

## Novel Patterns of Mutations in HBV Reverse Transcriptase Associated with Lamivudine Resistance in HBV+HIV Co-infected Patients

V Svicher<sup>1</sup>, C Alteri<sup>1</sup>, V Cento<sup>1</sup>, C Gori<sup>2</sup>, R Salpini<sup>1</sup>, F Marcuccilli<sup>1</sup>, A Bertoli<sup>1</sup>, M Arlotti<sup>3</sup>, M Puoti<sup>4</sup>, N Ladisa<sup>5</sup>, G Rizzardini<sup>6</sup>, F Ceccherini-Silberstein<sup>1</sup>, A D'Arminio Monforte<sup>7</sup>, CF Perno<sup>1</sup>, and the ICoNA study group.

1 University of "Tor Vergata" Rome, Italy; 2 INMI "L. Spallanzani", Rome, Italy; 3 University of Bologna; 4 Ospedali Civili, Brescia, Italy; 5 Hospital of Bari, Italy; 6 "L. Sacco" Hospital, Milan, Italy; 7 University of Milan, Milan, Italy

**Background:** To define lamivudine-resistance profiles in HBV reverse transcriptase (RT) and factors affecting lamivudine-driven anti-HBV virological-response in HBV+HIV co-infected pts.

**Methods:** 89 full-length HBV RT sequences from 63 HBV+HIV co-infected patients, receiving lamivudine including regimens were analyzed at baseline and at different time-points (up to 6 years) after starting lamivudine-therapy. All patients had detectable HBV-DNA at starting lamivudine and were not treated with other drugs effective against HBV. Virological-rebound is defined by a rebound of HBV-viremia  $>1\log\text{IU/ml}$  from the nadir value. The association of mutations with lamivudine-treatment and with virological-response at week-48 of lamivudine-treatment was assessed by Fisher exact test, and logistic-regression analysis.

**Results:** Among 63 patients, 31(49.2%) and 28(44.4%) are infected with HBV-D and -A genotypes, respectively, while the remaining 4 (6.4%) with HBV-G genotype.

HBV-failure is observed in 65.1% of patients after a median-time of 2.0[IQR:0.8-3.6] years with a median HBV-viremia of 6.0[IQR:4.6-7.2] $\log\text{IU/ml}$ . The proportion of patients with lamivudine-resistance mutations progressively increases over lamivudine-treatment: from 27.8% at 1 year to 70.0 at 2-3 years, and to 78.6 at  $>4$  years ( $P=0.009$ ). Novel HBV RT mutations are significantly associated with lamivudine-treatment. Among them, W243G, localized in the dNTP binding domain (near the active site of HBV-RT), is completely absent at baseline, increases up to 12.8% in lamivudine-failed patients, and correlates with the presence of M204I/V at failure ( $P<0.05$ ). The co-presence of M204I/V+W243G also correlates with increased HBV viremia at failure compared to M204I/V alone (6.9 $\log\text{IU/ml}$  versus 4.5 $\log\text{IU/ml}$ ).

Finally, the presence of specific polymorphisms at baseline can modulate the virological response to lamivudine at week-48. In particular, the baseline presence of Q149K correlates with an increased risk of virological failure at week-48 (OR:10.5[IQR:1.0-121.9],  $P=0.04$ ), while the baseline presence of Q130P correlates with a decreased risk of virological failure at week-48 of lamivudine-treatment (OR:0.09[IQR:0.008-1.1],  $P=0.04$ )

**Conclusions:** Our study shows that HBV-resistance profiles to lamivudine can be more complex than those observed in HIV, and highlights the existence of HBV-RT polymorphisms able to modulate lamivudine virological-response. Their knowledge is crucial for a correct set up of antiviral therapy in both HBV mono-infected and HBV+HIV co-infected patients.