

Severe Hepatotoxicity During Combination Antiretroviral Treatment: Incidence, Liver Histology, and Outcome

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Objectives: To assess incidence, risk factors, histology, and outcome of severe hepatotoxicity (SH) during antiretroviral treatment (ART).

Methods: Seven hundred fifty-five HIV-seropositive patients consecutively prescribed new ART were selected. Liver function tests were assessed at baseline, after 1 month, and every 4 months thereafter. Liver biopsy was recommended in case of SH (i.e., increase in liver enzymes ≥ 10 times the upper limit of normal or 5 times baseline if markedly abnormal).

Results: Twenty-six cases of SH were observed with an incidence of 4.2% person-years. Liver failure (LF) was rarely seen (1.1 per 100 person-years). Liver damage was invariably observed in patients with chronic viral hepatitis. Liver histology showed exacerbation of viral hepatitis in all 16 patients for whom a liver biopsy was available at the time of SH. A direct correlation was found between alanine aminotransferase increase and increase in CD4⁺ T-cell count in patients with SH ($r = 0.53, p < .001$). Death occurred during follow-up in 7 of 26 (27%) patients, all of whom showed LF and baseline CD4⁺ count less than 200 cells/mm³ (7/7 patients = 100% vs. 8/19 patients without LF; $p < .01$). Relapse of SH was observed after ART was recommenced in 7 of 17 (41%) patients. Five of these 7 patients did not show further SH relapse after treatment with interferon.

Conclusions: This study provides estimates of SH and LF in a large population-based setting where hepatitis C virus coinfection is highly prevalent and provides indications that liver damage may be caused by immune reconstitution and related exacerbation of viral hepatitis. A strict follow-up for hepatotoxicity is mandatory when ART is initiated in patients with < 200 CD4⁺ T cells/mm³. Antihepatitis pre- or co-medication could be an effective preventive or curative measure.

Key Words: Antiretroviral treatment—Liver damage—Immune reconstitution—Histology—Interferon.

Combination antiretroviral treatment (ART), decreasing HIV RNA, and increasing CD4 cell counts have slowed disease progression, decreased mortality, and improved the quality of life for many persons with HIV (1).

Issues concerning severe adverse events are becoming increasingly evident, however, limiting benefits in a significant proportion of patients (2).

Typical hepatic drug toxicity is exhibited by all classes of antiretrovirals; it is shown by a rise in transaminase levels and occasionally by signs of drug hypersensitivity or steatohepatitis (3). Last, but most important, liver toxicity is exacerbated by viral hepatitis (3), which is com-

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mon in HIV-seropositive patients, especially those with a history of exposure to blood or blood products (3). Incidence of severe hepatic cytolysis defined as grade III to IV elevation of liver enzymes has recently been reported as 5 to 10 per 100 person-years during ART (4–9). Occurrence of liver disease and death has been described anecdotally in patients undergoing combination antiretroviral regimens with (10–13) and without (14) protease inhibitors (PIs). The occurrence of hepatic decompensation was reported in 2% of 187 patients undergoing treatment with two nucleoside analogues (NRTIs) and a PI (15) and in 14% of 51 patients with chronic hepatitis C treated with these regimens (16).

Thus far, liver histology, etiology, and outcome of severe hepatotoxicity (SH) during ART have yet to be defined as well as risk factors associated with death due to decompensated liver disease in patients with SH (17). Preliminary observations have suggested that among the factors involved (18), immune reconstitution may (19,20) or may not (21) play a role in the occurrence of liver damage. Moreover, the impact of ART on liver histology after resolution of acute hepatotoxicity has not yet been explored.

In the current study, all patients who initiated any combination of ART during an 18-month period have been closely followed with clinical, biochemical, and histologic assessment to define prospectively the incidence and factors associated with the occurrence of SH. Moreover, patients have been followed with the aim of assessing clinical, biochemical, and histologic outcome from SH.

METHODS

Study Population

All patients with confirmed HIV-1 infection followed in the HIV/AIDS clinic of the Institute of Infectious and Tropical Diseases of the University of Brescia who, from January 1997 to June 1998, were consecutively prescribed new combination ART not including clinical trial drugs were considered eligible for the study. Inclusion criteria were age of 18 years or older and eligibility for ART according to Italian guidelines (22) for ART (Italian AIDS Committee, Italian Ministry of Health, unpublished, 1997); exclusion criteria were baseline aminotransferase levels higher than five times the upper limit of normal (UNL) and Child Pugh class B or C liver disease.

All recruited patients gave their informed consent, and the study was carried out in compliance with the declaration of Helsinki.

Follow-Up

At baseline, all patients filled out a standard questionnaire for previous and current alcohol consumption assessment and underwent a physical examination, routine liver tests (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST], total serum bilirubin, albu-

min, and prothrombin time [PT]), plasma HIV RNA quantification, markers for hepatitis viruses, and CD4 cell count. Combination ART was chosen independently by the treating physicians. During follow-up, all patients underwent a medical examination and alcohol consumption assessment as well as ALT, AST, albumin, bilirubin, and PT determinations after 1 month and at least every 4 months thereafter.

Study Outcomes

According to a standardized toxicity grade scale [modified from the scale used by the AIDS Clinical Trial Group (13)], two classes of outcomes have been defined: relevant hepatotoxicity (RH) and SH. RH was defined as any increase of liver enzymes of at least 5 times the ULN or 2.5 times baseline if markedly abnormal (i.e., over twice the ULN); in these patients, ART was generally not discontinued by the treating physician. SH was defined as an increase of liver enzymes of at least 10 times the ULN or 5 times baseline if markedly abnormal (i.e., over twice the ULN), followed by hepatic enzyme improvement after ART discontinuation. Liver failure (LF) was defined as the presence of noninflammatory ascites plus all the following: PT less than 75% of the control after at least 1 week of vitamin K administration, total serum bilirubin greater than 3.5 mg/dL, serum albumin less than 2.5 g/dL in the absence of wasting syndrome, and ultrasound-observed space-occupying lesions in the liver. In the presence of SH, all patients underwent the following: medical examination; alcohol and nonmedicinal drug consumption assessment; liver ultrasound examination and computed tomography scan when indicated; biochemical and hematologic profile, including arterial blood lactic acid and bicarbonate measurements, hepatitis C virus (HCV) RNA, hepatitis B virus (HBV) DNA in HBsAg⁺, hepatitis D virus (HDV) antibody (Ab), and IgM; and a complete workup intended to exclude any concurrent opportunistic infections or neoplasms in the liver (including cytomegalovirus [CMV] DNA detection and quantification by PCR technique; blood cultures for bacteria, fungi, and mycobacteria; detection of cryptococcal soluble antigens; serology for *Bartonella* sp.; and stool examinations for ova and parasites). Consenting patients without major contraindications underwent liver biopsy no more than 3 months after the occurrence of SH. Patients showing SH were followed up for at least 36 months. Combination ART was restarted after 4 months of wash-out in all consenting patients who had normalization or values equal to baseline or less than 5 times the ULN elevation of liver function enzymes. Drug regimens were not changed unless genotype resistance testing showed HIV resistance to antiretrovirals. Patients with chronic hepatitis showing SH relapse were treated with recombinant interferon α -2a (Roferon; Roche, Basel, Switzerland) at a dose of 6 million units (MU) three times weekly for 12 months; a third cycle of combination ART was provided during interferon treatment.

Assays

Hepatitis virus markers were measured with commercial immunoenzymatic assays (Ortho Diagnostic Systems, Raritan, NJ, U.S.A.; Abbott Laboratories, Abbott Park, IL, USA; Sorin Biomedica, Saluggia, Italy). Plasma HCV RNA was quantified by PCR with the Amplicor Roche Diagnostic System (Hoffman-La Roche, Basel, Switzerland).

Histology

All consenting patients underwent percutaneous liver biopsy with the Menghini technique. Ten-millimeter formalin-fixed and paraffin-embedded liver tissue sections were stained by hematoxylin-eosin and

Masson trichrome, periodic acid–Schiff (PAS), PAS diastase digestion (PASD), and Perls method for iron. Immunohistochemistry for HBsAg and HBcAg was also performed. Additional stainings were performed to identify opportunistic pathogens.

Liver sections were evaluated by a single pathologist who was unaware of the patient's clinical and laboratory data. For each biopsy, a grade of necroinflammatory activity and a grade of fibrosis were established according to the method of Ishak (23).

Statistical Analysis

The rate of incidence was calculated as the number of outcomes (RH, SH, or LF) per 100 person-years of use of ART, and each regimen was considered separately in the analysis. Incidence rates were compared using the Mantel-Haenszel χ^2 test for person-years. For preliminary analysis, patients were classified as those showing RH and those not showing RH. Patients were classified as those showing the main clinical outcome, SH, and those not showing SH; patients with SH were classified as those showing and not showing LF during ALT flare or no more than 1 month after.

Values of continuous variables are expressed as means \pm SD or median, with ranges when the distribution was not normal. Differences between means or median values were compared by the *t* test and Mann-Whitney *U* test wherever appropriate. Differences between proportions were assessed by the Mantel-Haenszel χ^2 test using the Fisher exact test where appropriate. The Spearman rank correlation coefficient was used to establish the degree of correlation between continuous variables. Logistic regression analysis was used to assess risk factors associated with the development of relevant hepatotoxicity. Variables considered in the multivariate analysis included age; gender; injection drug use status; HCV, HDV, and HBV infections; pretreatment ALT and AST levels; CD4 cell count; treatment schedules; single antiretrovirals; and HIV RNA level. All *p* values are two-tailed; a *p* value of less than .05 was considered significant. EPI INFO software version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA) and EGRET (Cytel Software Corporation, Cambridge, MA) were used for statistical analysis.

RESULTS

Incidence of Severe Hepatotoxicity

Seven hundred fifty-five patients underwent 915 treatment episodes for a duration of 611 person-years. Two NRTIs were used in 137 treatment episodes accounting for 92 person-years, two NRTIs and one PI were used in 716 treatment episodes for a total of 478 person-years, and two NRTIs and one nonnucleoside reverse transcriptase inhibitor (NNRTI) were used in 62 treatment episodes for a total of 41 person-years. Six hundred eighty-seven patients underwent 1 treatment episode, 44 underwent 2 treatment episodes, and 24 underwent 3 treatment episodes during follow-up. Five of 68 patients with more than 1 treatment episode during the study period were switched because of mild liver toxicity (i.e., grade III elevation of liver enzymes). Treatment episodes of these 5 patients were excluded from the analysis. All

recruited patients were followed up for at least 6 months during treatment.

One hundred five cases of RH were observed (17 per 100 person-years of treatment). Treatment was stopped in only 9 of 105 patients. Multivariate analysis revealed that only two variables were independently associated with the occurrence of RH: anti-HCV reactivity (OR = 4.0, 95% CI: 2.16–7.69; *p* < .001) and baseline ALT levels (OR = 1.04, 95% CI: 1.01–1.07 for each 10 U/mL; *p* < .001). No patient with RH continuing ART showed SH and/or LF at the following visits.

Twenty-six of 105 cases of RH satisfied the definition criteria for SH with an incidence of 4.2 per 100 person-years of treatment; 7 of 26 patients also developed LF during or no more than 1 month after ALT flare (1.1 per 100 person-years). No patient with liver enzyme flare failed to meet the definition of SH because of a lack of enzyme improvement after stopping treatment. The incidence of SH was not significantly different by treatment regimen (4 per 100 person-years in patients treated with two NRTIs plus one PI, 6 per 100 person-years in those treated with two NRTIs, and none in those treated with two NRTIs plus one NNRTI). No difference was found when comparing the incidence of SH according to prescribed drugs; however, treatment groups were not homogeneous. In fact, the 136 patients treated with ritonavir showed significantly lower ALT activity (20 ± 7 IU vs. 43 ± 58 IU in patients not treated with ritonavir; *p* < .05) and lower prevalence of anti-HCV serum reactivity (15% reactive for anti-HCV-Ab vs. 80% in patients not treated with ritonavir; *p* < .01). Patients treated with two NRTIs showed significantly higher baseline ALT levels (96 ± 43 vs. 39 ± 31 in patients treated with triple drug regimens; *p* < .05).

Risk Factors for Severe Hepatotoxicity

Patients who developed SH during combination ART differed from those who did not by the following factors (Table 1): they were more often male; had intravenous drug use as risk factor for HIV acquisition; were younger; were more often coinfecting with HCV, HBV, and HDV; and had higher baseline ALT and bilirubin values and longer PT. No difference in follow-up time was found between patients with or without these characteristics.

Etiology of Alanine Aminotransferase Flares

Anti-HCV and HCV RNA reactivity were detected in all but 1 of 26 patients with SH; HBsAg was detected in 5 patients, with none of them showing serum HBV DNA

TABLE 1. Baseline characteristics associated with the occurrence of severe hepatic cytolysis (SH) during combination antiretroviral treatment

	Patients without SH	Patients with SH	<i>p</i> value; odds ratio (95% confidence interval)
Number	729	26	
Males	73%	92%	<0.01; 7.6 (2.5–30.6)
Age <35 years	42%	85%	<0.01 4.7 (1.4–24.6)
HIV transmission category: intravenous drug users	62%	88%	0.01; 4.7 (1.4–24.6)
Naive for antiretrovirals	41%	38%	NS
Previous exposure to zidovudine	59%	61%	NS
Duration months (mean ± SD)	18 ± 12	17 ± 13	NS
Previous exposure to didanosine	44%	38%	NS
Duration, months (mean ± SD)	9 ± 5	9 ± 6	NS
Previous exposure to other NRTIs	29%	31%	NS
Duration, months (mean ± SD)	8 ± 4	7 ± 3	NS
Previous exposure to PIs	24%	19%	NS
Duration, months (mean ± SD)	6 ± 5	7 ± 6	NS
History of alcohol abuse	13%	19%	< 0.04; 4.6 (1–17.5)
Anti-HCV antibody	67%	96% ^a	<0.01; 12.3 (2–509)
HBsAg-positive	7%	19%	0.04; 3.2 (0.9–9.09)
Anti-HDV antibody	5%	19%	<0.01; 4.6 (1.3–13.4)
Baseline >1.5 × ULN	27%	65%	<0.01; 5.1 (2.1–12.6)
Baseline bilirubin >1 mg/dL	9%	27%	<0.01; 3.7 (1.4–9.7)
Baseline PT <75%	2%	11%	0.01; 7.8 (1.3–31.5)
Treatment with cotrimoxazole	32%	30%	NS
Baseline CD4 cell count <200/mm ³	40%	58%	NS

^a One patient without anti-HCV reactivity showed HCVRNA at baseline and anti-HCV reactivity after occurrence of SH.

UNL, upper normal limit; PT, prothrombin time; ALT, alanine aminotransferase; HCV, hepatitis C virus; HBsAg; hepatitis B surface antigen; HDV, hepatitis delta virus; NS, not significant.

reactivity; and anti-HDV IgM reactivity was detected in 5 patients. The patient without HCV-RNA reactivity showed HBsAg and HDV-Ab IgM reactivities. These data were comparable with those obtained at baseline in all patients except 1, who showed HCV RNA but not anti-HCV reactivity at baseline; this patient showed less than 50 CD4 cells/mm³ at baseline. In this patient, liver histology showed HCV-related cirrhosis. None of these 26 patients showed evidence of opportunistic infections and/or hypersensitivity reaction.

In the 26 patients with SH, a direct correlation was observed between increase of ALT and the increment of CD4 over baseline at ALT peak (Spearman rank correlation coefficient: $r = 0.53$, $p < .001$).

Sixteen patients agreed to undergo liver biopsy less than 3 months after the occurrence of SH. Figures 1 and 2 show grading scores of necroinflammatory activity in each biopsy and distribution of the stages of fibrosis according to Ishak (23), respectively. The highest scores were observed for portal inflammation and piecemeal necrosis, usually in association with immune reaction. Piecemeal necrosis involved most of the portal areas in 15 of 16 cases. Zone 3 necrosis was absent (i.e., confluent necrosis [CN] scores were less than 2) in 14 of 16 patients. The patient who showed anti-HCV seroconversion showed histologic evidence of chronic hepatitis C with cirrhosis; thus, seroconversion was interpreted as restoration of anti-HCV reactivity previously lost be-

cause of immune depletion and not as acute hepatitis C. Mild bile duct damage was present in 5 of 16 biopsies, lymphoid follicles in 3 of 16 biopsies, mild steatosis in 8 of 16 biopsies, and moderate steatosis in 2 of 16 biopsies; mild eosinophil granulocyte infiltration was present in 7 biopsies, and it was moderate in 2 of 16 biopsies; and Mallory inclusion bodies were present in 2 biopsies.

In 2 patients, a former liver biopsy performed 6 to 18 months before starting ART was available. Compared with the former biopsies pre-ART, the post-ART biopsies showed worsening of necroinflammatory activity score (from 5 to 9 and from 3 to 8, respectively).

Histologic examination did not reveal any evidence of active opportunistic infection in the study patients.

Outcome of Severe Hepatotoxicity

The outcome of the 26 patients who suffered from SH is illustrated in Figure 3 and described below in more detail. None of the patients without SH developed LF or died as a result of liver disease in the subsequent follow-up.

Seven of 26 (27%) patients showed LF 3 to 25 days after the ALT peak occurred, and all died. This incidence of LF was 1.1 per 100 person-years of combination ART treatment. In 6 patients, LF was irreversible; thus, these patients were not rechallenged with ART, and they died

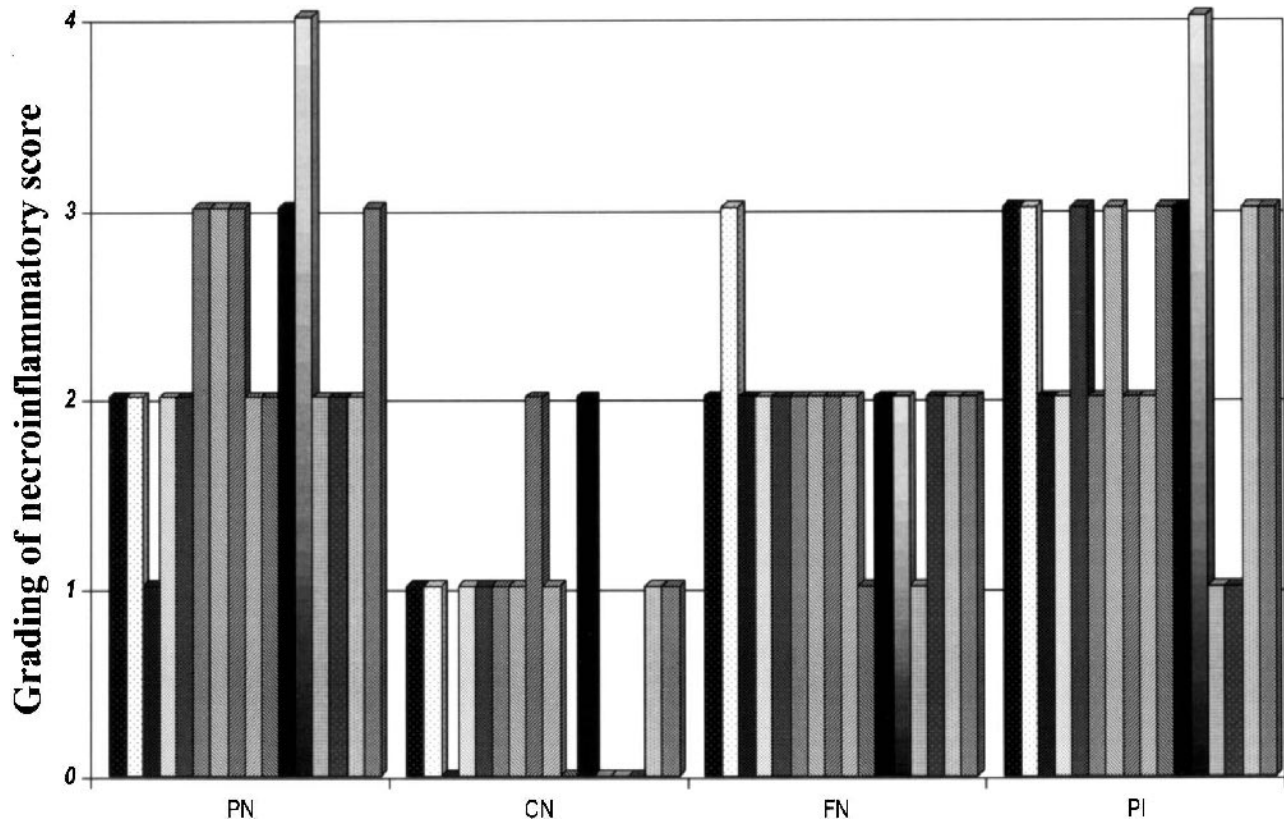


FIG. 1. Grading of necroinflammatory score according to Ishak classification (23) in the 16 liver biopsies. PN, piecemeal necrosis; CN, confluent necrosis; FN, focal necrosis; PI, portal inflammation. Each shaded bar represents a patient's biopsy result.

as a result of end-stage liver disease 3 to 12 months after the occurrence of SH. In 1 of these patients, LF was associated with lactic acidosis and pancreatitis, and the patient died after 3 days. The seventh patient showed an improvement of liver function 3 months after withdrawal of indinavir, zidovudine, and lamivudine, but the CD4 cell count dropped to less than 50 cells/mm³, and this patient developed relapsing disseminated *Mycobacterium avium* infection, candida esophagitis, and a new CMV retinitis. After successful treatment of these opportunistic infections, ART with stavudine plus didanosine plus saquinavir was recommenced. After 2 months, the patient showed a relapse of SH, with occurrence of irreversible LF 10 days after the ALT increase. He died 3 months later.

Table 2 shows a comparison of clinical characteristics between the 7 patients with LF and the remaining 19 with only SH. A lower baseline CD4 count was the only significant difference between the two groups.

Among 19 patients who did not show LF, 2 (10%) were lost to follow-up. Seventeen patients showed a decrease of ALT to below five times the ULN but without complete normalization; after a 4-month wash-out pe-

riod, they were rechallenged with the previous treatment regimens, with the exception of 2 patients who were treated with didanosine instead of lamivudine because of evidence of HIV genotype resistance in previous resistance tests.

Among 17 patients who underwent rechallenge, 7 (41%) showed a relapse of SH 2 to 4 months after treatment reinitiation. The remaining 10 patients did not show SH relapse during a retreatment period of 20 to 32 months.

Among the 7 patients who had SH relapse after rechallenge, 2 refused additional therapy and 5 (all with chronic hepatitis C on liver histology) were treated with interferon α -2a at 6 MU thrice weekly for 12 months. One of these 5 patients had normalized ALT and cleared serum HCV RNA and did not show an increase in ALT after ART was recommenced in combination with interferon treatment; the other patients did not show complete ALT normalization despite a 2 log decrease in HCV RNA and a 50% decrease in ALT activity after 1 month of interferon. These 4 patients underwent another rechallenge during interferon treatment with the same combination ART and did not show SH over a follow-up in-

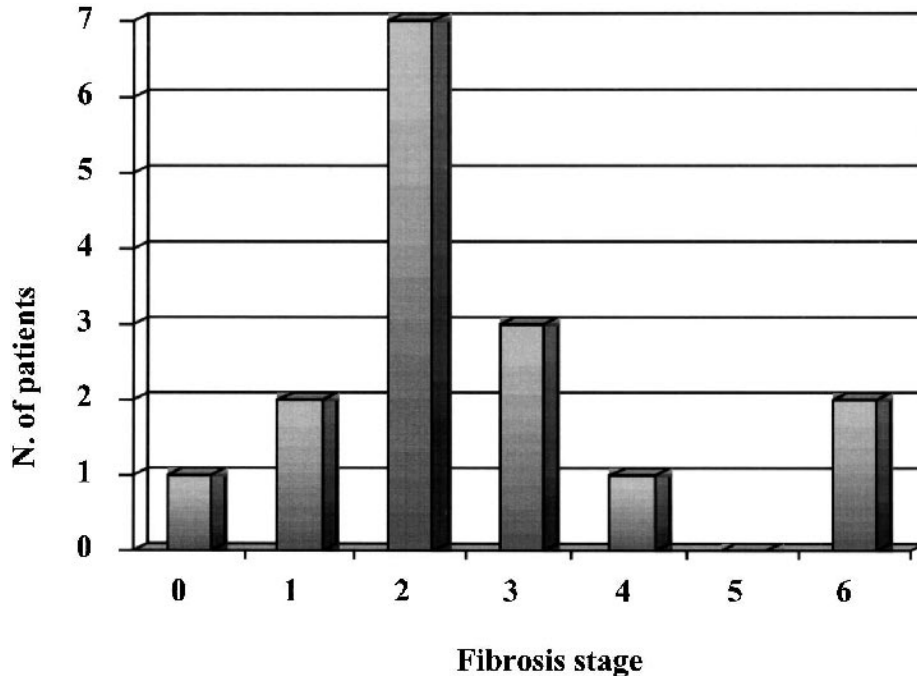


FIG. 2. Distribution of fibrosis scores in the 16 liver biopsies according to Ishak et al. (23). 0, no fibrosis; 1, fibrous expansion of some portal areas with or without short fibrous septa; 2, fibrous expansion of most portal areas with or without short fibrous septa; 3, fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging; 4, fibrous expansion of portal areas with marked bridging P-P as well portal to central (P-C) bridging; 5, marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis); 6, cirrhosis probable or definite.

terval of at least 30 months, including a period of at least 8 months after interferon had been withdrawn.

The 13 patients who had rechallenge with ART after the initial SH underwent a second liver biopsy 18 to 32 months after the first liver biopsy was performed. All these patients showed better necroinflammatory scores and stable or better fibrosis scores according to the Ishak classification (23).

DISCUSSION

Liver damage in patients treated with combination ART is an emerging problem because of the frequency of this phenomenon and the potentially severe adverse clinical outcome (10–16). Two studies have reported the occurrence of liver damage in 2% and 14% of patients, respectively, treated with two NRTIs plus one PI (15,16). In this study, the incidence of RH was 17 per 100 person-years of treatment and was similar to that reported in other studies. This study was focused on a more relevant outcome, however, showing an incidence of SH of 4.2 per 100 person-years and an incidence LF of 1.1 per 100 person-years.

Immune reconstitution against hepatitis virus antigens in liver cells may have played a major role in the pathogenesis of SH during ART in the study cohort as evidenced by the association of the following findings: (1) the occurrence of SH mainly in patients coinfecting with hepatitis viruses, (2) the positive correlation between

CD4 and ALT increases in patients with SH, (3) the liver histologic picture showing exacerbation of chronic hepatitis, and (4) the absence of relapse of SH of most patients rechallenged with the same ART regimens after a wash-out period and/or after interferon treatment. In addition, even the milder clinical outcome of RH was significantly associated with HCV coinfection and pretreatment hypertransaminasemia on multivariate analysis. These findings confirm the hypothesis formulated in previous studies (19,20) in contrast to other recent observations (21).

The inconsistency of our results with respect to the study reported by Martin-Carbonero et al. (21) might be a result of the fact that lower levels of transaminases were assumed as an outcome measure of liver damage (i.e., ≥ 1.5 times the ULN) in that study. This less strict end point may have encapsulated other causes of liver damage (e.g., direct drug toxicity, preexisting or concomitant liver damage by alcohol or concomitant medications); thus, the correlation between immune reconstitution and SH may have been confounded. Alternative explanations could be the low number of patients in that cohort and/or baseline differences in the patients studied (e.g., naive vs. mixed cohort) and/or differences in the immunologic response to ART (21).

A limitation of the current study is that multivariate analysis was not performed to assess risk factors because of the extremely strict criteria used to define SH (i.e., grade IV hepatic toxicity according to WHO adverse

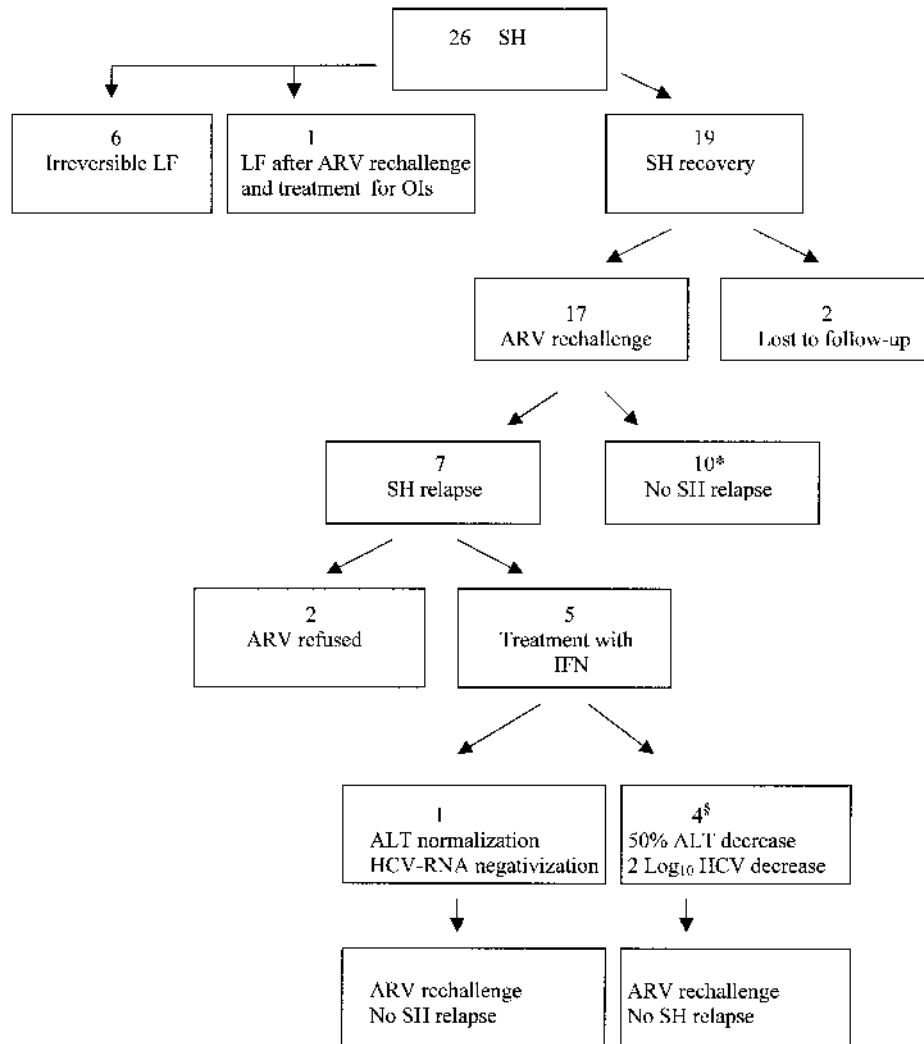


FIG. 3. Outcome of severe hepatotoxicity in the study patients. SH, severe hepatotoxicity; LF, liver failure; ARV, antiretroviral; IFN, interferon; ALT, alanine-aminotransferase; HCV RNA, hepatitis C virus viremia. *Nine of these patients underwent a second liver biopsy that did show better necroinflammatory scores and stable or better fibrosis scores according to the Ishak classification (23). §These patients underwent a second liver biopsy that did show better necroinflammatory scores and stable or better fibrosis scores according to the Ishak classification (23).

events severity scale) and the small number of events recorded. Notwithstanding, risk factors for SH identified in our cohort by univariate analysis are all linked to preexisting chronic viral hepatitis, and this is consistent with other European studies using multivariate analysis techniques (4,6–8). In addition, in the same cohort, multivariate analysis of a milder clinical outcome, RH, revealed an independent association with chronic hepatitis C.

With regard to irreversible LF after SH, an incidence of 1.1 per 100 person-years of combination ART was observed, unlike in other published cohort studies (4,6–8). For instance, LF occurred in only 0.3% of patients in the cumulative analysis of 21 AIDS Clinical Trial Group studies (9). This difference is probably related to the higher number of subjects with hepatitis virus coinfection in our cohort. More striking was the observation that LF occurred only in patients with severe CD4 depletion

at baseline. No other differences were found between patients showing LF and those without occurrence of LF over the follow-up period. This observation is consistent with the fact that baseline CD4 T-cell counts were below 200 cells/mm³ in all cases of LF without lactic acidosis reported on ART until now (6–10).

Three hypotheses may explain the occurrence of LF only in patients with severe CD4 depletion. First, severe CD4 depletion may be associated with more advanced chronic hepatitis. This seems to be ruled out in our study by the fact that baseline liver function parameters were comparable between patients with LF and without LF. Second, opportunistic infections or immune restoration against opportunistic pathogens present in the liver may have played a role in the pathogenesis of LF, but only 1 of the 7 patients with LF showed evidence of a concomitant opportunistic infection. Finally, more plausible is the interpretation that extensive liver damage could have

TABLE 2. Factors associated with the occurrence of liver failure after severe hepatic cytolysis induced by combination antiretroviral treatment

Characteristics	Liver failure	No liver failure
Number	7	19
Males	86%	95%
Age, years (mean \pm SD)	33 \pm 7	30 \pm 2
Naive for antiretrovirals	57%	16%
Duration of previous antiretroviral therapy, ^a months median (interquartile range)	13 (6–24)	14 (5–20)
HIV transmission category		
Intravenous drug users (%)	86%	89%
Baseline CD4 cell count <200/mm ³ (%)	100%	42% ^b
Baseline CD4 cells/mm ³ median (interquartile range)	94 (3–167)	260 (150–358) ^c
Baseline ALT, IU/L (mean \pm SD)	91 \pm 52	126 \pm 95
Baseline PT, % of control (mean \pm SD)	72 \pm 39	88 \pm 26
Baseline bilirubin mg/dL, median (interquartile range)	0.6 (0.4–2.5)	0.6 (0.4–0.9)
Baseline albumin g/dL (mean \pm SD)	3.8 \pm 0.5	4.1 \pm 0.7
Anti HCV antibody reactivity	71%	100%
HBsAg reactivity (%)	29%	13%
Anti-HDV reactivity (%)	15%	21%
Peak ALT IU/L median (interquartile range)	750 (522–1622)	646 (513–1085)
Nadir CD4 cells/mm ³ (mean \pm SD)	177 \pm 162	296 \pm 203

^a With at least one antiretroviral.

^b $p < .01$, Fisher exact test.

^c $p < .01$, Mann-Whitney U test.

UNL, upper normal limit; PT, prothrombin time; ALT, alanine aminotransferase; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; NS, not significant.

been related to the shock caused by immune reconstitution against hepatitis viruses in subjects with severe immune depletion before starting ART. This interpretation is also supported by the fact that relapse of SH after a 4-month wash-out period was observed only in 41% of patients retreated with combination ART. Consequently, this “stop, wash-out, and go” strategy allowed ART to be continued even after an episode of SH, indicating that direct hepatotoxicity by itself did not have a major role in the pathogenesis of SH. Moreover, histologic follow-up performed in 13 patients did not reveal any worsening of liver histologic findings after up to 32 months of follow-up.

Another important consideration is that in patients with SH relapse after rechallenge with ARV, interferon treatment was able to prevent a third relapse of SH after ART despite the persistence of HCV active replication in most patients. Even though not complete, inhibition of HCV replication by interferon could reduce the burden of HCV antigens in the liver cells, and this, in turn, could reduce the intensity of immune-mediated liver cell necrosis after immune reconstitution induced by ART. Controlled prospective trials are necessary to prove the efficacy of interferon with or without ribavirin in combination to prevent SH in HIV patients with HCV coinfection who are put on ART.

Although this is the first study focusing on the follow-up of patients with clinically significant ARV hepatotoxicity, it has some weaknesses that need to be acknowl-

edged. First, the association between chronic hepatitis and severe hepatotoxicity is not novel; however, we have confirmed it in relation to outcomes that are clearly relevant from a clinical point of view. Second, although histologic examination was available only in 16 patients, this is, to our knowledge, the largest series of biopsies performed in patients with ARV-induced hepatotoxicity. Third, treatment regimens were chosen by the treating physicians and therefore differed by baseline characteristics; however, only a few patients were treated with full-dose ritonavir or an NNRTI, which have been independently associated with hepatic cytolysis on treatment.

In conclusion, this study provides estimates of the incidence of ART-induced SH and LF in a large clinical setting of patients with a high prevalence of chronic hepatitis. Severe hepatotoxicity was related to preexisting chronic viral hepatitis followed by irreversible LF in a few patients, all with severe CD4⁺ T-cell depletion (i.e., <200 CD4⁺ T cells/mm³) before starting ART. Besides the fact that all patients with chronic viral hepatitis should be strictly monitored for liver damage after starting ART, this observation strengthens the importance of careful follow-up in patients with chronic hepatitis and a low CD4⁺ T-cell count. When the CD4⁺ T-cell count is 200 to 350 cells/mm³, the risk of SH resulting in LF may be low according to our data; thus, ART could be started quite safely. Only a few patients with chronic hepatitis and CD4⁺ cell counts <200 cells/mm³ at beginning of ART developed liver failure, so our data do not support

an earlier start of ART with higher CD4 counts to prevent liver failure in patients with chronic hepatitis C. Nevertheless, they indirectly underline the need for early treatment of chronic hepatitis C in patients with HIV coinfection before severe immune depletion occurs. Finally, for patients who start ART at low CD4⁺ T-cell counts, antihepatitis pre- or comedication could be an effective preventive or curative measure for SH, and this merits prospective evaluation in controlled clinical trials.

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