaques G, Wegmann B. Transfection of human insulin-like growth factor-binding protein 3 gene inhibits cell growth and tumorigenicity: a cell culture model for lung cancer. J Endocrinol. 2000; 166:553–63. [PubMed: 10974650]

19. Valentinis B, Bhala A, DeAngelis T, Baserga R, Cohen P. The human insulin-like growth factor (IGF) binding protein-3 inhibits the growth of fibroblasts with a targeted disruption of the IGF-I receptor gene. Mol Endocrinol. 1995; 9:361–7. [PubMed: 7539889]
20. Fanayan S, Firth SM, Butt AJ, Baxter RC. Growth inhibition by insulin-like growth factor-binding protein-3 in T47D breast cancer cells requires transforming growth factor-beta (TGF-beta) and the type II TGF-beta receptor. J Biol Chem. 2000; 275:39146–51. [PubMed: 10993898]
21. Burger AM, Leyland-Jones B, Banerjee K, Spyropoulos DD, Seth AK. Essential roles of IGFBP-3 and IGFBP-rP1 in breast cancer. Eur J Cancer. 2005; 41:1515–27. [PubMed: 15979304]
22. Barreca A, Artini PG, Cesarone A, et al. Interrelationships between follicle stimulating hormone and the growth hormone—insulin-like growth factor—IGF-binding proteins axes in human granulosa cells in culture. J Endocrinol Invest. 1996; 19:35–42. [PubMed: 8851690]
23. Congote LF. Monitoring insulin-like growth factors in HIV infection and AIDS. Clin Chim Acta. 2005; 361:30–53. [PubMed: 15970280]
24. Rockstroh JK. Influence of viral hepatitis on HIV infection. J Hepatol. 2006; 44:S25–7. [PubMed: 16338020]
25. Donaghy AJ, Delhanty PJ, Ho KK, Williams R, Baxter RC. Regulation of the growth hormone receptor/binding protein, insulin-like growth factor ternary complex system in human cirrhosis. J Hepatol. 2002; 36:751–8. [PubMed: 12044524]
26. Koutkia P, Canavan B, Breu J, Torriani M, Kissko J, Grinspoon S. Growth hormone-releasing hormone in HIV-infected men with lipodystrophy: a randomized controlled trial. JAMA. 2004; 292:210–8. [PubMed: 15249570]
27. Napolitano LA, Lo JC, Gotway MB, et al. Increased thymic mass and circulating naive CD4 T cells in HIV-1-infected adults treated with growth hormone. AIDS. 2002; 16:1103–11. [PubMed: 12004268]
28. Nguyen BY, Clerici M, Venzon DJ, et al. Pilot study of the immunologic effects of recombinant human growth hormone and recombinant insulin-like growth factor in HIV-infected patients. AIDS. 1998; 12:895–904. [PubMed: 9631143]
29. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's Inter-agency HIV Study. WIHS Collaborative Study Group. Epidemiology. 1998; 9:117–25. [PubMed: 9504278]
30. Ahdieh L, Gange SJ, Greenblatt R, et al. Selection by indication of potent antiretroviral therapy use in a large cohort of women infected with human immunodeficiency virus. Am J Epidemiol. 2000; 152:923–33. [PubMed: 11092434]
31. Calvelli T, Denny TN, Paxton H, Gelman R, Kagan J. Guideline for flow cytometric immunophenotyping: a report from the National Institute of Allergy and Infectious Diseases, Division of AIDS. Cytometry. 1993; 14:702–15. [PubMed: 8243200]
32. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004; 363:1346–53. [PubMed: 15110491]
33. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992; 41(RR-17):1–19.
34. Montgomery, D.; Peck, E. Introduction to linear regression analysis. New York: John Wiley & Sons; 1982.
35. Hosmer, D.; Lemeshow, S. Applied logistic regression. New York: John Wiley & Sons; 2000.
36. Miller, A. Subset Selection in Regression. 2. New York: Chapman & Hall; 2002.
37. Rodriguez B, Sethi AK, Cheruvu VK, et al. Predictive value of plasma HIV RNA level on rate of CD4 T-cell decline in untreated HIV infection. JAMA. 2006; 296:1498–506. [PubMed: 17003398]
38. Lima VD, Hogg RS, Montaner JS. Presenting plasma HIV RNA level and rate of CD4 T-cell decline. JAMA. 2007; 297:805–6. author reply 806 –7. [PubMed: 17327517]
39. Oufattole M, Lin SW, Liu B, Mascarenhas D, Cohen P, Rodgers BD. Ribonucleic acid polymerase II binding subunit 3 (Rpb3), a potential nuclear target of insulin-like growth factor binding protein-3. Endocrinology. 2006; 147:2138–46. [PubMed: 16455777]
40. Anastos K, Gange SJ, Lau B, et al. Association of race and gender with HIV-1 RNA levels and immunologic progression. J Acquir Immune Defic Syndr. 2000; 24:218–26. [PubMed: 10969345]

41. Anabwani GM, Woldetsadik EA, Kline MW. Treatment of human immunodeficiency virus (HIV) in children using antiretroviral drugs. Semin Pediatr Infect Dis. 2005; 16:116–24. [PubMed: 15825142]

42. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006; 355:2283–96. [PubMed: 17135583]

J Infect Dis. Author manuscript; available in PMC 2011 June 30.

Table 1

Selected baseline characteristics and their cross-sectional associations with insulin-like growth factor (IGF)–I and IGF-binding protein (IGFBP)–3 levels.

Variable	No. (%)	IGF-1 level, mean (95% CI), ng/mL	Final multivariate model of associations with IGF-I quartile		IGFBP-3 level, mean (95% CI), ng/mL	Final multivariate model of associations with IGFBP-3 quartile	
			OR (95% CI)[a]	P_{trend}[b]		OR (95% CI)[a]	P_{trend}[b]
Age				<.001			
<26 years	104 (7)	295 (280 to 310)	1.15 (0.92 to 1.39)***		3423 (3259 to 3588)	0.39 (0.14 to 0.63)**	
26–29 years	180 (13)	265 (253 to 276)	0.95 (0.75 to 1.15)***		3279 (3154 to 3404)	0.45 (0.24 to 0.65)***	
30–35 years	405 (28)	236 (228 to 243)	0.71 (0.54 to 0.87)***		3226 (3143 to 3310)	0.37 (0.19 to 0.55)***	
36–45 years	572 (40)	200 (193 to 206)	0.44 (0.28 to 0.60)***		2937 (2867 to 3007)	−0.39 (−0.56 to −0.22)***	
>45 years	161 (11)	178 (166 to 190)	Reference		3084 (2953 to 3217)	Reference	
Race/ethnicity							
Black, non to Hispanic	786 (55)	226 (220 to 232)	0.29 (0.16 to 0.42)***		3057 (2997 to 3118)	−0.45 (−0.61 to −0.29)***	
Hispanic	351 (25)	212 (204 to 309)	−0.03 (−0.18 to 0.12)		3049 (2960 to 3140)	−0.39 (−0.56 to −0.21)***	
Other	38 (3)	221 (193 to 208)	−0.09 (−0.4 to 0.22)		3163 (2889 to 3437)	−0.23 (−0.61 to 0.14)	
White	247 (17)	227 (216 to 237)	Reference		3384 (3276 to 3492)	Reference	
$CD4^+$ T cell count				.03			.51
<200 cells/mm^3	335 (24)	216 (206 to 225)	−0.13 (−0.28 to 0.01)		3230 (3137 to 3322)	0.06 (−0.09 to 0.21)	
200–350 cells/mm^3	346 (25)	219 (209 to 228)	−0.07 (−0.21 to 0.06)		3072 (2980 to 3164)	0.01 (−0.13 to 0.14)	
>350–500 cells/mm^3	309 (22)	227 (216 to 236)	0.04 (−0.09 to 0.17)		3099 (3002 to 3195)	0.01 (−0.12 to 0.15)	
>500 cells/mm^3	406 (29)	228 (220 to 237)	Reference		3077 (2992 to 3161)	Reference	
HIV RNA level				.22			.005
>100,000 copies/mL	277 (20)	219 (209 to 229)	−0.20 (−0.35 to −0.05)***		3258 (3156 to 3360)	0.22 (0.06 to 0.37)**	
20,001–100,000 copies/mL	381 (27)	221 (213 to 230)	−0.10 (−0.24 to 0.03)		3145 (3058 to 3232)	0.07 (−0.07 to 0.20)	
>4000–20,000 copies/mL	313 (22)	214 (205 to 224)	−0.15 (−0.28 to −0.02)*		2976 (2880 to 3072)	0.001 (−0.14 to 0.14)	
0–4000 copies/mL	446 (31)	231 (223 to 239)	Reference		3093 (3013 to 3173)	Reference	
Prevalent clinical AIDS							

Variable	No. (%)	IGF-1 level, mean (95% CI), ng/mL	Final multivariate model of associations with IGF-I quartile		IGFBP-3 level, mean (95% CI), ng/mL	Final multivariate model of associations with IGFBP-3 quartile	
			OR (95% CI)[a]	P_{trend}[b]		OR (95% CI)[a]	P_{trend}[b]
AIDS at baseline	412 (29)	218 (210 to 226)			3099 (3014 to 3183)		
No AIDS	993 (71)	224 (219 to 230)			3126 (3072 to 3181)		
AZT use							
Not currently using	573 (40)	222 (215 to 230)			3080 (3008 to 3151)		
Currently using	849 (60)	223 (217 to 228)			3139 (3081 to 3198)		
Body mass index				.007			
Underweight (<18.5 kg/m^2)	33 (2)	268 (238 to 297)	0.45 (0.13 to 0.76)**		3557 (3261 to 3853)		
Normal (18.5–25 kg/m^2)	561 (41)	229 (222 to 236)	0.41 (0.29 to 0.53)***		3094 (3022 to 3166)		
Overweight (>25.0–30.0 kg/m^2)	423 (31)	229 (221 to 237)	0.43 (0.31 to 0.56)***		3138 (3056 to 3221)		
Obese (>30.0 kg/m^2)	353 (26)	202 (193 to 211)	Reference		3078 (2988 to 3169)		
Smoking							
Not a current smoker	635 (45)	225 (219 to 232)			3205 (3138 to 3273)	−0.09 (−0.2 to 0.02)	
Current smoker	787 (55)	220 (214 to 226)			3043 (2982 to 3103)	Reference	
Injection drug use							
Current	133 (9)	197 (182 to 211)			2841 (2696 to 2987)		
Former	432 (30)	198 (190 to 206)			2965 (2884 to 3046)		
No history of	855 (60)	239 (233 to 244)			3232 (3175 to 3290)		
Alcohol consumption							
Heavy (>13 drinks/week)	125 (9)	210 (195 to 226)			2948 (2796 to 3101)		
Moderate (3–13 drinks/week)	231 (17)	219 (208 to 230)			3173 (3061 to 3285)		
Light (<3 drinks/week)	444 (32)	231 (223 to 239)			3160 (3080 to 3241)		
Abstains	582 (42)	220 (213 to 227)			3088 (3018 to 3159)		
Hemoglobin level							
≤11 g/dL	200 (14)	225 (213 to 237)			3245 (3125 to 3365)		
>11 g/dL	1209 (86)	222 (217 to 227)			3091 (3042 to 3139)		
Hepatitis C virus status							
Seropositive	574 (41)	196 (190 to 203)	−0.19 (−0.30 to −0.08)**		2919 (2850 to 2988)	−0.18 (−0.30 to −0.06)**	

Variable	No. (%)	IGF-1 level, mean (95% CI), ng/mL	Final multivariate model of associations with IGF-I quartile		IGFBP-3 level, mean (95% CI), ng/mL	Final multivariate model of associations with IGFBP-3 quartile	
			OR (95% CI)[a]	P_{trend}[b]		OR (95% CI)[a]	P_{trend}[b]
Seronegative	810 (59)	242 (237 to 248)	Reference		3266 (3208 to 3325)	Reference	
ALT level							
Elevated	244 (17)	188 (180 to 197)			2880 (2791 to 2969)		
Not elevated	1165 (83)	234 (229 to 239)			3196 (3144 to 3248)		
AST level							
Elevated	352 (25)	198 (187 to 208)			2936 (2830 to 3042)		
Not elevated	1057 (75)	228 (223 to 233)			3156 (3106 to 3206)		
Albumin level							
Low	84 (6)	198 (181 to 214)			2849 (2685 to 3013)		
Not low	1326 (94)	225 (220 to 229)			3139 (3091 to 3186)		
All liver tests (ALT, AST, albumin)							
All results abnormal	40 (3)	153 (128 to 180)			2448 (2182 to 2713)		
1–2 results abnormal	384 (27)	198 (190 to 207)			2961 (2876 to 3047)		
All results normal	985 (70)	235 (230 to 240)			3204 (3150 to 3257)		
IGFBP-3 level				<.001			
First quartile	348 (24)	156 (148 to 163)	−1.64 (−1.79 to −1.50)***				
Second quartile	388 (27)	203 (196 to 210)	−1.04 (−1.18 to −0.89)***				
Third quartile	329 (23)	246 (238 to 253)	−0.54 (−0.69 to −0.40)***				
Fourth quartile	357 (25)	287 (280 to 294)	Reference				
IGF-I level							<.001
First quartile	432 (30)				2516 (2448 to 2585)	−1.58 (−1.72 to −1.44)***	
Second quartile	329 (23)				2978 (2899 to 3056)	−1.02 (−1.15 to −0.89)***	
Third quartile	316 (22)				3349 (3269 to 3429)	−0.44 (−0.58 to −0.30)***	
Fourth quartile	345 (24)				3782 (3705 to 3858)	Reference	

NOTE. Percentages do not always total to 100% because of rounding. The total no. of subjects does not always equal 1422 because of the unavailability of the indicated data. Serocutoffs for IGF-I and IGFBP-3 were defined using the quartile values obtained in a random subsample of HIV-uninfected women enrolled in the Women's Interagency HIV Study. For IGF-I, these serocutoffs were 173, 219, and 275 ng/mL. For IGFBP-3, these serocutoffs were 2497, 3094, and 3660 ng/mL. The univariate analyses show results based on the absolute (continuous) values for IGF-I and IGFBP-3 (to demonstrate scale). However, the multivariate analysis is based on the quartile of IGF-I and IGFBP-3 level, consistent with the use of these quartiles in studying the associations of IGF-I and IGFBP-3 with the risk of incident AIDS. Thus, the effect estimates in the multivariate models indicate the strength of the association but do not relate to the SD of IGF-I or IGFBP-3 level (as would be the case if their continuous values were used in the analysis). ALT, alanine transaminase; AST, aspartate transaminase; AZT, azidothymidine; CI, confidence interval; OR, odds ratio.

[a] *$P < .05$; **$P < .01$; ***$P < .001$.

[b] P_{trend} is reported only for ordinal data and only if statistically significant (i.e., <.05).

Table 2

Statistical associations of incident clinical AIDS with patient characteristics and serum insulin-like growth factor (IGF)–I and IGF-binding protein (IGFBP)–3 levels in age-adjusted Cox regression models.

Variable	HR (95% CI)[a]	P_{trend}[b]
Age group (age as the only covariate)		
26–29 years	1.78 (0.58–5.48)	
30–35 years	2.28 (0.81–6.42)	
36–45 years	2.34 (0.84–6.52)	
>45 years	1.34 (0.39–4.58)	
<26 years old	Reference	
Race/ethnicity		
Black, non-Hispanic	1.16 (0.66–2.06)	
Hispanic	1.24 (0.64–2.24)	
Other	0.38 (0.05–2.91)	
White	Reference	
$CD4^+$ T cell count		<.001
<200 cells/mm^3	2.92 (1.74–4.87)***	
200–350 cells/mm^3	1.15 (0.64–2.09)	
>350–500 cells/mm^3	0.86 (0.45–1.62)	
>500 cells/mm^3	Reference	
HIV RNA level		<.001
>100,000 copies/mL	3.60 (2.07–6.28)***	
20,001–100,000 copies/mL	1.88 (1.07–3.30)*	
4000–20,000 copies/mL	1.52 (0.82–2.80)	
<4000 copies/mL	Reference	
AZT use	1.84 (1.20–2.81)***	
Body mass index		
Underweight (<18.5 kg/m^2)	3.37 (1.37–8.28)***	
Normal weight (18.5–25.0 kg/m^2)	1.09 (0.64–1.85)	
Overweight (>25.0–30.0 kg/m^2)	1.45 (0.86–2.44)	
Obese (>30.0 kg/m^2)	Reference	
IGF-1 level		
First quartile	1.21 (0.71–2.09)	
Second quartile	0.75 (0.40–1.39)	
Third quartile	0.95 (0.53–1.70)	
Fourth quartile	Reference	
IGFBP-3 level		
Fourth quartile	1.52 (0.86–2.63)	
Third quartile	1.43 (0.85–2.38)	

Variable	HR (95% CI)[a]	P_{trend}[b]
Second quartile	1.28 (0.76–2.17)	
First quartile	Reference	
Current smoker	1.38 (0.93–2.05)	
Injection drug use		
History of	1.44 (0.94–2.20)	
Current	1.28 (0.64–2.52)	
No history of	Reference	
Alcohol consumption		
Light drinker (<3 drinks/week)	0.84 (0.54–1.34)	
Moderate drinker (3–13 drinks/week)	0.78 (0.44–1.44)	
Heavy drinker (>13 drinks/week)	1.34 (0.70–2.62)	
Abstains	Reference	
Hemoglobin, g/dL		
≥11 g/dL	1.88 (1.16–3.05)**	
>11 g/dL	Reference	
HCV seropositive	2.09 (1.40–3.12)***	
Elevated ALT level	1.50 (0.96–2.36)	
Elevated AST level	1.88 (1.25–2.82)***	
Low albumin level	0.59 (0.22–1.59)	
All liver tests (ALT, AST, albumin)		
All results abnormal	1.91 (1.26–2.90)***	
1–2 test results abnormal	0.70 (0.26–1.94)	
All results normal	Reference	

NOTE. The 101 first AIDS events were as follows: 17% esophageal candidiasis, 15% herpes simplex, 13% encephalopathy, 12% pneumocystitis carinii pneumonia, 10% recurrent pneumonia, 8% tuberculosis, 6% wasting syndrome, 4% *Mycobacterium avium* complex, 3% cryptococcosis, and 12% other (i.e., <2% each for cervical cancer, Kaposi sarcoma, toxoplasmosis, uterine cancer, skin cancer, non-Hodgkin lymphoma, cytomegalovirus [CMV], CMV retinitis, and histoplasmosis). ALT, alanine transaminase; AST, aspartate transaminase; AZT, azidothymidine; CI, confidence interval; HR, hazard ratio.

[a] $*P < .05$; $**P < .01$; $***P < .001$.

[b] P_{trend} is reported only for ordinal data and only if statistically significant (i.e., <.05).

Table 3

Final multivariable Cox model of the associations of insulin-like growth factor (IGF)–I and IGF-binding protein (IGFBP)–3 levels with the risk of AIDS.

Variable	HR (95% CI)[a]	P_{trend}[b]
$CD4^+$ T cell count		<.001
<200 cells/mm^3	2.79 (1.64–4.76)***	
200–350 cells/mm^3	1.11 (0.61–2.01)	
>350–500 cells/mm^3	0.81 (0.42–1.56)	
>500 cells/mm^3	Reference	
HCV seropositive	2.18 (1.39–3.42)***	
Age group		
26–30 years	1.62 (0.53–5.01)	
31–35 years	1.59 (0.54–4.63)	
36–45 years	1.32 (0.45–3.90)	
>45 years	0.77 (0.22–2.78)	
<26 years	Reference	
IGF-I level		
Fourth quartile	0.64 (0.35–1.18)	
Third quartile	0.80 (0.42–1.51)	
Second quartile	0.70 (0.36–1.37)	
First quartile	Reference	
IGFBP-3 level		.02
Fourth quartile	2.65 (1.30–5.42)***	
Third quartile	1.77 (0.89–3.54)	
Second quartile	1.62 (0.86–3.07)	
First quartile	Reference	

NOTE. Although IGF-I level and age were not statistically significantly associated with incident AIDS, they were retained in the final model because of their perceived biological relevance to the association between IGFBP-3 level and incident clinical AIDS as well as this being the a priori statistical model determined before data analysis. CI, confidence interval; HR, hazard ratio.

[a] *$P < .05$; **$P < .01$; ***$P < .001$.

[b] P_{trend} is reported only for ordinal data and only if statistically significant (i.e., <.05).

Table 4

Multivariable logistic regression model of the associations of insulin-like growth factor (IGF)–I and IGF-binding protein (IGFBP)–3 levels with a rapid and persistent $CD4^+$ T cell decline (n = 83) vs. a stable or increasing $CD4^+$ T cell count (n = 190).

Variable	OR (95% CI)[a]	P_{trend}[b]
Initial $CD4^+$ T cell count stratum		
50–200 cells/mm^3	0.76 (0.34–1.67)	
200–500 cells/mm^3	0.38 (0.20–0.70)**	
>500 cells/mm^3	Reference	
HCV seropositive	0.76 (0.34–1.67)	
Age (continuous)	1.00 (0.96–1.04)	
IGF-I level		.02
Fourth quartile	0.32 (0.12–0.83)*	
Third quartile	0.48 (0.21–1.10)	
Second quartile	0.80 (0.38–1.702)	
First quartile	Reference	
IGFBP-3 level		.02
Fourth quartile	2.40 (0.95–6.09)	
Third quartile	2.37 (1.05–5.34)*	
Second quartile	0.94 (0.42–2.09)	
First quartile	Reference	

NOTE. Age was parameterized as a continuous (instead of as a categorical) variable because of its fairly monotonic association with AIDS in the above analyses (see table 3) and to minimize the degrees of freedom in the current model given the smaller no. of case patients and control subjects involved in this particular analysis. CI, confidence interval; OR, odds ratio.

[a] $*P < .05$; $**P < .01$; $***P < .001$.

[b] P_{trend} is reported only for ordinal data and only if statistically significant (i.e., <.05).