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Immune reconstitution inflammatory syndrome: incidence and implications for mortality

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Abstract

Objective—To describe incidence of immune reconstitution inflammatory syndrome (IRIS) and its association with mortality in a large multisite US HIV-infected cohort applying an objective, comprehensive definition.

Design—We studied 2 610 patients seen during 1996–2007 who initiated or resumed highly active combination antiretroviral therapy (cART) and, during the next 6 months, demonstrated a decline in plasma HIV-RNA viral load of at least 0.5 $\log_{10}$ copies/ml or an increase of at least 50% in CD4 cell count per microliter. We defined IRIS as the diagnosis of a type B or C condition [as per the Centers for Disease Control and Prevention (CDC) 1993 AIDS case definition] or any new mucocutaneous disorder during this same 6-month period.

Methods—We assessed the incidence of IRIS and evaluated risk factors for IRIS using conditional logistic regression and for all-cause mortality using proportional hazards models.

Results—We identified 370 cases of IRIS (in 276 patients). Median and nadir CD4 cell counts at cART initiation were 90 and 43 cells/μl, respectively; median viral load was 2.7 $\log_{10}$ copies/ml. The most common IRIS-defining diagnoses were candidiasis (all forms), cytomegalovirus infection, disseminated *Mycobacterium avium intracellulare*, *Pneumocystis pneumonia*, varicella zoster, Kaposi's sarcoma and non-Hodgkin lymphoma. Only one case of *Mycobacterium tuberculosis* was observed. IRIS was independently associated with CD4 cell count less than 50 cells/μl vs. at least 200 cells/μl [odds ratio (OR) 5.0] and a viral load of at least 5.0 $\log_{10}$ copies vs. less than 4.0 $\log_{10}$ copies (OR 2.3). IRIS with a type B-defining or type C-defining diagnosis approximately doubled the risk for all-cause mortality.

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Conflicts of interest

There are no conflicts of interest.

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Conclusion—In this large US-based HIV-infected cohort, IRIS occurred in 10.6% of patients who responded to effective ART and contributed to increased mortality.

Keywords

HAART; HIV; immune reconstitution inflammatory syndrome; mortality; opportunistic infections; risk factors; United States

Introduction

Treatment of HIV infection usually results in a variable degree of immune reconstitution accompanied by a reduction in the risk of opportunistic infections. In some instances, however, a paradoxical worsening of an existing opportunistic infection or the emergence of a new opportunistic infection can occur after initiation of antiretroviral therapy (ART). This type of event, termed immune reconstitution inflammatory syndrome (IRIS), has been reported most commonly in association with mycobacterial infections [*Mycobacterium tuberculosis* infection (TB) and disseminated *Mycobacterium avium* complex (MAC)] [1,2], but has also been reported with many other opportunistic infections, including those caused by fungi (e.g., *Pneumocystis pneumonia* (PCP), toxoplasmosis, coccidioidomycosis], viruses [e.g., hepatitis B virus (HBV) and hepatitis C virus (HCV), cytomegalovirus (CMV) infection, varicella zoster virus (VZV), progressive multifocal leukoencephalopathy], and parasites (e.g. leishmaniasis). An event has typically been considered IRIS, and not a new opportunistic infection, if it occurs within the first 4–8 weeks of ART initiation; however, events attributed to IRIS have occurred later [3-10] (reviewed in [11-14]). With the exception of IRIS in the context of TB [15], there has been no unifying definition with which to describe this entity and define its scope. Reports have varied both in definition of immune reconstitution and the scope of conditions considered related to this event. As a result, comparisons of the incidence and risk factors for IRIS across reports are difficult. Using data from a large, long-standing, and well characterized prospective cohort of HIV-infected adults, we explored IRIS incidence, risk factors, and consequences using a broad definition of IRIS that could be standardized for comparative reporting. We included as IRIS-defining events all AIDS-defining illnesses and a series of HIV-related and other (e.g. autoimmune) conditions previously reported in association with recovery of immune function during ART.

Methods

The HIV Outpatient Study

The HIV Outpatient Study (HOPS) is an open, prospective cohort study of HIV-infected patients seen at 10 university and private HIV specialty clinics in eight US cities since 1993 [16]. Patient data, including socio-demographic characteristics and all diagnoses, treatments, and laboratory values, are abstracted from medical charts and entered into an electronic database for central processing and analysis. All HOPS clinicians have extensive experience treating HIV-infected patients. Since its inception, the HOPS protocol has been reviewed annually and approved by the Centers for Disease Control and Prevention (CDC) (Atlanta,

Georgia, USA), Cerner Corporation (Vienna, Virginia, USA), and each local site's institutional review board; all participants have provided written, informed consent.

Study population and inclusion criteria

We included HOPS patients who between 1 January 1996 and 31 December 2007 were antiretroviral-naive and initiated highly active combination ART (cART, defined below); receiving antiretrovirals in a regimen that did not qualify as cARTand changed to a cARTregimen; or virologically failing or discontinued a cART regimen and started a new cARTregimen. Rather than requiring a minimum follow-up period (e.g. 180 days), which might have excluded IRIS events occurring before the minimum observation period had elapsed, we instead required each patient to have viral load values recorded at baseline and on at least one occasion during the initial 180 days of follow-up to show evidence of an adequate response to cART, defined as either a 0.5 $\log_{10}$ copies/ml or greater decrease in viral load within 6 months after initiating a new or different cART regimen or, in the absence of sufficient viral load reduction, by a 50% or greater increase in CD4 cell count during this same period. These criteria applied to both those who did and did not develop an IRIS-related condition.

Definitions of predictor variables

We defined cART per standard criteria [16]. Baseline was defined as the date a new or different cART regimen was initiated. Baseline plasma HIV-RNA viral load and CD4 cell count were defined as the values closest to the start of this regimen within the preceding 180 days; patients lacking these data were excluded. Follow-up values for plasma HIV-RNA and CD4 cell count were taken as the measurements that occurred within the first 180 days after the start of cART regimen and prior to the end of the regimen.

Chronic co-infection with HBV or HCV (not considered IRIS-defining events) was defined based on a positive value for any of the following tests performed any time prior to baseline and up to 180 days thereafter: HBV surface antigen, HBVe antigen, quantitative or qualitative HBV or HCV plasma viral load, HCV antibody, or HCV genotype (i.e., type specified). *Mycobacterium tuberculosis* exposure was defined as a diagnosis of TB, a positive TB skin test, or a positive interferon-γ release assay any time prior to baseline and up to 7 days thereafter.

Definitions of outcome variable

In addition to IRIS with a type B-defining or type C-defining diagnosis (per 1993 surveillance case definition for AIDS) [17], we included select autoimmune disorders and mucocutaneous conditions (see below) not otherwise classified as type B or C, but reported as associated with IRIS in the literature or by extrapolation might possibly be associated with IRIS. Accordingly, we defined a case of IRIS as a patient who developed type B or C illness [17], an autoimmune disorder, or a mucocutaneous condition not otherwise classified as type B or C between 7 and 180 days after initiating the qualifying cART regimen. Our initial list of diagnoses of autoimmune disorders that were IRIS-defining was broadly inclusive: Crohn's disease, idiopathic thrombocytopenic purpura, Grave's disease, Hashimoto's thyroiditis, systemic lupus erythematosis, sarcoidosis, Sjogren's syndrome,

myasthenia gravis, Raynaud's disease, rheumatoid arthritis, Addison's disease, Guillian–Barre syndrome, pernicious anemia, Wegener's granulomatosis, vitiligo, or ankylosing spondylitis. We also included in the outcome definition new diagnoses of any of the following mucocutaneous conditions not otherwise classified as type B or C: anogenital Herpes simplex virus infection, condylomata, folliculitis, tinea at any site, and molluscum contagiosum, all previously reported as conditions thought to be associated with IRIS [18-20]. We analyzed all IRIS events combined and then separately type B and C vs. mucocutaneous conditions. Diagnoses were defined as recurrent if 90 days had passed between the end date of the diagnosis' first occurrence and the start of its second occurrence. Diagnoses recurring fewer than 90 days from the stop date of a prior occurrence were not included. We restricted analyses of IRIS to conditions that were diagnosed after initiation of cART (i.e. not apparent at the time of cART initiation). We did not evaluate episodes of paradoxical worsening of a preexisting opportunistic infection after initiation of cART due to lack of existing standardized data in the HOPS to quantify if the severity of a condition worsened. For wasting (≥10% weight loss), we calculated each patient's percentage weight change between their heaviest weight measured in the year prior to baseline and their subsequent weight measured following initiation of cART. We used wasting to define a case of IRIS only in those cases in which no other IRIS-defining events were present.

Analysis methods

For estimating incidence of IRIS, patients who experienced IRIS contributed person-years of observation (pyo) from the time of initiating the qualifying cART regimen to the date of the IRIS-defining diagnosis, which by definition occurred within the first 6 months of therapy. Patients who did not experience IRIS contributed pyo from the time of initiating the qualifying cART regimen to the date 6 months later; regimens of shorter duration were censored at their end date. Individual patients could contribute pyo from multiple qualifying cART regimens and, therefore, more than one IRIS event. The denominator equaled the sum of pyo contributed by all patients meeting the inclusion criteria. The numerator equaled the sum of IRIS cases observed. We assessed crude differences in time to IRIS by type of IRIS event, and time from baseline to death for patients who did and did not experience IRIS, using the Wilcoxon rank-sum test.

We also conducted a case-control analysis to further assess risk factors for IRIS. Cases and controls were matched on the year a qualifying cART regimen was started and on ART status (naive vs. experienced) at the start of that regimen. We randomly selected four controls for each IRIS case, using incidence density sampling methodology. In our multivariable conditional logistic regression models, we included all factors explored in univariate analyses: viral load and CD4 cell count, HIV transmission risk group, race/ethnicity, age, sex, hepatitis co-infection status, and history of TB exposure (e.g. positive skin test) or known TB infection.

Finally, we investigated whether IRIS was associated with increased mortality in our study cohort using Cox proportional hazards analyses. The start of observation was the start date of the qualifying cART regimen during which a patient developed first IRIS event; it was the start of the first qualifying cART regimen for patients who did not develop any IRIS

events. The end of observation was either last HOPS contact, date of death, or 31 March 2008. We analyzed deaths documented within 180 days of last HOPS contact; patients not known to have died in that period were assumed alive.

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

Among 8 712 HOPS patients in the HOPS database as of 31 March 2008, we identified 2 610 patients meeting criteria for analyses. This study population included 81.0% men, 41.5% patients of nonwhite race/ethnicity, and 30.5% patients who were antiretroviral-naive [median age (interquartile range, IQR) at first qualifying cART: 40 (35, 46) years, median nadir CD4 cell count: 187 (54, 320) cells/μl].

The 2 610 patients contributed 3 557 qualifying cART regimens to analyses of IRIS rates. During follow-up, IRIS was documented during 370 (10.4%) cART regimens and affected 276 (10.6%) of 2 610 patients (Table 1). One hundred and seventy-two (46.5%) of the 370 cases of IRIS were type B or C events, affecting 6.6% of patients; 198 (53.5%) events were mucocutaneous manifestations, and there were no autoimmune disorders other than idiopathic thrombocytopenic purpura, which was already captured as type B event. There were 28 patients with multiple IRIS events.

Candidiasis of any type was the most common IRIS-defining event (Table 2). Other common IRIS events were CMV end-organ disease, MAC, and PCP. Common mucocutaneous events not otherwise classified as type B or C included anogenital Herpes simplex, condylomata, folliculitis, tinea, and molluscum contagiosum. The median time from the start of the qualifying cART regimen to an IRIS event was 63 days (range: 7–170, IQR: 28–120): for the 81 type B events, median 65 days (range: 8–169, IQR: 31–132), for the 91 type C events, median 40 days (range: 8–161, IQR: 17–92), and for the 198 mucocutaneous events, median 73 days (range: 7–170, IQR: 35–122) ($P < 0.001$ for difference by type of event).

Overall, the incidence of IRIS by our definition was 25.1 per 100 pyo (Table 3), and it was higher for patients with lower baseline CD4 cell count and with higher baseline viral load. Incidence of IRIS type B and C events only (i.e., excluding mucocutaneous events) was 12.0 per 100 pyo [with 95% confidence interval (CI): 10.4, 13.9].

In univariate conditional logistic regression analyses, development of IRIS was associated ($P < 0.05$) with female sex; nonwhite race/ethnicity; IDU or heterosexual risk category compared with MSM; baseline viral load at least 4 $\log_{10}$ copies/ml; and baseline CD4 cell count below 200 cells/μl; whereas age of 50 years and older was protective against developing IRIS (Table 4). In analyses limited to type B and C events, in addition to stronger associations with low CD4 cell count and high viral load, HCV or HBV infection was also associated with increased odds of IRIS (supplemental on-line Table 4a, http://links.lww.com/QAD/A202). For mucocutaneous events, factors associated with IRIS on univariate analyses included nonwhite race/ethnicity, heterosexual risk category, baseline

viral load at least 5 $\log_{10}$ copies/ml and baseline CD4 cell count less than 200 cells/μl (supplemental on-line Table 4b, http://links.lww.com/QAD/A202).

In multivariable analyses, the odds of any IRIS event were 2.3 times as high among patients with a baseline viral load at least 5 $\log_{10}$ copies/ml compared with baseline viral load less than 4 $\log_{10}$ copies/ml and 5.0 and 2.2 times as high among those with baseline CD4 cell counts less than 50 and 50–199 cells/μl, respectively, compared with those with baseline CD4 cell counts of at least 200 cells/μl (Table 4). Patients who were heterosexual or of nonwhite race also had higher odds of IRIS. In analyses limited to type B and C IRIS events, the adjusted associations with low CD4 cell count and high viral load were even stronger, whereas there was less evidence for association with HBV or HCV (supplemental Table 4a, http://links.lww.com/QAD/A202). For mucocutaneous events, these associations remained and age at least 35 years was also protective (supplemental Table 4b, http://links.lww.com/QAD/A202).

Among the 2 610 patients included in the analyses, we observed 263 deaths: 64 deaths among 276 patients who experienced IRIS, 199 deaths among those who did not. Among patients who died, the median time from baseline to death was 40.6 months (IQR: 19.2–90.2) and 53.1 months (IQR: 23.2–95.5), respectively, for persons who did vs. did not experience IRIS-defining events ($P = 0.009$). In univariate proportional hazards analyses, the mortality was significantly higher after the occurrence of a type B or type C IRIS event, but was not associated with mucocutaneous events (Table 5). Other baseline factors associated with mortality in univariate analysis included non-Hispanic black or Hispanic race/ethnicity, age more than 40 years, IDU history, viral load more than 5 $\log_{10}$ copies/ml, low CD4 cell count, a history of an AIDS-defining diagnosis, initiation of cART between 1996 and 2000, having public or other insurance (compared with private), and prior antiretroviral experience (Table 5). After adjusting for these covariates in multivariable analysis, type B and C IRIS events remained significantly associated with mortality (hazard ratios 2.3 and 2.4, respectively), whereas mucocutaneous events were associated with a reduced risk of mortality (hazard ratio 0.54, 95% CI: 0.32, 0.92, Table 5).

In sensitivity analyses, restricted to 1 518 patients who experienced suppression of viral load less than 1000 copies/ml on their first qualifying cART regimen (this viral load limit was chosen to account for the range of sensitivities of the various viral load assays used over the period of study), the incidence rate of IRIS ($n = 122$ events) was 18.7 per 100 pyo (95% CI: 15.6, 22.2) and was not statistically different for patients who were baseline antiretroviral-naive vs. antiretroviral-experienced (data not shown). In the same subset of patients, type C events remained associated with increased mortality in analyses controlling for viral load, CD4 cell count, and age (hazard ratio: 3.3, 95% CI: 1.6, 6.8); type B or mucocutaneous events were not associated with survival in this smaller subset of patients who experienced virologic suppression.

Discussion

We have developed a definition for IRIS that is broader than those used in earlier descriptions of this entity and have applied it to a substantially larger observational cohort

than previous studies. Broadening the definition to include type B and C events and mucocutaneous conditions increased the percentage of affected patients from 6.6 to 10.6%. The incidence of IRIS, using this broad inclusive definition, is lower than that in prior smaller cohort studies from single institutions in industrialized countries, some of which focused on subsets of opportunistic infections or included subgroups with demographic profiles more consistent with a developing country [2,5,21]. Our observed incidence may be lower for a number of reasons. First, although we and others observed that risk for IRIS was increased among persons with low CD4 cell count and elevated viral load, over 50% of the 'qualifying cART regimens' in our analyses had baseline CD4 cell count at least 200 cells/μl and more than one-fifth had baseline viral load less than 10 000 copies/ml. Using the large HOPS dataset, we were able to demonstrate that the incidence of IRIS varies by baseline CD4 cell count, which may explain the higher rates reported in prior studies focused on persons with CD4 cell count less than 200 cells/μl. Second, prevalence of TB in the United States is vastly lower than that in other regions where it is both a major AIDS-defining condition and IRIS-defining condition. Finally, and perhaps most important, our definition of an IRIS-defining event, in contrast to some previous studies, did not include paradoxical worsening of an existing condition. The nature of our data source (chart abstraction of diagnoses and laboratory values), like many observational HIV cohort studies, did not permit reliable characterization of the course of disease or change in the quality of illness.

The HOPS draws patients only from the United States, reflecting HIV-related conditions more often seen in industrialized countries. As a result, it is not surprising that mycobacterial diseases, and particularly TB, were rare as IRIS events in our cohort, whereas candidiasis was the preponderant event. In observational cohorts from Africa and Asia, TB is consistently the most common IRIS-related event [22-25]. In the largest such study to date among 423 treatment-naive South Africans, 44 (10.4%) patients developed IRIS for an incidence rate of 25.1 cases per 100 pyo, with 18 patients developing tuberculosis [22]. In a prospective study from Ethiopia among 186 HIV-infected patients, with a mean CD4 cell count of 123 cells/μl, and in whom more than 60% had an opportunistic infection prior to or at the time of initiation of cART, 32 (17.2%) patients experienced IRIS, including 22 who developed TB [23].

Our study contributes to the available evidence that IRIS-related events may fall outside the CDC case definition for HIV-associated and AIDS-defining events. These diagnoses have included oral manifestations such as parotid enlargement or candidiasis [26,27] and autoimmune diseases, such as autoimmune hepatitis [28], ulcerative colitis [29], sarcoidosis [30], Grave's disease [31], and Reiter's syndrome [32]. Only one such event was seen in the HOPS cohort. Skin manifestations such as molluscum contagiosum [20], cutaneous warts [19], herpes zoster [33], and genital herpes simplex virus [5,34] have also been observed as IRIS events. In the developing world, entities such as leprosy [35-37] and leishmaniasis [2,3,38] have also been observed.

A novel finding of our study was the striking association of having experienced an IRIS-defining event with an increased risk of death, after adjusting for baseline CD4 cell count. A similar result was observed in a small Mexican cohort, but differs from a South Korean

report that found no association of IRIS with mortality [39,40], potentially due to small sample size, shorter duration of follow-up, and differences in the definition of IRIS. In our study, the association between IRIS and increased mortality was evident for both HIV-associated and generally nonlife-threatening (type B) events as well as AIDS-defining and potentially life-threatening events (type C), but was not apparent for mucocutaneous events. Indeed, although mucocutaneous events were not associated with mortality in crude analyses (hazard ratio 0.99), they appeared to be protective for mortality after adjusting for CD4, viral load, and other factors. Most mucocutaneous events are not life threatening and would not be expected to contribute to death, and the appearance of a protective association in adjusted analyses is somewhat surprising and needs to be interpreted cautiously. Whether the mucocutaneous events should be included in the definition of IRIS is less important than to understand that their occurrence carries less clinical significance. We could not establish the relative contributions of individual type B and C events to mortality due to the relatively small number of events observed.

Our study is subject to several additional limitations. Diagnoses of some opportunistic infections in the HOPS do not require laboratory confirmation and some IRIS-defining events could, thus, have been misclassified. As with all observational data, we could not exclude the possibility of residual and unmeasured confounding (e.g. type of cART, adherence to prescribed ART) that might have affected the conclusions. We note that our inclusion criteria were based on virologic and immunologic responses to a new cART regimen regardless of its antiretroviral composition or patient adherence. Analyses using data from other large cohort studies to examine risk factors associated with IRIS and the potential contribution of IRIS to mortality could be helpful in determining whether the associations we observed are valid and generalizable. Further, the diagnoses we considered as IRIS-defining included only conditions endemic to North America and specifically the United States; the distribution of IRIS-defining events and their individual incidence rates likely differ in other regions where characteristics of patients initiating cART and prevalence of opportunistic infections may differ substantially. In our study, we did not evaluate episodes of worsening of a preexisting opportunistic infection after cART initiation (i.e., paradoxical IRIS), because we could not apply standardized criteria for ‘worsening’ of a condition based solely on review of existing medical records. As noted earlier, this limitation may explain why the incidence of IRIS we observed was relatively low compared with some smaller studies in the United States and Europe [2,5,21].

Little is known about the pathophysiologic mechanisms for IRIS. Elevated serum pro-inflammatory biomarkers have been observed both before and after cART initiation in patients who subsequently developed IRIS, findings consistent with the inflammatory nature of the syndrome [41,42]. Some data suggest a role for T-regulatory cells (Tregs) [43]. The observed association of HCV or HBV co-infection with IRIS that was seen in univariate analyses, limited to type B and C events, but that was less apparent in multivariable analysis was unexpected. The effect of chronic viral hepatitis on Treg function may contribute to dysregulation of immune recovery, which could contribute to the emergence of IRIS [44,45]. The implication that co-infections may selectively impact overlapping immune mechanisms for the emergence of IRIS must also be considered in understanding this phenomenon.

In conclusion, as others have observed, we found that IRIS was associated with low CD4 cell count and high viral load at the time of effective cART initiation or resumption. A novel association of IRIS-defining type B and C events with increased risk for subsequent mortality, if supported by other research, might provide another compelling reason for earlier cART initiation. Research to identify the biological mechanisms underlying IRIS may facilitate earlier identification of persons at risk for the condition, as well as effective interventions to prevent it.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of 2610 patients followed after initiating 3557 qualifying combination antiretroviral therapy regimens who did and did not develop immune reconstitution inflammatory syndrome in the HIV Outpatient Study, United States, 1996–2007

Baseline characteristic	Total qualifying regimens *N* = 3557 *n* (%)	Status during follow-up: IRIS *N*=370 *n* (%)	Status during follow-up: No IRIS *N* = 3187 *n* (%)	*P* value[a]
Age (years)				0.072
18–34	859 (24.2)	104 (28.1)	755 (23.7)	
35–49	2146 (60.3)	220 (59.5)	1926 (60.4)	
50+	552 (15.5)	46 (12.4)	506 (15.9)	
Sex				0.95
Female	726 (20.4)	76 (20.5)	650 (20.4)	
Male	2831 (79.6)	294 (79.5)	2537 (79.6)	
Race/ethnicity				0.007
White, non-Hispanic	2018 (56.7)	180 (48.7)	1838 (57.7)	
Black, non-Hispanic	1051 (29.6)	127 (34.3)	924 (29.0)	
Hispanic	374 (10.5)	51 (13.8)	323 (10.1)	
Other/unknown	114 (3.2)	12 (3.2)	102 (3.2)	
HIV transmission risk group				0.18
MSM	2142 (60.2)	207 (56.0)	1935 (60.7)	
IDU	394 (11.1)	48 (13.0)	346 (10.9)	
Heterosexual	819 (23.0)	97 (26.2)	722 (22.7)	
Other/unknown	202 (5.7)	18 (4.9)	184 (5.8)	
CD4 cell count category (cells/μl)				<0.001
<50	557 (16.7)	137 (41.0)	420 (14.0)	
50–199	905 (27.1)	93 (27.8)	812 (27.0)	
≥200	1881 (56.3)	104 (31.1)	1777 (59.1)	
HIV viral load (log_{10}copies/ml)				<0.001
<4	762 (21.4)	44 (11.9)	718 (22.5)	
4-<5	1491 (41.9)	115 (31.1)	1093 (34.3)	
≥5	1304 (36.7)	211 (57.0)	1093 (34.3)	
HCV co-infection				0.34
Yes	490 (13.8)	45 (12.2)	445 (14.0)	
No	3067 (86.2)	325 (87.8)	2742 (86.0)	
HBV co-infection				0.63
Yes	172 (4.8)	16 (4.3)	156 (4.9)	
No	3385 (95.2)	354 (95.7)	3031 (95.1)	
TB exposure				
Yes	156 (4.4)	20 (5.4)	136 (4.3)	0.31
No	3401 (95.6)	350 (94.6)	3051 (95.7)	

HBV, hepatitis B virus;HCV, hepatitis C virus; IRIS, immune reconstitution inflammatory syndrome;TB, tuberculosis.

[a] *P* value determined using the χ^2-test.

Table 2

Frequency of immune reconstitution inflammatory case-defining events in HIV Outpatient Study, United States, 1996–2007 (*N* = 370)

IRIS-defining condition	*N*	%	Type of condition
Candidiasis, any	85	23.0	-
Oral	64	17.3	B
Esophageal	15	4.1	C
Vaginal	6	2.0	MC
Folliculitis	51	13.8	MC
Herpes simplex infection, any	37	12.4	-
Genitourinary	21	5.7	MC
Anorectal	16	4.3	MC
Condyloma, any	45	12.2	MC
Genitourinary	27	7.3	MC
Anorectal	18	4.9	MC
Tinea	41	11.1	MC
Molluscum contagiosum, any	24	6.5	MC
Cutaneous	23	6.2	MC
Genitourinary	1	0.3	MC
Mycobacterial disease, any	15	4.1	-
Disseminated *Mycobacterium avium* complex	12	3.2	C
Atypical mycobacterial infection	2	0.5	C
Mycobacterium tuberculosis infection	1	0.3	C
Cytomegalovirus infection, any	13	3.5	C
Colonic	4	1.1	C
Retinal	5	1.4	C
Esophagitis	1	0.3	C
Other	3	0.8	-
Pneumocystis pneumonia	10	2.7	C
Kaposi’s sarcoma, any	9	2.4	C
Cutaneous	8	2.2	C
Gastrointestinal	1	0.3	C
Zoster	9	2.4	B
Non-Hodgkin’s lymphoma	8	2.2	C
Wasting syndrome	6	1.6	C
Cryptococcal disease, any	4	1.1	C
Meningitis	2	0.5	C
Systemic	2	0.5	C
Toxoplasmosis	3	0.8	C
Cryptosporidiosis	3	0.8	C

IRIS-defining condition	*N*	%	Type of condition
Histoplasmosis	2	0.5	C
Pelvic inflammatory disease	2	0.5	C
Progressive multifocal leukoencephalopathy	2	0.5	C
Idiopathic thrombocytopenic purpura	1	0.3	B

Conditions presented in order of decreasing frequency of the main category. B and C represents type B-defining or type C-defining diagnoses (per 1993 surveillance case definition for HIV/AIDS). IRIS, immune reconstitution inflammatory; MC, mucocutaneous condition.

Table 3

Incidence of immune reconstitution inflammatory among persons after initiating qualifying combination antiretroviral therapy regimens[a], by select patient characteristics, in HIV Outpatient Study, United States, 1996–2007

Baseline factor	Number of IRIS cases	Person-years of observation (pyo)	Incidence per 100 pyo (95% CI)
Overall	370	1474.2	25.1 (22.6, 27.8)
ART experience			
Naive	91	336.4	27.1 (21.8, 33.2)
Experienced	279	1137.8	24.5 (21.7, 27.6)
CD4 category (cells/μl)			
<50	137	197.5	269.4 (58.2, 82.0)
50–99	33	123.9	26.6 (18.3, 37.4)
100–199	60	245.4	24.4 (18.7, 31.5)
200–349	57	400.7	14.2 (10.8, 18.4)
≥350	47	418.5	11.2 (8.3, 14.9)
VL category (log_{10}copies/ml)			
<3	13	97.0	13.4 (7.1, 22.9)
3–< 4	31	235.2	13.2 (9.0, 18.7)
4–< 5	115	631.5	18.2 (15.0, 21.9)
5–< 6	198	491.4	40.3 (34.9, 46.3)
≥6	13	19.1	68.1 (36.2, 116.4)
Year qualifying cART regimen started			
1996–1997	106	372.4	28.5 (23.3, 34.4)
1998–1999	79	276.0	28.6 (22.7, 35.7)
2000–2001	66	243.0	27.2 (21.0, 34.6)
2002–2003	44	232.7	18.9 (13.7, 25.4)
2004–2005	50	219.2	22.8 (16.9, 30.1)
2006-2007	25	130.9	19.1 (12.4, 28.2)

An adequate response to cART was defined as either a ≥0.5 log_{10}copies/ml decrease in HIV-RNA viral load within 6 months after initiating a new or different cART regimen, or in the absence of sufficient viral load reduction, by a 50% increase in CD4 cell count during this same time period. ART, antiretroviral therapy; cART, combination ART; IRIS, immune reconstitution inflammatory; VL, HIV viral load.

[a]For 2610 patients, incidence of IRIS on 3 557 qualifying cART regimens was analyzed.

Table 4

Factors associated with immune reconstitution inflammatory in case-control conditional logistic regression univariate and multivariate models in the HIV Outpatient Study, United States, 1996–2007 (*N* = 1 850)

Baseline factors	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age (years)				
35–49	0.82 (0.63, 1.07)	0.14	0.68 (0.49, 0.95)	0.022
50+	0.65 (0.44, 0.95)	0.028	0.66 (0.42, 1.05)	0.076
18–34	Referent		Referent	
Sex				
Female	1.72 (1.27, 2.33)	<0.001	0.93 (0.58, 1.50)	0.77
Male	Referent		Referent	
Race/ethnicity				
White, non-Hispanic	Referent		Referent	
All other	2.45 (1.93, 3.10)	<0.001	1.50 (1.11, 2.03)	0.009
HIV risk group				
IDU	2.50 (1.70, 3.68)	<0.001	1.63 (0.96, 2.77)	0.069
HRH	2.21 (1.67, 2.92)	<0.001	1.63 (1.03, 2.56)	0.036
Other/unknown	1.34 (0.78, 2.31)	0.29	0.69 (0.35, 1.36)	0.29
MSM	Referent		Referent	
CD4 cell count (cells/μl)[a]				
<50	7.60 (5.44, 10.60)	<0.001	5.01 (3.46, 7.27)	<0.001
50–199	2.57 (1.87, 3.54)	<0.001	2.15 (1.54, 3.02)	<0.001
≥200	Referent		Referent	
HIV viral load (log_{10}copies/ml)[a]				
<4	Referent		Referent	
4-<5	1.46 (1.00, 2.14)	0.050	1.32 (0.85, 2.04)	0.22
≥5	3.73 (2.58, 5.38)	<0.001	2.33 (1.51, 3.61)	<0.001
HCV or HBV co-infection				
Yes	1.38 (0.997, 1.90)	0.052	1.16 (0.76,1.74)	0.49
No	Referent		Referent	
TB exposure				
Yes	1.40 (0.82, 2.36)	0.22	0.96 (0.52,1.80)	0.90
No	Referent		Referent	

CI, confidence interval; HCV, hepatitis C virus; HBV, hepatitis B virus; HRH, high-risk heterosexual; OR, odds ratio; TB, tuberculosis.

[a]Viral load and CD4 cell count values closest to the start of a new or different combination antiretroviral therapy within the preceding 180 days.

Table 5

Factors associated with mortality among patients demonstrating an adequate response to combination antiretroviral therapy in the HIV Outpatient Study, United States, 1996–2007 (*N* = 2 610)

Baseline factor	Univariate analysis HR (95% CI)	*P* value	Adjusted analysis HR (95% CI)	*P* value
Any IRIS (B, C, mucocutaneous)				
IRIS diagnosis	2.38 (1.80, 3.14)	<0.001	NA	
No IRIS diagnosis				
IRIS stratified				
Type C diagnosis	4.69 (3.15, 6.96)	<0.001	2.39 (1.58, 3.61)	<0.001
Type B diagnosis	4.28 (2.70, 6.79)	<0.001	2.29 (1.43, 3.67)	<0.001
Mucocutaneous diagnosis	0.99 (0.59, 1.64)	0.96	0.54 (0.32, 0.92)	0.021
No IRIS diagnosis	Referent		Referent	
Age (years)				
≥40	1.57 (1.23, 2.01)	<0.001	1.58 (1.23, 2.03)	<0.001
<40	Referent		Referent	
Sex				
Female	0.91 (0.67, 1.25)	0.57	0.96 (0.69, 1.34)	0.82
Male	Referent		Referent	
Race				
All other	1.31 (1.03, 1.67)	0.030	1.0 (0.8, 1.3)	0.95
White, non-Hispanic	Referent		Referent	
HIV risk				
IDU	2.11 (1.55, 2.85)	<0.001	1.41 (1.02, 1.94)	0.038
MSM/HRH/other	Referent		Referent	
HIV viral load (log_{10} copies/ml)[a]				
≥5	2.01 (1.56, 2.56)	<0.001	1.54 (1.19, 2.00)	0.001
<5	Referent		Referent	
CD4 cell count (cells/μl)[a]				
<50	6.93 (4.64, 10.33)	<0.001	3.89 (2.49, 6.09)	<0.001
50–200	2.30 (1.49, 3.55)	<0.001	1.51 (0.96, 2.38)	0.073
200–350	1.23 (0.75, 2.02)	0.42	1.03 (0.62, 1.71)	0.91
Missing	4.61 (2.83, 7.50)	<0.001	3.05 (1.84, 5.05)	<0.001
≥350	Referent		Referent	
Year of first qualifying cART				
1996–2000	1.98 (1.41, 2.78)	<0.001	1.78 (1.26, 2.52)	0.001
2001–2008	Referent		Referent	
Nadir CD4 cell count (cells/μl)				
<200	3.30 (2.44, 4.45)	<0.001		
≥200	Referent			
AIDS OI diagnosis at baseline[b]				

Baseline factor	Univariate analysis HR (95% CI)	*P* value	Adjusted analysis HR (95% CI)	*P* value
AIDS OI at baseline	3.22 (2.52, 4.10)	<0.001	1.58 (1.21, 2.05)	<0.001
No AIDS OI at baseline	Referent			
Insurance				
Public or other insurance	1.98 (1.54, 2.54)	<0.001	1.45 (1.11, 1.90)	0.007
Private	Referent		Referent	
Prior antiretroviral exposure				
Yes	3.21 (2.17, 4.74)	<0.001	2.80 (1.88, 4.18)	<0.001
No	Referent		Referent	

cART, combination antiretroviral therapy; CI, confidence interval; HR, hazard ratio; HRH, high-risk heterosexual; IRIS, immune reconstitution inflammatory syndrome; OI, opportunistic infection.

[a] Viral loads and CD4 values closest to the start of a new or different cART within the preceding 180 days.

[b] OI prior to the start of a new or different cART.