and design studies that are based primarily on safety endpoints in older people living with HIV. We now know that switching from tenofovir disoproxil fumarate allows a partial recovery of bone mass in men living with HIV aged 60 years or older, which will probably reduce the risk of fractures in this population and improve quality of life in older people living with HIV.

Nicola Gianotti, Antonella Castagna
Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan 20127, Italy (NG); and Vita-Salute San Raffaele University, Milan, Italy (NG, AC)
nicola.gianotti@hsr.it

We declare no competing interests.

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Engineered HIV antibody passes muster

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In *The Lancet HIV*, Gaudinski and colleagues[1] report promising results of a small first-in-human clinical trial involving VRC07-523LS, an artificial antibody that has been extensively modified to improve its activity against HIV. VRC07-523LS was safe and well tolerated, and no serious adverse events or dose-limiting toxic effects were observed. This is an important milestone for HIV antibody immunoprophylaxis as it opens up opportunities for designing ideal antibodies that could be used to halt the unrelenting spread of HIV infection.

VRC07-523LS targets the CD4 binding site of the HIV envelope glycoprotein and works by blocking viral entry into human CD4 cells.[2] It was derived from the same HIV-infected individual as VRC01, a related antibody that is currently undergoing large-scale efficacy trials for HIV prevention in the Americas and Africa. However, VRC01 falls short in terms of neutralisation coverage of global isolates and also requires high doses to mediate its effect.[3] For this reason, scientists have aimed to isolate broader and more potent antibodies and use structural and genetic information to engineer even better versions.[4]

VRC07-523LS shows substantial differences from VRC01, particularly the heavy-chain sequence which was further modified to improve its neutralising activity.[2] It is at least five times more potent and more broadly neutralising than VRC01, features that translated to higher antiviral efficacy in non-human primates.[5] Although engineered antibodies have been used in other settings, previous studies[6] with HIV antibodies suggest that even single amino acid changes could render them autoreactive, reducing their half-life. The study by Gaudinski and colleagues,[1] however, shows that an engineered antibody can be as safe as one that has been vetted by the human immune system.

Another potential drawback of using genetically altered antibodies is the risk of rendering them immunogenic. This seems not to have been the case for VRC07-523LS, with no evidence of anti-drug

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antibodies in any of the 26 individuals who received this antibody. However, it will be important to assess this among larger numbers of participants, especially following repeated administrations. The immunogenicity of HIV antibodies is of concern, given their high rate of mutation and unusual genetic features, although this has not been a factor in the clinical trials done to date.[7,8]

Perhaps somewhat disappointingly, the half-life of VRC07-523LS was shorter than that of VRC01LS by over a month, although it was still more than twice as long as the half-life of VRC01. The substitution of two amino acids (Met428Leu and Asn434Ser) in the Fc region of the antibody enhances binding to the neonatal Fc receptor, prolonging serum antibody concentrations.[9] The LS mutation extended the half-life of VRC01 four-fold, which substantially reduces the frequency of dosing required to maintain protective levels.[7] Because it seems unlikely that the LS mutation would function differently between antibodies, other properties affecting the pharmacokinetics of VRC07-523LS are probably responsible for its shorter serum half-life. Nevertheless, the improved potency of VRC07-523LS compensates in large part for the shorter serum half-life.

In addition to intravenous administration, subcutaneous administration of VRC07-523LS was tested, which is likely to be crucial if this intervention is to be deployed for clinical use. Similar to other antibodies, peak concentrations were achieved in serum within a few hours of intravenous administration. However, following subcutaneous administration, peak concentrations were only achieved on day 10 and were 50% lower, suggesting lower bioavailability via this route. The reasons for this are unclear, but administering VRC07-523LS subcutaneously might not provide immediate protection against HIV-1 infection.

VRC07-523LS is a leading candidate for immunoprophylaxis and is the mainstay of antibody combinations selected for optimal coverage and potency.[10,11] Unlike other CD4-binding site antibodies undergoing clinical testing, VR07-523LS is equally effective against clade B and clade C isolates.[12] This is an important finding, since the vast majority of new HIV infections occur in Africa and India, where HIV-1 subtype C dominates. In the absence of an effective HIV vaccine, passively infused antibodies could be used as long-acting pre-exposure prophylaxis, especially over periods when the risk of infection is highest. What remains to be established is whether the costs and practicalities of using antibodies to reduce global HIV incidence are manageable. Ongoing engineering efforts to develop bi-specific and tri-specific antibodies (single antibody molecules that can target more than one epitope) or bi-functional antibodies (those that bind both the virus and host proteins) could help to alleviate some of these challenges, but further research is required. We are therefore just at the beginning of an exciting new era in HIV-prevention biology, with the prospect of adding highly engineered antibodies to the armamentarium in the battle against HIV.

Lynn Morris
National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg 2131, South Africa; Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; and Center for the AIDS Program of Research in South Africa, University of KwaZulu-Natal, Durban, South Africa
lynnm@nicd.ac.za

LM participates in the laboratory aspects of the clinical testing of VRC07-523LS and VRC01.

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