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[1].

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[2]. 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[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, VRCO1-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[4]; however, VRCO1-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 *in vitro* potency of neutralisation and the dose required to afford protection against viral infection in monkeys[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.

HIV bnAbs for therapy and prevention

Intervention	Purpose	Study population	Status/trial NCT no.	Organisation
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 IIb NCT02716675 NCT02568215 Phase I/II NCT03208231 Phase II NCT03036709 Phase I NCT02591420	NIAID
3BNC117 + Romidepsin	Therapy	HIV-infected adults treatment interruption, HIV patients starting ART	NCT02850016 NCT03041012	Rockefeller University, University of Aarhus
3BNC117 + Albuvirtide	Therapy	HIV-infected viremic	Phase II NCT03719664	Frontier Biotechnologies
3BNC117, 10-1074 + Lefitolimod	Therapy	HIV-infected individuals on ART and during analytic treatment interruption (ATI)	Phase II NCT03837756	University of Aarhus
3BNC117, 10-1074 + Peg-Interferon Alpha 2b	Therapy	HIV-infected individuals on ART and during ATI	Phase I NCT03588715	University of Pennsylvania
3BNC117, 10-1074	Therapy and prevention	HIV-infected viremic +/- ART	Phase I NCT03571204 Phase I NCT03526848	NIAID
VRC01, 10-1074	Therapy	HIV-infected adults treatment interruption	Phase I NCT03831945	NIAID

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HIV bnAbs for therapy and prevention (continued)

Antibodies	Purpose	Study population	Status/trial NCT no.	Organisation
PGT121, PGDM1400, 10-1074, VRC07-523LS	Prevention	HIV-uninfected	Planned phase I NCT03928821	NIAID
VRC01, VRC01LS, VRC07-523LS	Prevention in exposed infants	HIV-exposed infants	Phase I NCT02256631	NIAID
VRC01LS and VRC07-523LS	Therapy and prevention	HIV-infected viremic, HIV uninfected	Phase I NCT02840474	NIAID
10E8VLS, VRC07-523LS	Prevention	HIV-uninfected	Suspended phase I due to adverse effects NCT03565315	NIAID
VRC07-523LS	Therapy and prevention	HIV-uninfected	Phase I NCT03735849 NCT03387150 NCT03803605 Phase II NCT03739996	NIAID ViiV
N6LS	Therapy and prevention	HIV-uninfected	Phase I NCT03538626	NIAID
AAV8-VRC07	Therapy	HIV-infected viremic	Phase I NCT03374202	NIAID
CAP256-LS	Therapy and prevention	HIV-uninfected and HIV-infected	Phase I planned	CAPRISA
VRC07-523LS, PGT121	Prevention	HIV-uninfected	Phase I PACTR20180891929-7244	CAPRISA
10-1074-LS, 3BNC117-LS	Therapy and prevention	HIV-uninfected and HIV-infected individuals on ART.	Phase I/II NCT03554408 NCT04250636 NCT04173819	Rockefeller University
3BNC117-LS	Therapy and prevention	HIV-infected on or off ART and HIV-uninfected individuals	Phase I NCT03254277	Rockefeller University
PGT121 + VRC07-523LS, PGT121 + VRC07-523LS + PGDM1400	Therapy and prevention	HIV-infected volunteers on ART, HIV-uninfected	Phase I/II ongoing NCT03721510	IAVI, VRC, NIH
PGDM1400, PGDM1400 + PGT121	Therapy and prevention	HIV-infected off ART, HIV-uninfected	Phase I NCT03205917	IAVI, Ragon Institute of MGH, MIT and Harvard
PGT121	Therapy and prevention	HIV-infected off ART, HIV-uninfected	Phase I NCT02960581	IAVI, Ragon Institute of MGH, MIT and Harvard
SAR441236 (VRC01–10E8v4-PDGM-1400-LS)	Therapy and prevention	HIV-infected viremic	Phase I NCT03705169	Sanofi

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HIV bnAbs for therapy and prevention (continued)

Antibodies	Purpose	Study population	Status/trial NCT no.	Organisation
iMab/10e8v2.0	Therapy and prevention	HIV-infected viremic, HIV-uninfected	Phase I NCT03875209	Aaron Diamond AIDS Research Center
PGT121.414.LS, VRC07-523LS	Prevention	HIV-uninfected	Phase I NCT04212091	NIAID

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SUPPLEMENT TO THE REPORT

Expanding access to monoclonal antibody-based products: A global call to action

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