Concomitant Highly Active Antiretroviral Therapy Leads to Smaller Decline and Faster Recovery of CD4+ Cell Counts During and After Pegylated Interferon Plus Ribavirin Therapy in HIV–Hepatitis C Virus Coinfected Patients

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Introduction. The impact of highly active antiretroviral therapy (HAART) on CD4+ cell course during treatment with pegylated interferon plus ribavirin (PegIFN-RBV) in patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is unknown.

Methods. We determined CD4+ cell count in 94 HIV-HCV coinfected patients undergoing treatment with pegylated interferon plus RBV at baseline, treatment weeks 4–48 (W4–W48), and months 1, 3, and 6 of follow-up. Of the 94 patients, 70 underwent concomitant HAART (group A) and 24 did not (group B).

Results. Group A showed smaller CD4+ cell decreases from W24–W48 (P = .027) and greater CD4+ cell increases after cessation of pegylated interferon plus ribavirin therapy (P = .002) than group B showed.

Conclusions. Concomitant HAART leads to smaller decreases and faster recovery of CD4+ cells during and after pegylated interferon plus RBV therapy.

Worldwide, 130 million and 40 million people are infected with the hepatitis C virus (HCV) and the human immunodeficiency virus (HIV), respectively; because of shared routes of transmission, coinfection with both viruses is common, affecting about 5 million patients [1]. In the era of highly active antiretroviral therapy (HAART), chronic HCV infection has become a major cause of morbidity and mortality in HIV patients [2]. Current guidelines recommend a combination of pegylated interferon α and ribavirin (RBV) for antiviral therapy of chronic HCV infection [3]. Sustained virologic response (SVR) rates of 40%–50% have been achieved in large registration trials with high rates of adverse events including hematologic abnormalities such as cytopenias [4, 5]. A decrease in white blood cell (WBC) count and consecutive development of leucopenia (WBC < 4 G/L) during antiviral therapy with pegylated interferon plus RBV is a common phenomenon [4–6], which also results in a proportional decrease of T-helper cells (CD4+ cells) and cytotoxic T cells (CD8+ cells) [4, 6]. Both CD4+ and CD8+ cells are important for controlling and clearing viral infections [7]. A high HCV-specific CD4+ cell count is associated with a better virologic response to antiviral therapy in patients with chronic HCV infection [8] and with resolution of acute HCV infection [9]. The CD4+ cell count is essential in controlling HIV disease [10] and represents the most important parameter of HIV disease progression [11]. Because the course of CD4+ cell count is an important prognostic marker for HIV patients, CD4+ cell count decreases during leucopenia caused by pegylated interferon should be carefully monitored during antiviral therapy [12]. Nevertheless, data on the changes of T-lymphocyte subsets during and after antiviral therapy in HIV-HCV coinfected patients are limited [4–6]. Effective HAART stabilizes and restores CD4+ cell counts in HIV-infected patients [13]. However, the influence of concomitant HAART on the course of CD4+ cell count during pegylated interferon plus RBV combination therapy has not been assessed in detail. Thus, the aims of our analysis were:

1. to describe the changes in CD4+ cell counts during and after antiviral therapy with pegylated interferon in combination with RBV
2. to evaluate the influence of concomitant HAART on the CD4+ cell decrease during antiviral therapy
3. to evaluate the influence of concomitant HAART on the CD4+ cell recovery after cessation of antiviral therapy

METHODS

Patients and Antiviral Treatment
Our study included HIV-HCV coinfected and interferon-naïve patients undergoing antiviral therapy with pegylated interferon
plus RBV at the Medical University of Vienna from 2003 to 2010. The treatment period for pegylated interferon plus RBV was 48 weeks, irrespective of HCV genotype. Dosing regimens were 180 μg/wk for pegylated interferon alfa-2a and 1.5 μg/kg/wk for pegylated interferon alfa-2b. Patients infected with HCV genotypes 2 or 3 received 800 mg/d RBV and patients infected with HCV genotypes 1 or 4 received 1000–1200 mg/d RBV. Patients had clinical visits for screening, at baseline, and every 4 weeks during antiviral therapy (W4–W48). Follow-up visits were performed at months 1, 3, and 6 after cessation of pegylated interferon plus RBV treatment (FU1, FU3, FU6).

**Laboratory Assessments**

We collected blood samples at each treatment visit before, during, and after antiviral therapy. We determined both HCV-RNA and HIV-RNA levels at each visit to evaluate antiviral efficacy of pegylated interferon plus RBV on HCV replication and on HIV replication. We performed flow cytometric analysis of blood lymphocyte subpopulations with a 4-color flow cytometer (FacsCalibur, Becton-Dickinson).

**Statistical Analysis**

We compared demographic and virologic data from HIV-HCV coinfected patients using the nonparametric Mann–Whitney U test. During the follow-up, we evaluated interpatient variations in CD4+ cell counts using the Wilcoxon signed rank test. We considered all P values <.05 statistically significant. We performed all statistical analyses using Statistica for Windows Version 6.0 (Statsoft).

**RESULTS**

**Patient Characteristics (Table 1)**

Our analysis comprised 94 eligible patients, with 74% receiving concomitant HAART (group A) and 26% without concomitant HAART (group B). Baseline demographic characteristics and hematologic parameters were similar between groups A and B. HCV genotypes, HCV-RNA loads, and META VIR fibrosis stages (including the proportion of patients with cirrhosis) were equally distributed between the 2 patient groups. HIV-RNA levels were significantly lower in patients on HAART than in patients not receiving HAART (P < .0001), and 97% of patients with HAART showed suppression of HIV replication. Prevalence of CDC stage 1 and 2 was similar in group A and group B, respectively. No patients with CDC stage 3 were included in group B without HAART compared with 4 patients with CDC stage 3 in the group A with HAART. CD4+ cell count at baseline was similar in both patient groups, whereas the pretreatment CD4+ cell nadir was significantly lower in group A than in group B (P < .0001). With growth factors (G-CSF & epo), all patients have received >80% of the planned dose of peg-IFN dose. There were no significant differences in the use of epo and G-CSF between group A and B.

**Treatment Outcome and Influence of Highly Active Antiretroviral Therapy**

In our study, SVR was achieved in 51 patients (54%), 19 had a virologic relapse (20%), and 24 were virologic nonresponders (26%) (Table 1). Baseline viral load was similar in groups A and B (P = .709). The decrease in HCV-RNA level was significantly greater in group A than in group B at treatment week 4 (P = .022) and at treatment week 12 (P = .031). The proportion of patients achieving HCV-RNA negativity at treatment week 4 (rapid virologic response [RVR]; P = .301) and at treatment week 12 (complete early virologic response; P = .395) was similar in groups A and B. Rates of end-of-treatment response (P = .168) and SVR (P = .306) were not significantly different between groups A and B.

**Influence of Antiviral Therapy With Pegylated Interferon Plus Ribavirin on CD4+ Cell Count**

Baseline CD4+ cell counts were similar in patients with and without concomitant HAART. When comparing WBC and CD4+ cell counts between patients with and without cirrhosis, we found significantly lower WBC counts (4.61 G/L vs 5.93 G/L; P = .11) and lower CD4+ cell count (340 cells/μL vs 552 CD4+ cells/μL; P < .0001) in patients with cirrhosis. Mean counts of CD4+ cells continuously decreased from baseline to treatment W12, from 512 ± 208 cells/μL to 332 ± 172 cells/μL. Thereafter, we noted a slight but nonsignificant decrease until the end of treatment, with 312 ± 182 CD4+ cells/μL at W48. CD4+ cells increased again to baseline values at FU6 (513 ± 279/μL). The percentage of CD4+CD3- cells on total CD3+ cell count increased from baseline (28.5% ± 2.6%) to W4 (32.1% ± 3.1%) and to W8 (34.0% ± 5.2%) with no further significant changes until the end of treatment. CD4+CD3- percentage on CD3+ cells decreased again to baseline values at FU1 (30.0 ± 2.9%), FU3 (27.6 ± 3.6%), and FU6 (29.1 ± 3.1%).

**Influence of Concomitant Highly Active Antiretroviral Therapy on Changes in CD4+CD3- Cells (Figure 1)**

Comparing the absolute numbers of CD4+ cells, we found a nonsignificant trend for lower CD4+ cell counts in group B than in group A between baseline and W48. A faster recovery of absolute CD4+ cell counts was noted in group A compared with that of group B at FU3 (464 ± 193/μL vs 420 ± 149/μL; P = .049) and at FU6 (538 ± 205/μL vs 442 ± 189/μL; P = .028).

Concerning the relative changes in CD4+ cells compared with baseline, there was a greater decrease of CD4+ cell count in group B than in group A from W24 (~40% vs ~35%; P = .042) to W48 (~45% vs ~38%; P = .027; Figure 1A). After cessation of pegylated interferon plus RBV therapy, patients in group A showed a faster recovery of CD4+ cell count at FU1 (82% vs 71%; P = .019), at FU3 (100% vs 82%; P = .007), and at FU6 (106% vs 88%; P = .003) compared with those of group B (Figure 1A).

In a subanalysis of patients with CD4+ cell counts >500/μL (Centers for Disease Control and Prevention [CDC] stage 1) at
baseline, the differences in CD4$^+$ cell decrease between group A and group B were significant from treatment W24 to W48 ($P < .05$; Figure 1B). In patients with high CD4$^+$ cell count at baseline (>500/µL), the recovery of CD4$^+$ cells after cessation of pegylated interferon plus RBV was significantly faster and stronger in group A than in group B at FU1 ($P < .05$), FU3 ($P < .01$), and FU6 ($P < .01$).

In the subgroup of patients with baseline CD4$^+$ cell counts of 200–499 cells/µL (CDC stage 2), we observed similar effects of concomitant HAART in group A for smaller decreases during
and faster recovery after antiviral therapy with statistical significance at W12, W36, and W48 and at FU1, FU3, and FU6 (Figure 1C).

**DISCUSSION**

This study demonstrates beneficial effects of concomitant HAART treatment in HIV-HCV coinfected patients undergoing antiviral combination therapy with pegylated interferon plus RBV for smaller decreases of CD4+ cell counts during antiviral therapy and faster recovery of CD4+ cell counts after cessation of therapy.

Concomitant HAART during HCV-treatment prevented profound decreases of CD4+ cell counts compared with patients without concomitant HAART, especially in patients with high pretreatment CD4+ cell counts (>500/µL). In addition, a faster recovery of CD4+ cell counts after cessation of pegylated interferon plus RBV therapy was observed in patients receiving concomitant HAART. These findings provide further evidence for a beneficial effect of an “early” start of HAART in HIV-HCV coinfected patients, especially in those who are eligible for antiviral treatment, to enable a faster immune reconstitution after cessation of pegylated interferon plus RBV therapy.

A previously published study using standard interferon for treatment of HIV-HCV coinfected patients already demonstrated a beneficial effect of concomitant antiretroviral therapy with zidovudine on CD4+ count decrease during antiviral treatment [14] But detailed data concerning the CD4+ cell course during and after pegylated interferon plus RBV treatment were not reported in the large registration trials [4, 5] in HIV-HCV coinfected patients. As the CD4+ cell count represents the most important marker of HIV disease progression [11] and may also influence HCV treatment response [15], the possibility to prevent profound decreases of CD4+ cell counts is of particular importance for coinfected patients undergoing HCV-therapy.

The beneficial effect of HAART was independent of the presence of cirrhosis (which also affects WBC and CD4+ cell count), because the proportion of patients with cirrhosis was not different between patients with and without concomitant HAART. Despite similar RVR and SVR rates in HAART and non-HAART patients, we found significantly greater HCV-RNA decreases at treatment week 4 and treatment week 12 in the patients with concomitant HAART in our analysis. Moreover, a quick immune reconstitution defined by a fast recovery of CD4+ cells, which can be accelerated by administration of concomitant HAART is very desirable.

**Additional Findings**

Overall, 26 patients developed CD4+ cell counts <200 cells/µL and and 3 patients developed CD4+ cell counts <100 cells/µL during pegylated interferon plus RBV therapy. During treatment and follow-up, 2 participants in each group (3% in the HAART group and 8% in the non-HAART group) developed opportunistic infections ($P = 299$).

We found no significant differences in CD4+ cell counts during or after antiviral therapy between patients with SVR and patients without SVR.

Patients without concomitant HAART had a significant decrease of HIV-RNA at W4 ($-1.19 ± .39$ log copies/mL) and at week 12 ($- .90 ± .17$ log copies/mL) and a reincrease to baseline HIV-RNA levels at FU1, FU3, and FU6.
The retrospective nature of this analysis and the small numbers of HIV-HCV coinfected patients are potential limitations of this study, but in absence of prospective data from larger randomized trials these data provide information of clinical relevance. Current guidelines recommend initiation of HAART in HIV-HCV coinfected patients if CD4$^+$ cell count is below 500/μL [12] and state that “treatment of HCV infection should be regarded as high priority in this population” [3]. As a consequence, several HIV-HCV coinfected patients not in need of HAART according to current guidelines would be started with antiviral combination therapy using pegylated interferon plus RBV without concomitant HAART. We demonstrate here that HIV-HCV coinfected patients, especially this group with well-preserved immune function, defined by a CD4$^+$ cell count >500/μL, achieved the greatest benefits through concomitant HAART administration.

In accordance with prior studies reporting an antiretroviral effect of PegIFN, we observed a transient decrease of about 1 log copies/mL in HIV-RNA levels during pegylated interferon plus RBV therapy.

The achievement of SVR did not influence CD4$^+$ cell course during therapy nor the recovery of CD4$^+$ cell count after pegylated interferon plus RBV therapy.

In summary, our data suggest that most patients would benefit from initiation and continuation of concomitant HAART during antiviral therapy with pegylated interferon plus RBV + for prevention of profound decreases in CD4$^+$ cell counts and acceleration of immune reconstitution after antiviral therapy ends. Prospective evaluation of benefits, costs, and potential harmful side effects of concomitant HAART in HIV-HCV coinfected patients with well-preserved CD4$^+$ cell count undergoing antiviral therapy in randomized trials is indicated.

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**References**


