The more is not always the merrier

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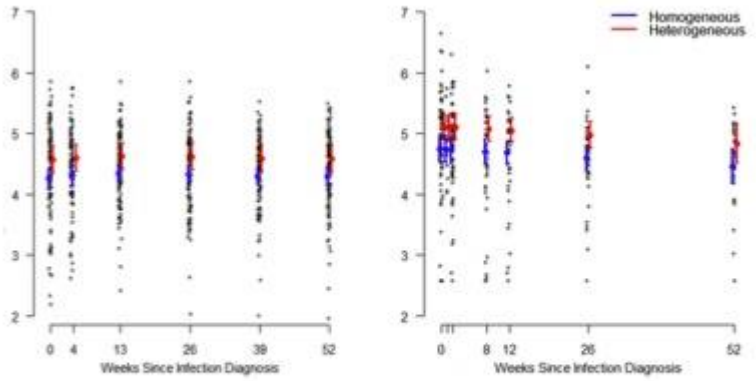

HIV-1 viral load measurements over the first year since HIV-1 diagnosis in the RV144 (left) and Step (right) trials. The mean viral load and associated 95% confidence interval at each time is shown for subjects with homogeneous vs. heterogeneous founding viral populations at the time of diagnosis. Means are estimated using models that adjust for baseline subject characteristics and assume that the effects of heterogeneity are constant over time.

Image provided by Dr. Holly Janes.

The term viral load denotes the number of HIV particles, quantified by detection of the viral RNA, in a milliliter of blood. This value increases soon after the infection then drops and stabilizes at a value termed viral set point. A lower set point correlates with a slower progression of the infection. Viral load set point, while being fairly stable for a single individual, varies across individuals, highlighting the importance of host characteristics in establishing it. This variability may be accounted for by host-virus interactions as well as by differences in characteristics of the viral infection, such as an infection with multiple HIV variants. While this is a rare event as compared to the infection with a single variant, it accounts for 20-35% new infections.

To evaluate whether infection with multiple HIV founders is associated with a higher viral load, Dr. Holly Janes from the Vaccine and Infectious Disease Division at Fred Hutch and collaborators from other institutions in US and Thailand analyzed two sets of data, obtained from breakthrough infections in RV144 and Step vaccine efficacy trials. RV144, also known as the Thai trial, tested a vaccine designed to induce antibodies against the envelope (Env) protein of HIV, and recruited volunteers in Thailand. The vaccine evaluated in the Step study induces T cell responses and was tested on subjects recruited at several study sites located in the Americas. Two different measures of the diversity of the founder virus population at the time of HIV diagnosis were used, a categorical

measure (homogeneous vs. heterogeneous virus population) and a continuous measure of *env* gene diversity.

In the samples from the RV144 trial, a higher average viral load was observed in the subjects with heterogeneous viral infections as compared to those with homogeneous infections at the time of detection of HIV infection as well averaged over times within 1- and 2-years of infection diagnosis. Accordingly, a lower average CD4+ T cell count was observed in subjects with heterogeneous infections. Interestingly, although the associations with viral load at later time points were similar for the Step study, heterogeneous infections were not found to be correlated with a higher viral load at the time of infection and the average CD4+ T cell count was comparable in subjects with heterogeneous and homogeneous founding virus populations. The difference between the two studies was not explained by the differences between the vaccines.

The study identified infection with multiple HIV founders as a factor potentially involved in the establishment of the viral set point. "This research suggests that a prophylactic intervention that reduced the number of founding viruses in a person who becomes HIV infected could have clinical benefit, and motivates measuring the number of founding viruses in future efficacy trials of these interventions" said Dr. Janes commenting on the results. Given the relevance that the viral set point has on the progression of the disease, the finding is important not only to better understand the progression of HIV infection, but it might have a clinical relevance.

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Janes H, Herbeck JT, Tovanabutra S, Thomas R, Frahm N, Duerr A, Hural J, Corey L, Self SG, Buchbinder SP, McElrath MJ, O'Connell RJ, Paris RM, Rerks-Ngarm S, Nitayaphan S, Pitisuttihum P, Kaewkungwal J, Robb ML, Michael NL, Mullins JI, Kim JH, Gilbert PB, Rolland M. 2015. HIV-1 infections with multiple founders are associated with higher viral loads than infections with single founders. *Nat Med.* 21(10):1139-41. doi: 10.1038/nm.3932.