Hepatitis Virus Coinfection in the Strategic Management of Antiretroviral Therapy (SMART) Study: A Marker for Nonliver, Non–Opportunistic Disease Mortality

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The Strategic Management of Antiretroviral Therapy (SMART) study was undertaken with the hypothesis that minimizing exposure to antiretroviral drugs—and, thus, their toxic effects—would be beneficial. It was proposed that a minimum level of immune function (defined by CD4 cell count or percentage) could be maintained using intermittent antiretroviral therapy. The original randomized, prospective study included a drug conservation arm in which intermittent antiretroviral treatment was guided by CD4 cell count and a viral suppression arm that continued antiretroviral therapy with the goal of maximal viral suppression. Results of this study revealed increased rates of opportunistic disease and/or death in the drug conversation arm without a decrease in any toxic effects associated with antiretroviral therapy [1]. In this issue of *Clinical Infectious Diseases*, the SMART study authors present their findings from a subgroup analysis of hepatitis B virus (HBV) and/or hepatitis C virus (HCV)–coinfected patients from the study [2].

Because of shared routes of transmission, hepatitis coinfection is common among HIV-infected persons: 15%-30% are coinfected with HCV, and ~10% are coinfected with HBV [3, 4]. In addition, the rates of progression and complications from chronic viral hepatitis are accelerated in patients with HIV coinfection [5, 6]. Studies performed in the pre-HAART era documented elevated fibrosis progression rates and shorter times to cirrhosis in HCV-coinfected persons [7, 8]. After initiation of HAART, HCV-coinfected patients are at increased risk of experiencing significant elevations of liver enzyme levels, with rare reports of rapid progression or death and excess toxic effects due to altered antiretroviral pharmacokinetics [9–12]. Some studies also suggest that the mitochondrial toxic effects related to nucleosides may be magnified in HCV-coinfected patients [13, 14]. Together, these aspects suggest that antiretroviral toxic effects may be enhanced in hepatitis virus–coinfected patients, perhaps making an argument for delayed or intermittent therapy. On the other hand, accumulating evidence suggests that HAART treatment can slow the progression of HCV infection and decrease liver-related mortality in patients with concurrent HIV infection and hepatitis [15, 16]. In the case of hepatitis B, potent antiretroviral therapy that uses agents with HBV activity (often in combination; e.g., tenofovir-emtricitabine) could be expected to have a positive direct effect on HCV disease and liver-related mortality. Given these opposing forces, an analysis of the data from the SMART study in hepatitis virus–coinfected patients is particularly intriguing.

The hepatitis subgroup (930 of 5472 subjects) was defined as those individuals who had tested positive for hepatitis B surface antigen for >6 months and/or who had a positive HCV antibody test result. A number of significant differences were found in the baseline characteristics of the hepatitis group, including several that could be expected to have an impact on non–opportunist disease mortality (e.g., race, age, and alcohol abuse). In looking at the primary end point (opportunistic disease or death) from the SMART study and the individual components of opportunistic disease and non–opportunistic disease death, individuals were at higher risk of reaching an end point in the drug conservation group than in the viral suppression group, regardless of the hepatitis coinfection status (interaction P values of .72, .24, and .84, respectively).

When the analysis was changed to look at the hepatitis virus–coinfected group,
The omission of HIV-monoinfected group is not reported as a factor in the hepatitis group versus the comparison of participants; the breakdown of this risk factor in the hepatitis group (2.5 vs. 0.7), with an adjusted HR of 2.9 (95% CI, 1.8–4.6).

Finally, the excess non–opportunistic disease mortality appears to be exacerbated in the hepatitis virus–coinfected drug conservation subgroup \( (n = 483; HR, 1.9; 95\% CI, 1.0–3.9) \). The top 3 causes of non–opportunistic disease deaths in hepatitis virus–coinfected patients were unknown, other (presumably includes accident, suicide, violence, or non–opportunistic disease infection), and substance abuse. Only 2 hepatic deaths occurred, and no increase in hepatic deaths was seen in the original SMART study in the drug conservation group.

How do we explain the results and what are their implications? There is precedence for HCV infection being associated with all-cause mortality and non–liver-related mortality in HIV-uninfected populations \([17]\)—perhaps a reasonable surrogate for non–opportunistic disease death in the present study. Deaths related to drug or alcohol abuse and trauma or suicide were increased in HCV–positive groups in several studies \([18, 19]\). In particular, injection drug use as a risk factor for acquisition of HCV seems to predispose patients to non–liver-related deaths \([18]\). The original SMART study reported injection drug use as a risk factor in 9.7% of participants; the breakdown of this risk factor in the hepatitis group versus the HIV-monoinfected group is not reported for the current analysis. The omission of injection drug use rates—and, thus, no adjustment for potential difference in injection drug use rates between the groups—is a limitation of the results presented. One would expect rates of injection drug use to be much higher in the coinfected patients.

Large baseline differences were also found in the coinfected group compared with the HIV-monoinfected group, with more patients of black race, of older age, and with a history of alcohol abuse in the coinfection group. Although the results were adjusted for these baseline factors, controlling for all these covariates that have an impact on mortality is difficult. The secondary analysis of the coinfection population with undetectable hepatitis virus nucleic acids showed a similarly elevated risk of non–opportunistic disease death, supporting the premise that it is not a direct effect of the viruses on non–opportunistic disease mortality.

Overall, the study results suggest an elevated mortality rate for hepatitis virus–coinfected patients, compared with HIV-monoinfected patients, irrespective of their treatment assignment in the SMART study. In addition, findings in the subset without detectable hepatitis virus nucleic acids, a short median follow-up (1.3 person-years), and a lack of increased liver-related deaths all suggest that the increased non–opportunistic disease mortality is not a property of the viruses themselves; thus, specific treatment geared toward the hepatitis virus of interest would not be expected to affect this mortality. It seems most likely that hepatitis antibodies or antigen in this case serves as a marker for other mortality risk factors, such as drug or alcohol abuse and socioeconomic factors.

The higher absolute rate of non–opportunistic disease death in the coinfected drug conservation group \((3.3 \text{ deaths per 100 person-years})\), compared with the HIV-monoinfected drug conservation group \((0.9 \text{ deaths per 100 person-years})\) suggests that treatment interruption may be particularly harmful for coinfected patients. However, the HRs for drug conservation and viral suppression in both groups were similar \((1.9 \text{ and } 1.8, \text{ respectively})\), with 95% CIs that included 1.0 and an interaction \( P \text{ value} \) for coinfection status and treatment group of 0.84. In light of additional data pointing to the beneficial effects of HAART therapy in HCV–coinfected patients, a treatment interruption strategy in HCV-HIV–coinfected patients seems like a particularly risky strategy. Finally, although the number of HBV-HIV–coinfected patients in the study was too small to make conclusions about this subgroup, a drug interruption strategy could be particularly harmful for coinfected patients with chronic HBV infection. Complications related to chronic HBV infection are closely correlated with HBV loads, and flares of hepatitis occur during recurrent HBV viremia because of resistance or discontinued use of medication \([20, 21]\). The use of an adefovir “bridge” during treatment interruption, although reasonable at the time the study was conceived, would now be questionable, given the poor efficacy of adefovir when compared with tenofovir, which is a common component of current HAART therapy \([22, 23]\).

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**References**


**EDITORIAL COMMENTARY**

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