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In response to Martin et al:

We agree with Martin et al that, as yet, late recurrence of hepatitis C following treatment has not been studied in this highly-exposed group of patients. To clarify the point made in our study "Next generation sequencing sheds light on the natural history of hepatitis C infection in patients that fail treatment",(1) the majority of cases labelled as HCV reinfection within the 24 week window post-treatment are likely to represent viral rebound rather than reinfection, even in the presence of a switch in genotype or subtype. In the absence of detailed sequencing data, it indeed seems likely that patients with recurrent HCV infection have a high rate of reinfection, (2) although there is a need to carry out an appropriately designed study to confirm this as some studies in other highly exposed cohorts have shown that relapse is associated with recrudescence of similar strains, others have lacked analysis of paired samples and none have employed a next generation sequencing approach.(3, 4) In the meantime, the proposed adjustment to the reinfection rate following removal of the 7% of patients that relapsed within the 24 week posttreatment would seem entirely appropriate. (5, 6) We also agree that retreatment is indicated in patients with recurrent HCV infection. The role of the emergence of resistant variants will be of particular interest as DAAs are rolled out, in particular when interferon-free regimens are used, as interferon resistance is likely to be heavily influenced by the host response and is unlikely to occur solely due to mutations within the viral genome.

<sup>1.</sup> Abdelrahman T, Hughes J, Main J, McLauchlan J, Thursz M, Thomson E. Next generation sequencing sheds light on the natural history of hepatitis C infection in patients that fail treatment. Hepatology 2014.

<sup>2.</sup> Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, Fisher M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. Aids 2007;21:983-991.

<sup>3.</sup> Soriano V, Vispo E, de Mendoza C, Labarga P, Plaza Z, Fernandez-Montero JV, Poveda E, et al. Very late relapse after discontinuation of antiviral therapy for chronic hepatitis C. Antivir Ther 2013.

<sup>4.</sup> Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich DT, Abergel A, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology 2010;139:1593-1601.

<sup>5.</sup> Martin TC, Martin NK, Hickman M, Vickerman P, Page EE, Everett R, Gazzard BG, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. Aids 2013;27:2551-2557.

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6. Lambers FA, Prins M, Thomas X, Molenkamp R, Kwa D, Brinkman K, van der Meer JT, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. Aids 2011;25:F21-27.