Influence of Human Immunodeficiency Virus 1 Infection and Degree of Immunosuppression in the Clinical Characteristics and Outcome of Infective Endocarditis in Intravenous Drug Users

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Background: Immunosuppression caused by human immunodeficiency virus 1 (HIV) infection appears to modify the clinical characteristics and to increase the severity of several bacterial infections. The impact of HIV infection and the degree of immunosuppression on the clinical characteristics and outcome of infective endocarditis (IE) in intravenous (IV) drug users has not been well characterized.

Methods: Prospective cohort study among 292 consecutive IV drug users with IE diagnosed in 2 academic institutional hospitals in Barcelona, Spain, from January 1, 1984, to October 31, 1995. Serostatus of HIV infection was documented in 283 patients. We measured demographics, clinical and biological data, cause, echocardiographic findings, HIV serostatus and classification, CD4 cell count, complications, and mortality.

Results: Among the 283 episodes of IE, 216 (76.3%) were in HIV-infected patients and 67 (23.7%) in non–HIV-infected patients. Rate of IE per 1000 admissions ranged from 0.17 to 0.82 per year, peaking in 1989. Characteristics of IE independently associated with HIV infection were right-side involvement (odds ratio [OR], 7.6; 95% confidence interval [CI], 3.5-16.7), a micro-organism different from viridans streptococci (OR, 2.5; 95% CI, 1.1-5.9), duration of drug abuse longer than 5 years (OR, 5.0; 95% CI, 2.4-10.3), and white blood cell count of no more than \(10^9/L\) (OR, 2.2; 95% CI, 1.1-4.2). There were no significant differences in mortality due to IE according to HIV serostatus. Among the 216 patients with HIV infection, the variables independently associated with worse outcome were CD4 cell count lower than \(0.200 \times 10^9/L\) and left-sided or mixed IE.

Conclusions: Although there is a difference in clinical presentation in IE in IV drug users, outcome was similar according to their HIV status. However, among HIV-infected patients, severe immunosuppression and mixed or left-side valvular involvement were strong risk factors for mortality.

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INFECTIVE ENDOCARDITIS (IE) is a classic complication of intravenous (IV) drug addiction. Since the first descriptions in the 1930s, the clinical pattern of IE in IV drug users has remained unchanged worldwide. Infectious endocarditis in IV drug users usually involves the tricuspid valve. It is usually caused by Staphylococcus aureus, and it has a relatively good prognosis. However, IV drug addiction is 1 of the most important risk factors for human immunodeficiency virus type 1 (HIV) infection. Currently, the prevalence of HIV infection among IV drug users with IE is very high, ranging from 44% to 90%. However, whereas the number of patients with acquired immunodeficiency syndrome (AIDS) among IV drug users dramatically increased in the 1990s, the incidence of IE in this population simultaneously decreased. Some authors have suggested that this decrease is due to changes in drug administration techniques to avoid HIV infection.

Although most IV drug users with IE are coinfected with HIV, only 3 retrospective studies have analyzed the clinical pattern and prognosis of IE in this population. Nahass et al and Valencia et al found no statistical difference in clinical characteristics and outcome between HIV-infected and HIV-noninfected IV drug users with IE. However, in the first study, IV drug users with symptomatic HIV disease and IE had a significantly higher mortality rate than those with asymptomatic HIV and IE. Pulvirenti et al reported that IE in IV drug users had a different clinical pattern and outcome depending on the degree of HIV-induced immunosuppression. Mortality was significantly higher in subjects with CD4 lymphocyte counts of less than \(0.200 \times 10^9/L\). With available...
PATIENTS AND METHODS

STUDY DESIGN AND PATIENTS

Patients with IE admitted to Hospital General Vall d’Hebron or to Hospital Clinic i Provincial were prospectively recruited into an institutional protocol. The centers involved in the study are academic tertiary care hospitals serving as referral centers for other hospitals in the area with a catchment area of 1.5 million persons. All patients with IE who admitted to the use of IV drugs from January 1, 1984, to October 31, 1995, underwent evaluation. All patients with documented HIV serostatus were eligible for enrollment in the study. The possible or definite diagnosis of IE was made according to the criteria of Durack et al.9 All patients with possible IE had 1 major and 2 minor criteria, without any other source of infection. Seropositivity for HIV was defined as positive results of enzyme-linked immunosorbent assay and Western blot testing before or during hospitalization for IE. Patients were defined as seronegative for HIV if results of serological tests were negative during or after hospitalization for IE. All patients received antimicrobial therapy according to results of antimicrobial sensitivity tests and an established protocol that was revised yearly. The criteria for surgery during the acute phase of the disease were the same as those previously described in non-IV drug users10 and were independent of HIV serostatus.

MEASUREMENTS

The following parameters were recorded for each episode of IE: demographics, predisposing conditions (congenital or acquired cardiac lesions, prosthetic cardiac implants, previous episodes), clinical and biological data, results of chest radiography, causative organism, echocardiographic findings, results of HIV serological tests, classification of HIV disease, CD4 cell count for patients with HIV infection, complications of IE (confirmed by the pertinent explorations in each case), surgery during hospitalization for IE, and mortality during the active phase of IE.

Results of 2-dimensional transthoracic echocardiography routinely were evaluated in each patient. In February 1990, transesophageal echocardiography became available in our hospitals, and since then it has been performed for suspected left-sided endocarditis poorly defined by transthoracic echocardiography and for suspected intracardiac complications.

Detection of HIV antibodies was performed using enzyme-linked immunosorbent assay according to the manufacturer’s instructions. All positive results were confirmed by results of Western blot assay. Measurement of HIV antibodies has been available in our hospitals since the end of 1985. Some patients admitted before that time underwent testing for HIV antibodies using stored serum from the date of the IE episode. Infection with HIV was classified as asymptomatic (stages I and II) or symptomatic (stages III and IV) according to the 1987 recommendations of the Centers for Disease Control and Prevention.11 Subsets of T cells were measured by our Immunology Laboratories using flow cytometry. Cell counts of CD4 were measured during the infectious episode or within 3 months of diagnosis. To identify valvular involvement, we used clinical, echocardiographic, surgical, and autopsy data.

STATISTICAL ANALYSIS

Differences between HIV-infected and HIV-noninfected patients were evaluated using the χ² test or the Fisher exact test for categorical variables and the unpaired Student t test or the Mann-Whitney U test for continuous variables. Comparisons between the 4 groups of immunosuppression according to CD4 cell count (<0.100 × 10⁹/L, 0.100-0.199 × 10⁹/L, 0.200-0.499 × 10⁹/L, and ≥0.500 × 10⁹/L) in the HIV-infected patients were made using the χ² test for categorical variables and 1-way analysis of variance (ANOVA) or the Kruskal-Wallis test, when necessary. Adjustments were made for multiple comparisons using the Tukey test for 1-way ANOVA and the Bonferroni method for other statistical analysis (total error rate, 0.05). Furthermore, the relationship between the CD4 cell count and selected quantitative variables was measured using the Pearson correlation coefficient (r).

Two additional multivariate analyses were performed with a multiple logistic regression model (the LR program from the BMDP statistical package and the stepwise MLR method; BMDP Statistical Software Inc, Los Angeles, Calif). In each model we included the variables that were significantly associated with the dependent variable in the univariate analysis. Each category of the categorical variables was considered as a single variable in the model. The cutoff point that better differentiated between both categories of the dependent variable of the logistic regression model was arbitrarily chosen for the continuous variables. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were examined. The first model sought variables independently associated with HIV infection. The second multivariate model sought factors predictive of mortality in HIV-infected patients.

All the hypothesis tests were 2-sided. Statistical significance was defined as P < .05.

RESULTS

CHARACTERISTICS OF IE ACCORDING TO HIV STATUS

Patients

During the study, 292 consecutive episodes of IE were identified in IV drug users. Nine patients were excluded because of unknown HIV serostatus. Three patients died dur-
ing hospitalization for IE. Four returned to the hospital 3 to 5 years later and were seropositive for HIV, with CD4 cell counts from $0.380 \times 10^9/L$ to $0.650 \times 10^9/L$. No additional data were available for the remaining 2 patients.

Among the 283 patients with IE and known HIV serostatus included in the study, 216 (76.3%) were infected with HIV, and 67 (23.7%) were not. The Figure depicts the study population by year of IE, HIV serostatus, and annual rate per 1000 patients admitted to our hospitals. The incidence of IE increased from 1984 to 1989 and declined after. However, there were no differences in the percentage of patients with IE with and without HIV infection during the 12 years of the study.

As shown in Table 1, there were no age or sex differences between the HIV-infected and HIV-noninfected patients. Duration of drug abuse was higher in the HIV-infected group, as 137 (63.4%) vs 20 (29.8%) non–HIV-infected patients used parenteral drugs longer than 5 years. Predisposing heart disease was present in 93 patients (32.9%), and there was a significantly higher frequency of prosthetic valves in patients without HIV infection.

**Clinical Presentation**

Almost all study patients were febrile (98.6% [213/216] of HIV-infected and 98.5% [66/67] of non–HIV-infected patients). However, the mean duration of fever before hospitalization was 9.7 days for HIV-infected and 15.7 days for non–HIV-infected patients ($P = .007$) (Table 1). Chest pain and pulmonary infiltrates were more common in HIV-infected patients. Patients with HIV infection had skin lesions suggestive of systemic embolisms more frequently than non–HIV-infected patients. White blood cell, neutrophil, lymphocyte, and platelet counts were significantly lower in the HIV-infected patients.

The tricuspid valve was the most frequently affected valve in both groups (Table 2). However, right-side or unknown location was more frequent in HIV-infected than in noninfected patients (178 patients [82.4%] vs 30 patients [44.8%]; $P < .001$), and left-sided location was less frequent in HIV-infected than in noninfected patients (22 patients [10.2%] vs 32 patients [47.8%]; $P < .001$). Mixed location (right and left sides simultaneously) was similar in both groups.

**Staphylococcus aureus** was the most common isolated organism in both groups (Table 2). However, a
higher percentage of HIV-infected patients were infected with this microorganism (73.6% vs 56.7%; \( P = .009 \)), whereas \textit{Streptococcus viridans} was isolated more often from the non–HIV-infected group (11.1% vs 29.8%; \( P < .001 \)).

### Complications and Outcome

Table 3 and Table 4 show complications and outcome for both groups. More non–HIV-infected patients had left-sided heart failure, renal failure, and systemic emboli than did HIV-infected patients. Furthermore, more non–HIV-infected patients required surgical treatment during hospitalization, although the rates of surgery for right-sided IE and for left-sided or mixed IE were similar in both groups. There were no significant differences in hospital mortality due to IE between HIV-infected and HIV-noninfected patients. This was true for overall mortality rate and after stratification by location, etiological agent, first or recurrent episode, and native or prosthetic valve involvement. However, there was higher mortality in non–HIV-infected patients with right-sided IE (particularly IE caused by \textit{S aureus}) and a trend toward higher mortality in HIV-infected patients with left-sided IE (particularly IE caused by \textit{S viridans}). All but 1 death in HIV-infected patients and all deaths in non–HIV-infected patients were directly attributed to IE.

### Multivariable Predictors of HIV Infection

Results of multivariate analysis of significant variables associated with HIV infection are depicted in Table 5. Analysis identified the following 4 variables associated with HIV infection: right-sided IE, more than 5 years of drug abuse, absence of leukocytosis, and etiological agent other than \textit{S viridans}. Left-sided IE, shorter duration of drug abuse, leukocytosis, and \textit{S viridans} as etiological organism were associated with non–HIV-infected patients.

### HIV-INDUCED IMMUNOSUPPRESSION AND IE CHARACTERISTICS

#### Clinical Characteristics

Table 6 and Table 7 depict study variables in IE in the HIV-infected study population according to CD4 lymphocyte count. Patients with a high degree of immunosuppression had IV drugs longer than patients with a lower degree of immunosuppression. There was a trend between increasing duration of fever before admission and increasing CD4 cell count that was close to statistical significance (\( r = 0.14 \)). Neurological complications increased as CD4 cell counts decreased. There were significant correlations between decreasing CD4 cell count...
and decreasing leukocyte neutrophil or decreasing lymphocyte count \( r = 0.61 \). There were no notable differences in CD4 cell count by location or cause of IE.

### Prognostic Factors

There were no deaths in patients with CD4 cell counts above \( 0.200 \times 10^9/L \). A progressive increase in mortality rate was observed in patients with lower CD4 cell counts (Table 7). Six (14.6\%) of 41 patients with symptomatic HIV infection and 11 (6.3\%) of 175 asymptomatic patients died (crude OR, 2.6; 95\% CI, 0.7-8.1; \( P = .10 \)). Among symptomatic HIV-infected patients, mortality was higher in those with CD4 cell counts below \( 0.100 \times 10^9/L \) (6 [30.0\%] of 20 vs 0 of 16 patients; \( P = .02 \)).

Only the following 2 variables were independent risk factors for death in HIV-infected patients by multivariate analysis (Table 5): CD4 cell counts below \( 0.200 \times 10^9/L \) (\( P < .001 \)) and left-sided or mixed location IE (OR, 12.6; 95\% CI, 3.8-41.9; \( P < .001 \)).

### COMMENT

The consequences of HIV infection in IV drug users with IE have not been defined completely. Our study shows that the causative organism and clinical characteristics of IE are different in HIV-infected and HIV-noninfected IV drug users. Infected patients had higher rates of tricuspid infective involvement and of IE not due to \( S \) viridans than non–HIV-infected patients (\( P = .04 \)). Mortality among HIV-infected IV drug users with IE was significantly higher in the severely immunodepressed group (CD4 cells, \( < 0.200 \times 10^9/L \)).

Three retrospective studies have reviewed this subject. The first study\(^2\) compared clinical characteristics and outcome of 40 episodes of IE in HIV-infected IV drug users with 14 episodes in non–HIV-infected IV drug users. Although HIV-infected patients had a mortality rate twice as high as the non–HIV-infected patients, the authors found no statistically significant differences in demographic variables, valve involved, echocardiographic findings, cause, surgery, and mortality between both groups. Among HIV-infected IV drug users with IE, the authors found that 2 of 30 patients with asymptomatic HIV infection died, compared with 4 of 10 patients with symptomatic HIV infection (\( P = .02 \)). They concluded that IV drug users with symptomatic HIV infection are at higher risk for death due to IE.

The second study\(^3\) compared clinical characteristics and outcomes of 143 episodes of IE in HIV-infected IV drug users with 21 episodes in non–HIV-infected users. They observed no statistical differences between HIV-infected and HIV-noninfected groups in clinical characteristics and mortality. However, IV drug users with AIDS had a mortality rate 3 times higher than HIV-infected IV drug users without AIDS.

A third study\(^4\) compared characteristics of 45 episodes of IE in HIV-infected IV drug users with 57 episodes in non–HIV-infected users. The HIV-infected patients had a significantly higher incidence of right-sided IE, lower ratios of valve vegetations, and lower mean white blood cell counts. No statistical differences were observed regarding cause, surgery, and mortality. However, 10\% of non–HIV-infected IV drug users needed surgery, compared with only 2\% of HIV-infected users. The mortality rate was also slightly higher in infected patients (13\% vs 9\%). However, higher mortality rates correlated strongly with lower CD4 cell counts. Five (55.6\%) of 9 patients vs 1 (9.1\%) of 11 vs 0 of 16 patients died with CD4 cell counts of less than \( 0.200 \times 10^9/L \), \( 0.200 \) to \( 0.500 \times 10^9/L \), and greater than \( 0.500 \times 10^9/L \), respectively. Intravenous drug users with CD4 cell counts below \( 0.200 \times 10^9/L \) had a 15-fold higher mortality rate than...
those with cell counts above $0.500 \times 10^9/L$. An analysis of HIV stage and mortality could not be performed because only 5 of the 45 HIV-infected patients had AIDS.

Although outcome was poor in IV drug users with symptomatic HIV disease or severe immunosuppression, these studies did not identify significant clinical differences between HIV-infected and HIV-noninfected users with IE. The small number of patients enrolled in the studies and their retrospective design may have prevented identification of significant variables. We included large numbers of IV drug users with IE to analyze more clearly the influence of HIV infection and degree of immunosuppression on the clinical characteristics and outcome in IE.

There was a steady increase in the number of cases during the first years of the study, which peaked during 1988 and 1989 and decreased thereafter. This was mirrored by other increased infectious complications (IE, acute hepatitis, systemic candidiasis) in Spanish IV drug users.12 During the same period, the number of AIDS cases in IV drug users also increased dramatically. Some authors have suggested that declines in infectious complications in the 1990s seen in this population are due to changes in drug administration techniques.1,8 These

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<th>Table 6. Characteristics of Infective Endocarditis in HIV-Infected Intravenous Drug Users According to the CD4 Lymphocyte Count*</th>
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<td>CD4 Cell Count, $\times 10^9/L$</td>
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<td>Characteristics</td>
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<td>Age, mean ± SD, y</td>
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<td>Sex male</td>
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<td>Duration of drug abuse, mean ± SD, y</td>
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<td>Previous endocarditis</td>
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<td>Symptomatic HIV</td>
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<td>Duration of fever at admission, mean ± SD, d</td>
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<td>Leukocyte count, mean ± SD, $\times 10^9/L$</td>
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<td>Lymphocyte count, mean ± SD, $\times 10^9/L$</td>
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<td>CD4 cell count, mean ± SD, $\times 10^9/L$</td>
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*Data are given as number (percentage) of patients, unless otherwise indicated. The CD4 cell count was not available for 39 patients. HIV indicates human immunodeficiency virus.

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<th>Table 7. Complications and Outcome of Infective Endocarditis in HIV-Infected Intravenous Drug Users According to CD4 Lymphocyte Count*</th>
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<td>CD4 Cell Count, $\times 10^9/L$</td>
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<td>Characteristics</td>
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<td>Duration of fever, mean ± SD, d</td>
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<td>Respiratory failure</td>
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<td>Central nervous system involvement</td>
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<td>Overall mortality</td>
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<td>Mortality by endocarditis location</td>
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*Data are given as number (percentage) of patients, unless otherwise indicated. HIV indicates human immunodeficiency virus. The CD4 cell count was not available for 39 patients, 5 (12.8%) of whom died.
changes also have been observed in Spain, and are associated with decreases in new HIV infections13,14 and reductions in the incidence of IE in IV drug users.14 In our study, 76.3% of IV drug users with IE had positive results of HIV serological tests. Although the prevalence of HIV infection was high in our study, it remained in the range of other studies of IE in IV drug users published in the 1990s.2-7 The high prevalence of HIV infection among IV drug users with IE may reflect that IE and other infectious complications are more likely to develop in individuals who are more likely to be infected with HIV due to injection practices. However, some studies have shown that HIV infection is an independent risk factor for IE in IV drug users.15,16

In our study population, multivariate analysis identified the following 4 variables as being independently associated with HIV infection: more than 5 years’ use of IV drugs, right-sided IE, infection not due to S. viridans, and white blood cell count at admission of no more than $10 \times 10^9/L$. The reason for the higher predominance of tricuspid valve involvement in HIV-infected IV drug users is not known. It may be due to longer duration of drug addiction and the continuous endothelial damage caused by bombardment of the tricuspid valve by impurities and adulterants contained in the injected drugs.17 Overall, S. aureus was the most common etiological agent in both groups. Drug addicts who were infected with HIV had a higher incidence of infections other than those caused by S. viridans, and non–HIV-infected addicts had a higher incidence of viridans streptococci. The skin and nasal mucous membranes of IV drug users are highly colonized by S. aureus,18 which reaches the bloodstream through the IV injections. Several studies have shown that HIV-infected patients have a higher incidence of nasopharyngeal colonization than non–HIV-infected patients. Also, patients with AIDS have the highest incidence of nasopharyngeal colonization among HIV-infected patients.19,20

Non–HIV-infected IV drug addicts had a higher incidence of left-sided heart failure, systemic emboli, renal failure, and surgery than HIV-infected addicts. This probably reflects the higher incidence of left-sided involvement in noninfected patients. The incidence of surgery was higher in non–HIV-infected IV drug users with IE, also due to their higher rate of left-side involvement. However, surgical intervention does not worsen the short-term prognosis of HIV infection.21-23 Response to antibiotic therapy was similar in both groups. Recent studies in HIV-infected IV drug users with right-sided IE caused by S. aureus have shown very good response rates to 2-week courses of cloxacillin sodium (with or without gentamicin sulfate)7 and to oral combinations of ciprofloxacin hydrochloride and rifampin.24

The mortality rate was slightly higher in the non–HIV-infected population (difference was nonsignificant). When mortality was analyzed in HIV-infected IV drug addicts by HIV stage and CD4 cell counts, we found that patients with AIDS had a mortality rate 2.5 times higher than that of drug addicts without AIDS. These differences were not statistically significant. Combining cases in the studies by Nahass et al2 and Valencia et al2 with ours, we found that patients with AIDS and IE had a statistically significantly higher mortality rate than HIV-infected IV drug users without AIDS (14 [14.1%] of 99 vs 16 [5.3%] of 300; P = .004). As in the study by Pulvirenti et al,3 we found an inverse correlation between CD4 cell counts and mortality rates. Patients with CD4 cell counts of less than 0.100 $\times 10^9/L$ or from 0.100 $\times 10^9/L$ to 0.200 $\times 10^9/L$ had mortality rates of 19% and 12%, respectively, and no patient with a CD4 cell count above 0.200 $\times 10^9/L$ died. These differences were highly significant (P < .001). Multivariate analysis, including only HIV-infected IV drug users with known CD4 cell counts, identified CD4 cell counts below 0.200 $\times 10^9/L$ and left-sided or mixed involvement as independently associated with a greater risk for mortality. Our study showed that severe immunosuppression (AIDS or CD4 cell count <0.200 $\times 10^9/L$) in IV drug users with IE was associated with a poorer prognosis. Although the effects of HIV infection on cell immunity are well known, HIV infection can also affect humoral immunity and phagocytic cell function. This may explain the increased susceptibility of HIV-infected patients to bacterial infections. Several studies have shown that neutrophils in non–IV drug users with HIV infection have severely impaired chemotaxis, phagocytosis, and/or intracellular bacterialidal capacity. The degree of impairment is more pronounced in patients with AIDS or low CD4 cell counts.25-28

In conclusion, the presentation and outcome of IE in IV drug addicts differed depending on HIV status. Intravenous drug users with IE who were seropositive for HIV had been addicted longer, had a higher incidence of right-sided IE, had fewer infections due to S. viridans, and had lower white blood cell counts than IV drug users who were seronegative for HIV. Overall mortality rates between the HIV-infected and HIV-noninfected drug users with IE were similar. However, among HIV-infected users, mortality was significantly higher in the severely immunosuppressed patients.

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