Immune Reconstitution Syndrome in HIV: Validating a Case Definition and Identifying Clinical Predictors in Persons Initiating Antiretroviral Therapy

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Background. Clinical deterioration after initiation of antiretroviral therapy may result from restored immunity. There is no standard clinical definition for immune reconstitution syndrome. The objectives of this study were to validate a proposed definition and to identify factors predictive of immune reconstitution syndrome.

Methods. This was a retrospective case-control study from an academic university medical practice. Cases were matched to ⩾2 control subjects by $CD4^+$ cell count at the time of initiation of antiretroviral therapy. Cases and "mock cases" were blindly reviewed by 2 human immunodeficiency virus (HIV) experts.

Results. Twenty possible cases of immune reconstitution syndrome were identified; HIV experts excluded all cases of herpes zoster (shingles), with agreement on real and mock cases of 92%. For 14 confirmed case patients (compared with 40 control subjects), immune reconstitution syndrome was associated with a higher number of prior opportunistic infections ($P = .003$) and higher $CD8^+$ cell counts at baseline ($P = .05$) and at week 12 ($P = .02$). Immune reconstitution syndrome was associated with lower baseline levels of alanine aminotransferase ($P = .05$) and hemoglobin ($P = .02$). On multivariate analysis, the number of prior opportunistic infections (odds ratio, 2.7; $P = .007$) and lower hemoglobin level at baseline (odds ratio, 0.8; $P = .003$) were independently associated with development of immune reconstitution syndrome. A predictive model was defined by classification and regression tree analysis with a sensitivity and specificity of 78.57% and 87.50%, respectively, for an importance score of ⩾4 (on a scale of 0.0 to 100.0), and 92.86% and 80.00%, respectively, for a score of ⩾2, using the number of prior opportunistic infections, $CD8^+$ cell count, and hemoglobin level.

Conclusions. A standard definition for immune reconstitution syndrome is possible. Patients with a greater severity of illness at initiation of antiretroviral therapy are at risk for immune reconstitution syndrome. The model defined by classification and regression tree analysis may provide a basis for risk stratification before initiation of antiretroviral therapy.

The introduction of combination antiretroviral therapy has dramatically improved outcomes for persons living with HIV infection. Successful suppression of viral replication is followed by an increase in $CD4^+$ lymphocytes and a partial recovery of T cell–specific immune responses, which correlates with decreased susceptibility to opportunistic pathogens [1]. Some persons, however, experience a clinical deterioration following initiation of antiretroviral therapy that is believed to be a consequence of the restored ability to mount an inflammatory response. This phenomenon has been termed immune reconstitution syndrome, immune restoration disease, immunorestitution disease, or immune reconstitution inflammatory syndrome. Immune reconstitution syndrome has been reported in association with a number of diseases and inflammatory conditions [2, 3]. In many cases, immune reconstitution syndrome may be mild and resolve without treatment. Deaths, however, have been reported, particularly in cases in which there is CNS involvement with progressive multifocal leukoencephalopathy or infection with *Cryptococcus* species or *Mycobacterium tuberculosis* [3–5]. Be-

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cause the manifestations of immune reconstitution syndrome vary widely, depending on the target to which the restored inflammatory response is directed, it is difficult to describe as a single clinical entity. The incidence of this disorder has been estimated to be 10% among persons starting antiretroviral therapy and as high as 25% among patients starting therapy who have a $CD4^+$ cell count of <50 cells/mm^3 [6]. The true incidence of immune reconstitution syndrome, however, is yet to be determined, in part because no consensus has been achieved regarding a clinical definition.

It is important to define immune reconstitution syndrome as a clinical entity to facilitate diagnosis and further characterization of this disease. Identification of risk factors associated with the development of immune reconstitution syndrome may make it possible to characterize a population of patients that may benefit from preemptive treatment with anti-inflammatory agents. The objectives of this study were to validate a proposed clinical definition of immune reconstitution syndrome and to determine clinical or routine laboratory factors associated with its development.

MATERIALS AND METHODS

In a retrospective case-control study, cases of presumed immune reconstitution syndrome and control subjects were identified from records of patients at the University of Cincinnati Infectious Disease Center who started taking combination antiretroviral therapy between 1996 and 2002. All records of persons who initiated antiretroviral therapy during this time period were reviewed to determine whether an opportunistic illness developed subsequent to starting therapy. To define cases of immune reconstitution syndrome, we used the following modification of criteria proposed by a working group in the AIDS Clinical Trials Group: new onset or worsening symptoms of an infection or inflammatory condition following the initiation of antiretroviral therapy; symptoms not explained by a newly acquired infection, the predicted course of a previously diagnosed infection, or the adverse effects of drug therapy; and demonstration of a ⩾1-log decrease in the number of HIV RNA copies (Judith, Feinberg, personal communication). Control subjects were HIV-infected patients who did not develop clinical events consistent with the proposed study definition for immune reconstitution syndrome. Each control subject was matched to a case patient by $CD4^+$ cell count and year of enrollment in the clinic. Twenty possible case patients with immune reconstitution syndrome were identified and matched to 40 control subjects. Data for case patients and control subjects were abstracted by 2 authors (M.M. and J.W.) and were reviewed by a senior author (C.J.F.) for accuracy. A blinded panel of 2 infectious disease experts with >15 years of experience in treating persons with AIDS reviewed the cases to determine their validity. To avoid bias and to validate the proposed definition of immune reconstitution syndrome, 4 "mock cases" were created (by J.W. and C.J.F.) to represent classical presentations of common opportunistic infections (2 cases of dermatomal zoster and 1 case each of cryptococcal meningitis and *Mycobacterium avium* complex infection). Mock cases were chosen to ensure that sufficient data were available to render an opinion and represent diseases commonly seen at the clinic. Experts received a case summary and laboratory information with the instruction that although there is no widely accepted definition of immune reconstitution syndrome, consensus opinion suggests that a response to antiretroviral therapy is required at a minimum. Experts were then asked to render an opinion for each case regarding whether or not it represented a case of immune reconstitution syndrome. Demographic data, history of opportunistic infections, and a baseline symptom history were abstracted for each case patient. Data from complete blood cell counts and liver enzyme tests were collected for the period prior to initiation of antiretroviral therapy for all control subjects and case patients and at the time of presentation of immune reconstitution syndrome for case patients. HIV load, $CD4^+$ cell count, and $CD8^+$ cell count data were collected for intervals corresponding to baseline (before initiation of antiretroviral treatment) and 4–12 weeks, 12–16 weeks, and 16–28 weeks after the start of therapy.

Data were analyzed for differences between case patients and control subjects with respect to baseline demographic information, complete blood cell count, liver enzyme measurements, and symptoms. HIV load, $CD4^+$ cell count, $CD4^+$ cell percentage, $CD8^+$ cell count, $CD8^+$ cell percentage, change in $CD4^+$ or $CD8^+$ cell count, and ratio of $CD4^+$ to $CD8^+$ cell counts were analyzed at baseline and at each time interval. All statistical analyses were performed using SAS software, version 8.2 (SAS), with χ^2 or Fisher's exact tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. Variables entered into the multivariate model required a P of <.1. Multivariate analysis was performed using stepwise logistic regression. Classification and regression tree (CART) analysis was used to identify subgroups of patients with a higher likelihood of a diagnosis of immune reconstitution syndrome, using multiple significant predictors from the multivariate analysis [7]. The accuracy of CART for prediction of immune reconstitution syndrome was analyzed using a receiver operating characteristic curve. CART analysis was performed using CART software, version 5.0 (California Statistical Software), and the receiver operating characteristic curve was plotted using SPLUS, version 6.0 (Insightful).

RESULTS

Case definition. Twenty cases meeting the proposed study definition of immune reconstitution syndrome were initially identified. Four mock cases were added. HIV expert reviewers

agreed on 92% of 24 total cases that were reviewed. There was disagreement on 2 cases. One expert misidentified a single mock case as being consistent with immune reconstitution syndrome. This simulated case involved a patient with a diagnosis of biopsy-confirmed lymphadenitis due to *M. avium* complex that involved multiple lymph node groups. This case was characterized by no significant change in $CD4^+$ cell count (from 5 to 8 cells/mm^3) and an increase in HIV load from 265,355 to 599,364 copies/mL following initiation of antiretroviral therapy. The second disagreement involved a patient with culture-negative inflammatory meningitis following initiation of antiretroviral therapy that met the proposed study definition of immune reconstitution syndrome. This patient had a prior diagnosis of cryptococcal meningitis, which was being treated. The inflammatory meningitis was concurrent with an increase in $CD4^+$ cell count and a decrease in HIV RNA level in response to antiretroviral therapy. One expert excluded the case because the time interval between initiation of therapy and the event was thought to be too long. The immune reconstitution syndrome event occurred 5 months after initiation of antiretroviral therapy. The patient's regimen, however, had been changed 2 weeks before the event, because the patient was experiencing virological failure. This case was included in the final analysis of cases. The 2 HIV experts excluded all 6 cases of herpes zoster (shingles), because the occurrence of this disease could not be distinguished from typical cases of shingles observed in persons with lower $CD4^+$ cell counts not treated with antiretroviral therapy. The remaining 14 confirmed cases are summarized by diagnosis in table 1.

Table 1. Cases of immune reconstitution syndrome, by diagnosis.

Diagnosis, by etiologic agent	No. (%) of cases
Mycobacterium avium complex	
Osteomyelitis	1 (7)
Pneumonia	2 (14)
Focal lymphadenitis	4 (29)
Disseminated infection	2 (14)
Total	9 (64)
Cytomegalovirus	
Colitis	1 (7)
Total	1 (7)
Mycobacterium tuberculosis	
Pneumonia	1 (7)
Total	1 (7)
Cryptococcus species	
Meningitis	2 (14)
Focal lymphadenitis	1 (7)
Total	3 (21)

Baseline characteristics. Sex, age, ethnicity, and baseline symptoms did not differ significantly between case patients and control subjects (table 2). There was a higher median number of prior opportunistic infections among the case patients than among the control subjects (1.5 infections vs. 1.0 infection) that was highly significant ($P = .003$). There was a nonsignificant trend toward higher frequency of protease inhibitor use and history of an AIDS-defining illness in case patients ($P = .063$ and $P = .088$, respectively). Baseline alanine aminotransferase levels (table 3) were significantly lower among case-patients than among control subjects ($P = .045$), as were hemoglobin levels ($P = .023$), hematocrits ($P = 024$), RBC counts ($P = .014$), and lymphocyte percentages ($P = .012$).

Lymphocyte and viral load data. There were no significant differences between case patients and control subjects with respect to baseline $CD4^+$ cell count (figure 1), indicating appropriate matching. Similarly, the interval $CD4^+$ cell counts were not different, with the exception of the $CD4^+$ cell percentage at week 12, which was significantly higher in case patients ($P = .029$). $CD8^+$ cell counts were significantly lower among case patients at baseline ($P = .048$), week 12 ($P = .017$), and week 28 ($P = .048$) and week 16 ($P = .052$). The ratio of $CD4^+$ to $CD8^+$ cell counts was significantly higher in case patients at week 12 ($P = .025$). There was no significant difference between case patients and control subjects with respect to change in $CD4^+$ or $CD8^+$ cell count by week 12. In case patients with immune reconstitution syndrome ($n = 13$), a median 5-log decrease (range, −6269 copies/mL to −999,678 copies/mL) in the number of HIV RNA copies from baseline to week 12 was observed. Adequate virological response was observed in both case patients and control subjects, with no significant differences observed with respect to baseline viral load, interval viral load, or change in viral load at week 12 (data not shown).

Multivariate analyses. Variables included in the multivariate analysis were number of prior opportunistic infections; baseline hemoglobin level, $CD8^+$ cell count, alanine aminotransferase level, and absolute lymphocyte count; and protease inhibitor use. The number of prior opportunistic infections (OR, 2.7; 95% CI, 1.3–5.4; $P = .007$) and hemoglobin level at baseline (OR, 0.8; 95% CI, 0.7–0.9; $P = .003$) were independently associated with the likelihood of immune reconstitution syndrome on multivariate analysis. Models using 3 or 4 of these variables did not significantly alter the results.

CART analysis and receiver operating characteristic curve. Four variables—the number of prior opportunistic infections, baseline hemoglobin level, baseline $CD8^+$ cell count, and use of protease inhibitors—were assessed in a CART model to distinguish patients with or without immune reconstitution syndrome. The number of prior opportunistic infections and hemoglobin level at baseline were chosen because they had shown significance in both the multivariate analysis and the Wilcoxon rank-sum test. The other 2 variables, $CD8^+$ cell count at baseline

Table 2. Baseline characteristics of case patients and control subjects in a study of immune reconstitution syndrome.

Characteristic	Case patients (n = 14)	Control subjects (n = 40)	P
Age, median years	40	38	.226
Median no. of symptoms	2.5	2.0	.500
Median no. of previous opportunistic infections	1.5	1.0	.003
History of AIDS-defining illness	11	21	.088
Protease inhibitor in regimen	11	20	.063
Male sex	13	38	.763
Race			.421
White	5	21	
African American	9	19	

NOTE. Data are no. of patients, unless otherwise indicated.

and use of a protease inhibitor, had shown significance in the Wilcoxon rank-sum tests.

In the CART analysis, use of a protease inhibitor was found to be of least importance in predicting immune reconstitution syndrome (importance score of 8.10 on a scale of 0.00–100.00) and, thus, was excluded from the tree. The remaining 3 predictors were used to identify subjects with a higher likelihood of having a diagnosis of immune reconstitution syndrome. The results are shown in figure 2. A clinical scoring system based on the 3 predictors used in CART could be developed by classifying patients from the least likely to develop immune reconstitution syndrome (a score of 0) to the most likely to develop immune reconstitution syndrome (a score of 4). The receiver operating characteristic curve (figure 3) showed that the sensitivity and specificity for predicting immune reconstitution syndrome were 78.57% and 87.50%, respectively, for a score of $\geqslant$4, and 92.86% and 80.00%, respectively, for a score of $\geqslant$2.

DISCUSSION

Immune reconstitution syndrome can manifest with a wide variety of clinical symptoms, depending on the target of the inflammatory response. It is difficult to define as a single clinical entity. In this study, we were successful in validating a proposed definition of immune reconstitution syndrome, because it was confirmed by a blinded panel of reviewers (92% overall agreement). The 1 notable exception was dermatomal herpes zoster,

Table 3. Baseline laboratory values for case patients and control subjects in a study of immune reconstitution syndrome.

Measure	Case patients (n = 14)	Control subjects (n = 40)	P
Alanine aminotransferase level, U/L	22 (11–95)	35 (11–220)	.045
Aspartate aminotransferase level, U/L	36 (19–115)	31 (14–114)	.332
Albumin level, g/dL	3.7 (1.8–4.5)	3.8 (2.4–4.8)	.212
Alkaline phosphatase level, U/L	95 (43–155)	85 (42–143)	.132
Bilirubin level, mg/dL	0.40 (0.1–0.6)	0.40 (0.1–0.8)	.087
Total protein level, g/dL	7.25 (5.6–7.9)	7.50 (5.9–9.8)	.092
WBC count, cells $\times$ $10^3/\mu$L	3.55 (2.4–6.5)	3.43 (1.2–15.1)	.224
Hematocrit, %	0.323 (0.243–0.409)	0.362 (0.234–0.447)	.024
Hemoglobin level, g/dL	10.95 (8.3–13.5)	12.30 (2.81–14.9)	.023
RBC count, cells $\times$ $10^6/\mu$L	3.645 (2.80–4.75)	4.180 (2.81–5.07)	.014
Platelets, cells $\times$ $10^3/\mu$L	217.5 (97–371)	194.0 (94–472)	.198
Neutrophils, %	0.63 (0.41–0.85)	0.59 (0.22–0.91)	.074
Lymphocytes, %	0.130 (0.020–0.290)	0.195 (0.05–0.50)	.012
Monocytes, %	0.08 (0.07–0.17)	0.09 (0.01–0.026)	.398
Basophils, %	0.003 (0.000–0.010)	0.002 (0.000–0.020)	.422
Eosinophils, %	0.013 (0.000–0.230)	0.030 (0.00–0.350)	.287
HIV RNA level, copies/mL	373,096 (6668–1,000,000)	296,343 (2276–1,569,426)	.816

NOTE. Data are expressed as median (range).

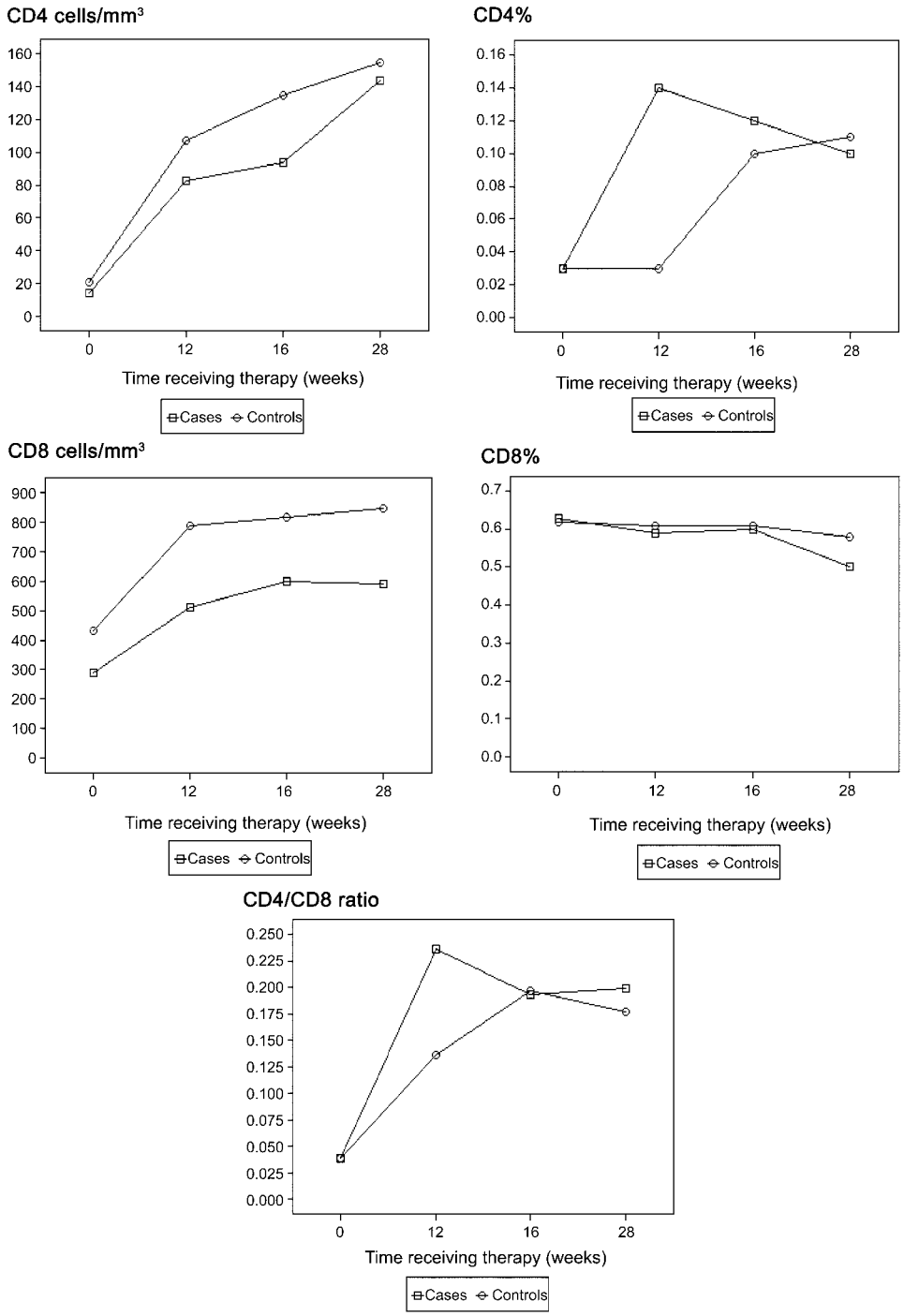

Figure 1. Change in $CD4^+$ cell count, $CD4^+$ cell percentage (CD4%), $CD8^+$ cell count, $CD8^+$ cell percentage (CD8%), and ratio of $CD4^+$ to $CD8^+$ cells (CD4/CD8 ratio) versus number of weeks of therapy. Statistically significant differences ($P < .05$) between case patients and control subjects were observed for $CD4^+$ cell percentage at week 12; $CD8^+$ cell count at baseline, week 12, and week 28; and ratio of $CD4^+$ to $CD8^+$ cells at week 12.

presumed to be a manifestation of immune reconstitution syndrome. Reviewers rejected zoster as a manifestation of immune reconstitution syndrome, because herpes zoster may manifest irrespective of the host's ability to generate an inflammatory response, and there is no established way to clinically distinguish cases occurring as a result of immune reconstitution from cases occurring coincidentally following the administration of antiretroviral therapy. Herpes zoster was previously reported to develop at a constant rate, regardless of the degree of immunosuppression, although it has been shown to increase in incidence 2-fold to 5-fold among HIV-infected patients treated with antiretroviral therapy [8–11]. In contrast, Gebo et al. [12]

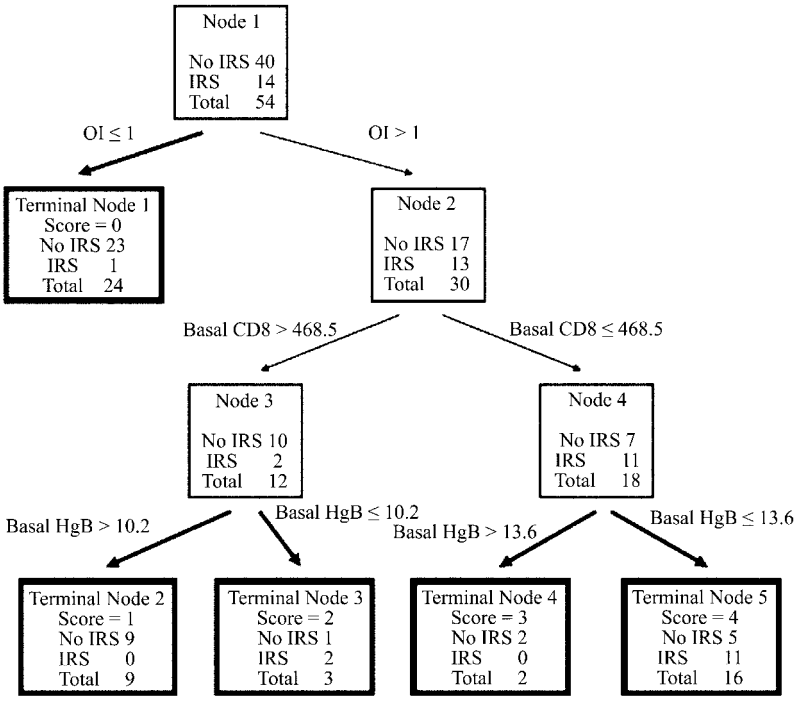

Figure 2. Classification and regression tree (CART) analysis for the assessment of the clinical diagnosis of immune reconstitution syndrome. The importance score equals 0 if there is ⩽1 opportunistic infection; the importance score equals 1 if there is >1 opportunistic infection, baseline $CD8^+$ cell count is >468.5 cells/mm^3, and baseline hemoglobin level is >10.2 g/dL; the importance score equals 2 if there is >1 opportunistic infection, baseline $CD8^+$ cell count is >468.5 cells/mm^3, and baseline hemoglobin level is ⩽10.2 g/dL; the importance score equals 3 if there is >1 opportunistic infection, baseline $CD8^+$ cell count is ⩽468.5 cells/mm^3, and baseline hemoglobin level is >13.6 g/dL; and the importance score equals 4 if there is >1 opportunistic infection, baseline $CD8^+$ cell count is ⩽468.5 cells/mm^3, and baseline hemoglobin level is ⩽13.6 g/dL. Basal CD8, baseline $CD8^+$ cell count; Basal HgB, baseline hemoglobin level; IRS, immune reconstitution syndrome; OI, opportunistic infection.

reported the overall incidence of herpes zoster to be similar in the pre- and post-HAART eras. Further research will be required to determine whether there are unique pathological differences in herpes zoster occurring in the setting of antiretroviral administration and immune reconstitution.

We have demonstrated that immune reconstitution syndrome can be defined as a clinical entity by the following modification of criteria proposed by a working group of the AIDS Clinical Trials Group: presence of symptoms of infection or inflammatory disease, presence of symptoms occurring after initiation of antiretroviral therapy, demonstration of adequate virological response to therapy (⩾1 $\log_{10}$ decrease in viral load), and presence of symptoms not explainable by a newly acquired infection or inflammatory condition (table 4). Shelburne et al. [3] used the following criteria to identify patients with immune reconstitution syndrome: current receipt of antiretroviral therapy, clinical evidence of an inflammatory process that is not consistent with the usual course of an established infection or a new infectious process, increasing $CD4^+$ cell count, and decreasing HIV-1 RNA level. Conceptually, this definition is very similar to ours. Both definitions incorporate a temporal relationship to the initiation of antiretroviral therapy, evidence of response to therapy, and demonstration that the manifestations of the disease cannot be explained in the context of the expected course of a newly acquired opportunistic infection or illness. We elected to remove an increase in $CD4^+$ cell count as an absolute criterion, because plasma levels do not necessarily reflect function. Indeed, some early reports of immune reconstitution syndrome were noted with administration of zidovudine monotherapy in the absence of an increase in $CD4^+$ cell count, suggesting that even small reductions in HIV replication may be sufficient to produce immune reconstitution syndrome [13–15]. In addition, some immune responses may be restored before a rise in plasma $CD4^+$ cell count is detected. Thus, we propose that an increase in $CD4^+$ cell count should be viewed as supportive of the diagnosis rather than required for it. Pathological evidence of well-formed granulomas may also be regarded as evidence of a restored inflammatory response and should also be considered to be supportive of the diagnosis of immune reconstitution syndrome, because this is uncommon in patients with severe immune deficiency due to AIDS.

This definition serves as a framework for considering the diagnosis of immune reconstitution syndrome, but it is limited by the absence of criteria for establishing that a restored immune response has occurred. An increase in $CD4^+$ cell count is not an adequate marker of restored immune function, be-

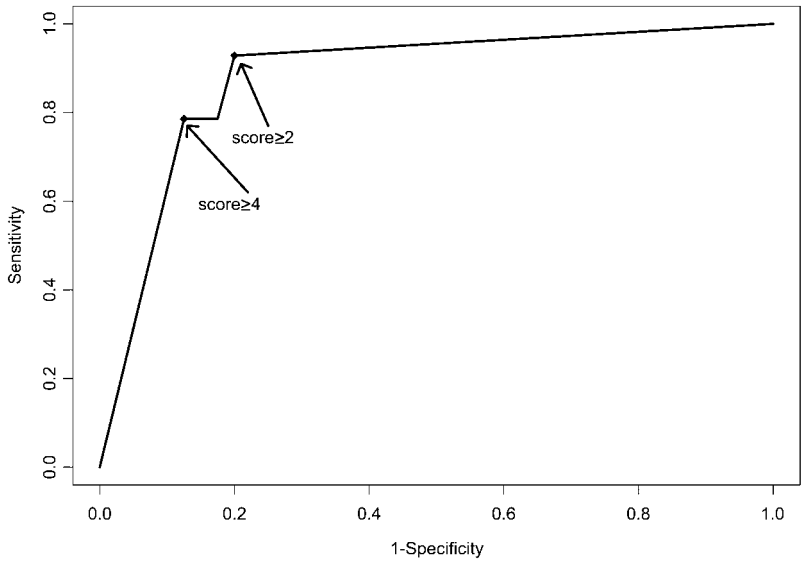

Figure 3. Receiver operating characteristic curve of diagnostic accuracy using clinical scores developed from classification and regression tree analysis. In a scenario of a case patient having a score of ⩾4 or >1 opportunistic infection, baseline $CD8^+$ cell count of ⩽468.5 cells/mm^3, and baseline hemoglobin level of ⩽13.6 g/dL, the sensitivity and specificity for predicting immune reconstitution syndrome will be 78.57% and 87.50%, respectively. In another scenario, in which a case patient has a score of ⩾2 or >1 opportunistic infection, baseline $CD8^+$ cell count of >468.5 cells/mm^3, and baseline hemoglobin level of ⩽10.2 g/dL, the sensitivity and the specificity for predicting immune reconstitution syndrome will be 92.86% and 80.00%, respectively.

cause pathogen-specific responses may remain deficient despite an increase in $CD4^+$ cell count or may recover before a measurable increase in $CD4^+$ cell count [1]. Such considerations highlight the need for better methods to demonstrate the restoration of immune responses to aid in the diagnosis of immune reconstitution syndrome. One potential means to accomplish this would be to demonstrate pathological evidence of an exuberant inflammatory response. The utility of this approach, however, is limited by the inability to obtain a biopsy specimen in all clinical situations. Another approach may be to identify laboratory tests, such as those for cytokines and immunologic markers, that can demonstrate a restored immune response. IL-6 and soluble IL-6 receptor levels have been shown to be increased in HIV-infected patients with a history of immune reconstitution syndrome, but the relationship between IL-6 and immune reconstitution syndrome is yet to be determined [16]. The level of soluble CD30, a marker of a Th2-predominant cytokine environment, has been shown to be elevated in patients with a history of cytomegalovirus-associated immune reconstitution syndrome [17, 18]. Further delineation of laboratory correlates with immune reconstitution syndrome is needed.

Identifying clinical or laboratory predictors of immune reconstitution syndrome would be useful in stratifying persons at greater risk. Shelburne et al. [19] reviewed patients with a history of infection with *M. avium, M. tuberculosis,* or *Cryptococcus* species who developed immune reconstitution syndrome and noted the following risk factors: initiating antiretroviral therapy more proximal to the time of diagnosis of opportunistic infections, being antiretroviral-naive at the time of diagnosis of opportunistic infection, and having a more-rapid initial decrease in HIV-1 RNA level in response to HAART [16]. In our study, we demonstrated that a greater number of prior opportunistic infections, a higher baseline $CD8^+$ cell count, and a lower baseline hemoglobin level are associated with immune reconstitution syndrome. A greater number of

Table 4. Clinical definition of immune reconstitution syndrome in the context of HIV infection.

Required criterion	Supportive criterion
Worsening symptoms of inflammation/infection	Increase in $CD4^+$ cell count of ⩾25 cells/mm^3
Temporal relationship with starting antiretroviral treatment	Biopsy demonstrating well-formed granulomatous inflammation or unusually exuberant inflammatory response
Symptoms not explained by newly acquired infection or disease or the usual course of a previously acquired disease	
⩾1 $\log_{10}$ decrease in plasma HIV load	

prior opportunistic infections may signify the presence of significant residual antigens that may confer increased risk for immune reconstitution syndrome. This idea is consistent with the finding of Shelburne et al. [19] that patients who start antiretroviral therapy in close proximity to the diagnosis of an opportunistic infection are at increased risk for immune reconstitution syndrome. We could not confirm, however, that time from diagnosis of an opportunistic infection to initiation of antiretroviral therapy was predictive of the development of immune reconstitution syndrome (data not shown). Lower hemoglobin levels may be a reflection of more advanced disease, presence of a coinfecting pathogen affecting the bone marrow, or greater severity of illness. Likely, they are an indirect marker associated with the development of immune reconstitution syndrome. $CD8^+$ cell counts likely represent the presence of immune activation. CART analysis demonstrated that it is possible to develop a clinical model predictive for developing immune reconstitution syndrome. However, it would be useful to develop more refined models with greater sensitivity and specificity. The absence of a reference standard definition or specific test also limits our ability to develop predictive models. For these reasons, it is important that this model and future models be validated in a prospective fashion.

In summary, it is possible to develop a standard clinical definition to fit most cases of immune reconstitution syndrome. Some cases of immune reconstitution syndrome may be difficult to distinguish from newly acquired infections, underscoring the need for better diagnostic tests. This is especially true for the occurrence of dermatomal zoster after initiation of antiretroviral therapy. It is also possible to define a clinical model with predictive value for immune reconstitution syndrome. Thus, in patients with lower $CD4^+$ cell counts (<100 cells/mm^3), the likelihood of immune reconstitution syndrome may be predicted by a history of more frequent opportunistic infections, higher $CD8^+$ cell counts, and lower hemoglobin levels. Additional research to identify other risk factors for immune reconstitution syndrome and to develop confirmatory diagnostic tests will help to refine and validate clinical models. Use of the clinical model defined by CART analysis may provide a basis for risk stratification of patients. Preemptive treatment strategies will likely rely on prior identification of a population at greater risk for immune reconstitution syndrome to minimize the risk of exposing low-risk patients to potential harm.

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