The development of HIV-specific broadly neutralising antibodies

While there has been remarkable progress in reducing HIV transmission rates and AIDS-related deaths over the last decade, infection rates remain persistently high. In 2019 there were approximately 1.7 million new HIV infections globally, of which more than 60 per cent occurred in sub-Saharan Africa.

Novel HIV prevention products, including long-acting injectable antiretrovirals and HIV-specific mAbs, are therefore being pursued to help further abate the spread of the virus. Broadly neutralising antibodies (bnAbs) are monoclonal antibodies (mAbs) that bind conserved epitopes common across multiple strains, thereby enabling broad protection against this rapidly mutating virus. Numerous single bnAbs and combinations of bnAbs that each bind distinct conserved epitopes on the HIV envelope protein are now in clinical testing to both treat and prevent HIV infection (Table, next page). The HIV bnAbs in development include natural mAbs, engineered bnAbs designed for improved potency, breadth and extended serum half-life, combinations of bnAbs covering multiple conserved epitopes, multispecific formats, and vectored bnAb gene delivery using adeno-associated virus vectors.

HIV bnAbs are an attractive therapeutic option because they could be dosed less frequently than daily antiretroviral regimens, and therefore make adherence less of an issue. Like other full-length antibodies, HIV bnAbs also have the potential to promote cell-mediated viral killing through their Fc-domains.

While administration of single bnAbs to HIV-infected individuals can result in transient but significant reduction in viremia, this approach also selects for resistant variants, whereas a combination of two bnAbs that bind to distinct conserved epitopes has been shown to maintain viral suppression for extended periods of time (on average 21 weeks), and prevent the selection of de novo resistance in clinical studies. Combinations of more than two bnAbs, as well as bi- or trispecific bnAbs with longer half-lives, are currently in clinical development to promote broader coverage and sustained viral suppression.

Combinations of bnAbs and/or multispecific antibodies with extended half-lives and increased potency, and in some instances enhanced cell-killing potential, are also being explored as a component of a potential HIV cure strategy. So far, bnAbs have not been shown to have a significant effect on reducing the reservoir of latent HIV-infected cells that is established early in the course of infection and persists indefinitely, which is why curing HIV is so challenging.

Of the HIV-specific bnAbs in development for prevention, the furthest along is a mAb referred to as VRC01 which binds to the HIV envelope protein at the CD4 binding site, which is the primary region on the HIV surface glycoprotein that is responsible for virus binding to target cells – an essential first step in the process of virus infection of host T cells. It is being tested clinically in two phase IIb trials known as the Antibody-Mediated Protection or AMP studies, involving 4,600 individuals at high risk of HIV infection in sub-Saharan Africa and in the Americas. Results of these proof-of-concept studies are expected in late 2020 (NCT02716675, NCT02568215).

The AMP study is testing the concept of whether an HIV-specific mAb can prevent HIV infection; however this mAb is not engineered for optimal potency or neutralisation breadth and is therefore not expected to become a licensed product.

Several next-generation HIV bnAbs are already in development, many of which are combination or multispecific products that offer the best hope for preventing infection from multiple strains of the virus. Modelling studies suggest that combinations of bnAbs will be needed to prevent infection from the global diversity of circulating
HIV strains\textsuperscript{3}, which presents additional challenges in making these products globally affordable.

Next-generation bnAbs are engineered for optimal potency, breadth, stability and half-life. One example is the engineered bnAb VRC01-LS, a modified version of VRC01 designed to extend serum half-life. In the clinic, VRC01-LS has a serum half-life of approximately 71 days (plus or minus 18 days), more than four-fold longer than the half-life of the unmodified antibody. This extended half-life should translate into a product that can be delivered less frequently and therefore at lower cost\textsuperscript{4}; however, VRC01-LS only binds to a single conserved epitope on the HIV envelope protein and a combination of optimised bnAbs targeting different epitopes or multispecific bnAbs will likely be needed to provide protection from the diversity of circulating HIV strains.

By engineering more potent bnAbs that bind to multiple conserved epitopes on the HIV envelope protein, researchers are hopeful they can also develop lower-dose multispecific and combination products at a lower cost. However, the clinical benefits of improvements in antibody potency aren’t as easily predicted in preclinical studies. For HIV bnAbs, preclinical studies have suggested that there is a correlation between \textit{in vitro} potency of neutralisation and the dose required to afford protection against viral infection in monkeys\textsuperscript{5}. However, this observation is yet to be confirmed for the optimised, more potent bnAbs currently in development.

Finally, while multispecific antibody formats currently in clinical development are another way to lower costs, the safety and immunogenicity of these highly engineered antibodies will need to be carefully monitored through clinical development.

Given the robust clinical pipeline of HIV bnAbs and the forthcoming results of the first proof-of-concept trial testing whether a single bnAb can prevent HIV infection, it is essential to define a pathway for eventual product access. Access will require that bnAb products are both widely available and affordable, particularly in low- and middle-income countries where the majority of new HIV infections occur.

\begin{table}[h]
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\begin{tabular}{|l|l|l|l|l|}
\hline
\textbf{Intervention} & \textbf{Purpose} & \textbf{Study population} & \textbf{Status/trial NCT no.} & \textbf{Organisation} \\
\hline
VRC01 & Therapy and prevention & SSA women HIV-uninfected and MSM HIV-uninfected, HIV-infected infants on antiretroviral therapy (ART), HIV-infected adults treatment interruption, Acute infection +/- ART, HIV-infected viremic & Phase Ib & NIAID \\
& & & NCT02716675 & \\
& & & NCT02568215 & \\
& & & Phase II & \\
& & & NCT03208231 & \\
& & & Phase II & \\
& & & NCT03036709 & \\
& & & Phase I & \\
& & & NCT02591420 & \\
& & & & \\
3BNC117 + Romidepsin & Therapy & HIV-infected adults treatment interruption, HIV patients starting ART & NCT02850016 & Rockefeller University, University of Aarhus \\
& & & NCT03041012 & \\
3BNC117 + Albuvirtide & Therapy & HIV-infected viremic & Phase II & Frontier Biotechnologies \\
& & & NCT03719664 & \\
3BNC117, 10-1074 + Lefitolimod & Therapy & HIV-infected individuals on ART and during analytic treatment interruption (ATI) & Phase II & University of Aarhus \\
& & & NCT03837756 & \\
3BNC117, 10-1074 + Peg-Interferon Alpha 2b & Therapy & HIV-infected individuals on ART and during ATI & Phase I & University of Pennsylvania \\
& & & NCT03588715 & \\
3BNC117, 10-1074 & Therapy and prevention & HIV-infected viremic +/- ART & Phase I & NIAID \\
& & & NCT03571204 & \\
& & & NCT03526848 & \\
VRC01, 10-1074 & Therapy & HIV-infected adults treatment interruption & Phase I & NIAID \\
& & & NCT03831945 & \\
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\caption{HIV bnAbs for therapy and prevention}
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**HIV bnAbs for therapy and prevention (continued)**

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<thead>
<tr>
<th>Antibodies</th>
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<td>10E8VLS, VRC07-523LS</td>
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<td>HIV-uninfected</td>
<td>Suspended phase I due to adverse effects NCT03565315</td>
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<td>SAR441236 (VRC01–10E8v4-PGDM-1400-LS)</td>
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HIV bnAbs for therapy and prevention (continued)

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References