

## **Impact of Ribavirin Therapy on HIV Variability in HIV-HCV Coinfected Patients Not Receiving Antiretroviral Treatment**

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**Background:** The guanosine analogue ribavirin (RBV) has antiviral activity against different RNA and DNA viruses. Several mechanisms of action have been proposed to explain the antiviral properties of RBV, including indirect effects (IMP inhibition, immunomodulatory properties) and direct mechanisms (RNA capping interference, polymerase inhibition, and lethal hypermutagenesis). Although RBV has not shown clinical benefit against HIV infection, the impact of RBV on HIV replication and variability in vivo has not been investigated in detail.

**Methods:** A retrospective case-control study was conducted in HIV-HCV coinfecting individuals who initiated therapy for chronic hepatitis C with pegylated interferon (peg IFN) plus RBV (1000-1200 mg daily) in the absence of any antiretroviral therapy at our institution. Sequence analysis of 1302 bases from the HIV pol gene was performed in plasma specimens before beginning RBV therapy and at the end of hepatitis C therapy (6 months HCV genotypes 2 to 3 and 12 months HCV genotypes 1 to 4). In controls, HIV sequences from drug-naïve subjects were examined at 2 similar time points. Evolution of amino acid changes in the HIV pol gene, as well as hypermutation G to A, A to G, and synonymous and non-synonymous changes were analyzed using HYPERMUT and SNAP programs (available at [www.hiv.lanl.gov](http://www.hiv.lanl.gov)).

**Results:** A total of 23 individuals were examined; 15 HIV-HCV coinfecting and 8 controls. Mean plasma HIV-RNA was 3.8 logs at baseline and mean interval between the 2 tested specimens was 9 months, without differences between groups. No specific amino acid substitutions at the HIV RT gene were recognized consistently under RBV therapy, which hypothetically could represent signature RBV resistance mutations. However, the overall nucleotide (NT) change was significantly higher in patients taking RBV compared with controls (23 vs 10;  $P < 0.05$ ). In addition, a significant proportion of patients under RBV showed G to A transitions than controls (86% vs 50%;  $P < 0.05$ ). Finally, patients on RBV versus controls tended to show greater median number of NT mixtures in the pol gene sequence (6.5 vs 3), median A to G substitutions (3 vs 1), synonymous substitutions (6 vs 4), potential synonymous changes (261 vs 233), potential non-synonymous changes (955 vs 867), and S/NS ratio (6 vs 4). The limited size of the study population most likely precluded to obtain significant differences testing these variables.

**Conclusions:** RBV seems to enhance HIV variability in vivo, most likely increasing the mutation rate, as it does for other RNA viruses (enterovirus, poliovirus, and perhaps hepatitis C virus). This mechanism of antiviral activity does not result in the selection of signature resistance mutations in the viral polymerases, as occurs with classical nucleoside analog inhibitors which act as chain terminators.

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