Small steps forward for HIV vaccine development

A trial of a therapeutic vaccine against HIV induces cellular immunity and, although it provides hope, it highlights the hurdles for the development of such strategies.

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they met the criteria for two consecutive determinations of viremia > 1,000 copies per ml, 1 week apart. As the authors concluded, the trend in delayed rebound was too short to positively affect clinical management of the infection, but it partially reproduced the delayed rebound observed in the non-human primate model.

Still, despite the modest clinical effect, we feel that a number of lessons can be learned from the study by Colby et al., especially with regard to future trial design and possible readouts in the cure field. First, the question of whether a placebo group is indeed needed for scientific validity in pilot studies involving such unique and scarce HIV groups that also present an almost-universal viral rebound and for which efficacy comparisons among groups cannot be sufficiently powered. Second, stratification by HLA genotype upon randomization between arms might be necessary to limit the potential effects of host genetics on the results, as highlighted in the present RV405 study. As alluded to by the authors, the conservative ART-resumption criteria used in the study here may have blunted the possibility of detecting any potential post-rebound control of the virus after an initial phase of transient viremia. Such post-rebound control may occur only after vaccine-induced memory T cell responses are first re-stimulated by the rebounding virus to regain full effector functions and/or home to the relevant tissue to eliminate infected cells. Alternatively, innate immune mechanisms known as ‘vaccinal effects’ triggered by a transient viremia may also be required before the virus can be effectively controlled. Since more than 30% of cases of post-treatment control can occur after transient viremia higher than 10,000 copies per milliliter (ref. 1), more-relaxed ART-resumption criteria may need to be employed to offer those entering an analytic treatment interruption (ATI) the possibility of achieving an effective post-rebound control. However, elevated levels of viremia over a prolonged period of time also considerably increase the risk for viral transmission during ATI, and any such approach would require effective risk mitigation to avoid such transmission. As shown in the study by Colby et al., therapeutic vaccination was able to induce robust and broad immune responses. However, it remains to be determined whether the lack of control of the virus may have been due to still-insufficient stimulation of immune responses, inadequate response profiles, lack of reservoir mobilization, limited coverage of autologous viruses or the expansion of T cell and B cell responses to irrelevant targets in the virus. Comparison analyses of sequences of pre-existing and rebounding viruses, known as ‘sieve effect’ analyses, as well as detailed characterization of host immunity before ART initiation and during ATI, will hopefully help to elucidate the mechanisms that determine the rebound kinetics.

Finally, the results from Colby et al. cannot hide the fact that the HIV cure field is still a long way from reproducing the recent advances made in the non-human primate model. In particular, there is an urgent need to better understand mechanisms associated with primary infection and viral rebound during ATI, not only to facilitate the design of new interventions aimed at reproducing post-treatment controller phenotypes but also to help to optimize cure trial designs. However, the positive indications from the work of Colby et al. clearly warrant further testing of improved vaccines and/or combinational strategies.

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Competing interests
The authors declare no competing interests.

DISEASE GENETICS

Unraveling the genetic contributions to complex traits across different ethnic groups

Trans-ethnic study shows promise in the identification of genetic commonalities and differences for the contribution of traits to lifespan across genetically diverse populations.

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The use of diverse ethnic and racial groups in genetic studies is vital for identification of the genetic risk factors unique to specific populations and for determining whether the results can be generalized to other populations. However, a major shortcoming of human-genetic-association studies has been the relative lack of non-European participants, despite more than 75% of the world’s population being of African or Asian ancestry. For example, as of early 2019, only about 22% of participants in the commonly used genome-wide association study (GWAS) paradigm were non-European. Furthermore, the