Preventive and therapeutic features of broadly neutralising monoclonal antibodies against HIV-1

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The viral plasticity and the vast diversity of HIV-1 circulating strains necessitates the identification of new approaches to control this global pandemic. New generation broadly neutralising monoclonal antibodies (bnMAbs) against the HIV-1 viral envelope protein (Env) can prevent virus acquisition, reduce viraemia, enhance immunity, and induce the killing of infected cells in animal models of HIV-1 infection. Most importantly, passively administered bnMAbs are effective at decreasing viraemia and delaying viral rebound in people chronically infected with HIV-1. Single antibody treatment is associated with the emergence of viral escape mutants, and virus suppression is not maintained in the long term. However, a combination of bnMAbs and bioengineered multivalent antibodies that target different sites on Env might increase the efficacy of immunotherapy, adding a new relevant tool for clinical use. The aim of this Review is to highlight the potential benefits of this novel prophylactic and therapeutic approach to fight HIV-1.

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Introduction

In the absence of an effective vaccine against the vast diversity of HIV-1 strains, antiretroviral therapy (ART) has arisen as the most effective therapeutic and prophylactic approach against the infection. By targeting HIV-1 gene products, ART terminates the virus infection cycle. When used by people infected with HIV-1, ART reduces plasma and genital viral load to undetectable amounts, thereby preventing mother-to-child transmission and horizontal transmission of HIV-1.[1–4] Moreover, ART-sustained viral suppression is associated with an improvement in immunity and clinical wellbeing, and a reduction in mortality resulting from opportunistic infections and cancer.[5–7] Additionally, when used consistently as pre-exposure prophylaxis, ART can reduce the risk of transmission to people who are not infected but are at high risk of acquiring infection.[8] Although increased ART coverage has led to a global reduction in AIDS-related deaths, ART does not eliminate the virus from individuals who are already infected and lifelong treatment is required. Consequently, several challenges are associated with ART, such as incomplete immune restoration due to persistent inflammation, low adherence, emergence of resistant viral variants, and short-term and long-term toxicities.[9,10] Experts in the field are in general agreement that new approaches for preventing and treating HIV-1 infection are needed to control the epidemic. In this regard, HIV-specific broadly neutralising monoclonal antibodies (bnMAbs) could contribute to preventing and controlling HIV-1 infection via different antiviral mechanisms (ie, the neutralisation of free viral particles and Fc-mediated effector functions).

HIV-1 has developed some of the most effective immune evasion mechanisms described to date, including viral transcription shutdown, immune dysregulation, viral escape, conformational complexity, and the reduced display of functional viral envelope protein (Env). However, a small subset of individuals with HIV-1 (about 1%), known as elite neutralisers, develop bnMAbs that neutralise more than 80% of circulating HIV-1 strains with remarkable potency.[11–13] In the past decade, the development of novel technologies (ie, high-throughput neutralisation assays, epitope-specific memory B-cell sorting, high-throughput microculture methods, and highly sensitive recovery of antibody heavy-chain and light-chain sequences, among others) has allowed the isolation of several bnMAbs with different Env specificities from these individuals.[14–23] Of note, as viral escape has been well documented during natural infection even in elite neutralisers, these individuals do not have any clinical benefits from their endogenous neutralising antibodies[24] (table).

Antiviral activity

Killing of HIV-1-infected cells

The mechanisms that contribute to protection and control of viraemia by bnMAbs are not limited to neutralisation of free virions, but also by Fc-mediated effector functions. In this regard, neutralisation can prevent viral infection in the first place, and the rapid clearance of free virus or virus-infected cells can interfere with the establishment of the viral reservoir. Towards this goal, bnMAbs can engage the Fc receptor present on the surface of innate effector cells (such as natural killer cells and phagocytes, among others) to stimulate antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, and antibody-dependent cellular viral inhibition. Additionally, bnMAbs can induce complement-dependent cytotoxicity through their Fc domain. Several studies done in non-human primates and humanised mouse models reported the contribution of Fc-mediated effector functions in controlling viraemia.[49,50] In individuals with HIV-1, HIV-1-specific ADCC antibodies are associated with lower viral loads, higher CD4-cell counts, and improved clinical outcomes.[51,52] Bruel and colleagues[53] reported the elimination of target cells (Gag positive) in the presence of bnMAbs and natural killer cells as a readout of ADCC. They also observed that Fc receptor stimulation and cell killing was not induced equally by all bnMAbs tested.[53]

Of note, some studies in non-human primates have shown that passive infusion of bnMAbs (administered

either pre-exposure or postexposure) can effectively interfere with the establishment of the viral reservoir. In the first of these studies, Hessell and colleagues[54] showed that a combination of PGT121 and VRC07 bnMAbs administered 24 h postchallenge was effective in clearing chimeric simian-HIV (SHIV) infection in only 2 weeks. At treatment initiation, viral RNA and proviral DNA were found in several tissues far from the site of viral entry, indicating a very rapid viral spread. Remarkably, passively administered bnMAbs cleared viruses that had already disseminated throughout the body, interfering with the establishment of the viral reservoir. Because specific CD8-cell responses were not detected, the authors hypothesised that antibodies could have mediated the clearance of free virus and infected cells.[54] This clearance could have occurred via innate immune effector cells (eg, natural killer cells and phagocytes, among others). When the same bnMAb combination was given 10 days after infection, it did not clear the virus reservoir, suggesting that the therapeutic window to impede the establishment of the viral reservoir might be very short.[55] In a subsequent study, Liu and colleagues[56] reported that pre-exposure administration of PGT121 interfered with the reservoir establishment by inducing the killing of infected cells through Fc engagement in peripheral tissues far from the viral entry site.

Supporting the potential of bnMAbs to kill HIV-1 infected cells, Lu and colleagues[57] used a mathematical model to show that the administration of 3BNC117 antibody in individuals chronically infected with HIV-1 not only accelerated the clearance of free virus particles but also directed the clearance of persistently infected cells.[57] Then, they used a humanised mouse model of HIV-1 to show that the elimination of HIV-1-infected CD4 cells by 3BNC117 was dependent on a mechanism that involved Fc receptor engagement.[57] Besides preventing viral acquisition by killing HIV-1-infected cells, bnMAbs might be more successful in suppressing viraemia during chronic infection and have the potential to induce viral eradication.

	Potency (μg per mL)*	Breadth (%)†
gp120		
CD4 binding site		
b12‡[25]	1·8;[17] 2·82[23]	17%[17]; 10%[16,23]
VRC01 (01-03)[17]	0·33;[17,23] 0·22;[26] 0·3;[21] 0·9[15]	72%[17]; 74%[23]; 77%[26]; 75%[21]
VRC07[26]	0·11;[26] 0·16[27]	83%[26,27]
3BNC117 (55,60,117)[15]	0·134;[27] 0·11[21]	79%[27]; 77%[21]
NIH45-46[15]	0·2;[21] 0·41[15]	76%[21]
G54W	0·04[28]	NC
12A12[15]	NC	NC
VRCPG04[29,30]	0·196;[29] 0·2[23]	64%[29]; 65%[23]
VRC-CH31 (30-34)[29]	0·098[29]	70%[29]
HJ16[31]	ND	ND
N6	0·038[14]	96%[14]
V3 loop		
447-52D‡[32]	NC	NC
HGN194[31]	NC	NC
V1 or V2-glycan site		
PG9[16]	0·23;[16,23] 0·142;[27] 0·2[21]	57%[16]; 54%[23]; 73%[27]; 65%[21]
PG16[16]	0·15;[16] 0·15[21]	51%[16]; 59%[21]
CH01-04[33]	NC	40%[33]
PGT145 (141-145)[23]	0·2[23]	52%[23]
CAP256-VRC26.25[34]	0·001	60%[34]
PGDM1400[35]	0·003	83%[35]
V3-glycan supersite (conformational epitope linked to Asn332)		
2G12‡[36,37]	2·38[16,23]	11%[23]
PGT121 (121-123)[23,38,39]	0·03[23]	57%[23]
PGT128 (125-128)[23,40]	0·02;[23] 0·096[27]	60%[23]; 56%[27]
10-1074[22,23]	0·4[27]	54%[27]
PGT130-131[23]	0·16-0·52[23]	ND
PGT133-134[23]	ND	ND
PGT135 (135-137)[23,41]	0·17[23]	23%[23]
gp41		
gp41 membrane-proximal external region		
4E10‡[42]	3·41;[16,23] 1·93[21]	13%[23]; 37%[21]
2F5‡[43]	2·30;[16] 14·6[21]	19%[16]; 16%[21]
Z13[44]	ND	ND
10E8[21]	0·389;[27] 0·35[21]	74%[27]; 72%[21]
HK20[31]	ND	ND

(Table continues on next page)

Boosting of endogenous immune response

In addition to the previously outlined functions, bnMAbs can bind HIV-1 antigens to form immune complexes that could enhance antigen presentation and boost endogenous immune responses. Using a highly pathogenic model of HIV-1 in newborn macaques, those working in the Nancy Haigwood lab found that non-sterilising concentrations of anti-SHIV-neutralising IgG, administered before oral challenge, reduced viraemia and boosted the development of endogenous neutralising antibodies.[58,59] Of note, enhanced endogenous neutralising antibodies controlled viraemia in the long term, allowing all infected animals to survive.[58] Supporting these results, Schoofs and colleagues,[60] reported that immunotherapy with 3BNC117 bnMAb in individuals with HIV-1 enhanced host humoral immunity to HIV-1 in 14 of 15 patients. Purified IgG from these individuals showed enhanced heterologous neutralisation by week 24. In 2017, Nishimura and co-workers[61] reported CD8-cell-mediated long-term control of viraemia in macaques given a single 2-week course of a combination of 3BNC117 and 10-1074 bnMAbs 3 days after SHIV infection. The enhancement of both humoral and cellular adaptive immunity by bnMAbs could be explained by three independent but related mechanisms: bnMAbs modulate virus replication preventing adaptive immunity dysregulation, bind antigens into immune complexes increasing B-cell and T-cell activation, and exert neutralisation pressure on Env, driving viral diversity and increasing intra-host viral variability, an essential process for broadening neutralising antibody

response.[62] Altogether, these observations highlight that bnMAbs are promising therapeutics regardless of whether neutralisation or effector function, or a combination of both, are the keys to their protective mechanism (figure).

Prophylactic and therapeutic effects in animal models

The potential role of bnMAbs in preventing HIV-1 infection has been investigated in different animal models. When administered before viral exposure, bnMAbs were effective in blocking SHIV infection in non-human primates and HIV-1 infection in humanised mice.[26,63–67] The level of protection for each bnMAb was associated with antibody half-life and the in-vitro neutralisation potency of each specific bnMAb against the challenging virus. Using a low-dose iterative mucosal challenge in non-human primates, Gautam and colleagues[68] showed that a single dose of an extended half-life version of VRC01 (VRC01-LS) prevented SHIV acquisition for up to 23 weeks. Together, these studies highlighted that bnMAbs provided long-lasting and robust protection in animal models at amounts that can be achieved by intermittent passive immunisation in humans.

In another series of preclinical studies investigating the therapeutic effect of bnMAbs in animal models, it was shown that a single dose of bnMAb combination could suppress HIV-1 in humanised mice and SHIV-chronic viraemia in non-human primates.[69–71] These studies emphasised that low baseline viral load, high viral neutralisation sensitivity, and the combination of bnMAbs with different Env specificities were associated with longer suppression of virus replication. Compared with single bnMAb therapy, bnMAb cocktails avoided the selection of resistant viral variants, as observed by single genome amplification on rebound viruses, suggesting that the co-administration of bnMAbs targeting different HIV-1-Env determinants might be necessary to avoid emergence of resistant viral variants and consequently, augment treatment efficacy.[69,71] The infusion of PGT121 in one of these studies resulted not only in a rapid and profound suppression of plasma viral RNA but also substantial reduction of proviral DNA in peripheral tissues, suggesting that some mAbs might be able to affect the viral reservoir.[69]

Clinical trials

Therapeutic effects

The positive outcomes of several preclinical trials prompted the testing of HIV-1 bnMAbs in humans. Since 2015, at least six clinical trials with bnMAbs have been completed and the results published.[72–78] In the first series of studies, the safety, pharmacokinetics, and efficacy of two prototypic antibodies that target the CD4 binding site (VRC01 and 3BNC117) were assessed. In general, both antibodies were well tolerated in healthy volunteers and individuals with HIV-1, and showed similar pharmacokinetics to other IgGs (with an average half-life of 15 days). Moreover, infused antibodies retained functional activity (neutralisation, ADCC, and antibody-dependent cellular phagocytosis) and no anti-MAb response was detected after repeated immunisations.

	Potency (μg per mL)*	Breadth (%)†
(Continued from previous page)		
gp41-gp120 Interface		
N-linked glycans adjacent to CD4 binding site and gp41		
8ANC195[15,45]	ND	ND
Quaternary structure of pre-fused gp41		
35O22[20]	ND	ND
Quaternary structure of pre-fused and cleaved gp41		
PGT151 (151-158)[19,46]	ND	ND
Fusion peptide (gp41) and glycan at Asn88 (gp120)		
N123-VRC34.01[18]	ND	ND
Quaternary structure of pre-fused gp41 and a glycan at Asn88 (gp120)		
3BC176, 3BC315[47,48]	1·69–10·00[47,48]	ND

ND=no data is available. NC=data available cannot be compared. *Median in-vitro half maximal inhibitory concentration (μg per mL); results were obtained from TZM-bl neutralisation assay. †Percentage of virus neutralised in vitro with a half maximal inhibitory concentration <1 μg per mL; results were obtained from TZM-bl neutralisation assay; panels of 100 to 200 pseudoviruses, representative of all HIV-1 clades were used to measure potency and breadth. ‡First generation broadly neutralising monoclonal antibodies.

Table: **HIV-1-specific broadly neutralising monoclonal antibodies categorised by envelope protein subunit**

Additionally, Lynch and colleagues[75] tested the infusion of VRC01 in eight individuals with HIV-1 subtype B with detectable viraemia. A single intravenous administration of VRC01 (40 mg/kg) led to a reduction of 1·1 to 1·8 $\log_{10}$ in plasma viraemia in six of eight participants. In two of these individuals, viral rebound occurred as VRC01 concentration decreased whereas, in the remaining four individuals, VRC01 selected for neutralisation resistant viruses. Of note, VRC01 treatment did not reduce viraemia in two participants with pre-existing viral strains resistant to this antibody.

Two subsequent trials (National Institutes of Health, 15-I-0140 [NCT02463227] and AIDS Clinical Trials Group, A5340 [NCT02471326]),[72] tested the ability of VRC01 infusion in the delay of virus rebound in patients with chronic HIV-1 infection who were undergoing analytic treatment interruption.[72] None of the participants were prescreened for VRC01 sensitive viruses. The median time to rebound was 4·0 weeks in the AIDS Clinical Trials Group trial (n=13, up to three infusions of 40 mg/kg of VRCO1) and 5·6 weeks in the National Institutes of Health trial (n=10, six infusions of 40 mg/kg of VRCO1), showing an association between rebound time and the antibody dosing protocol. Although statistically significant viral suppression was observed in participants from both studies (compared with historical controls), VRC01 treatment did not maintain viral suppression by week 8 and in most cases, viral rebound occurred despite high plasma concentrations of the antibody (50 μg/mL). Sequence based and neutralisation analyses done in these individuals suggested that VRC01 selected for

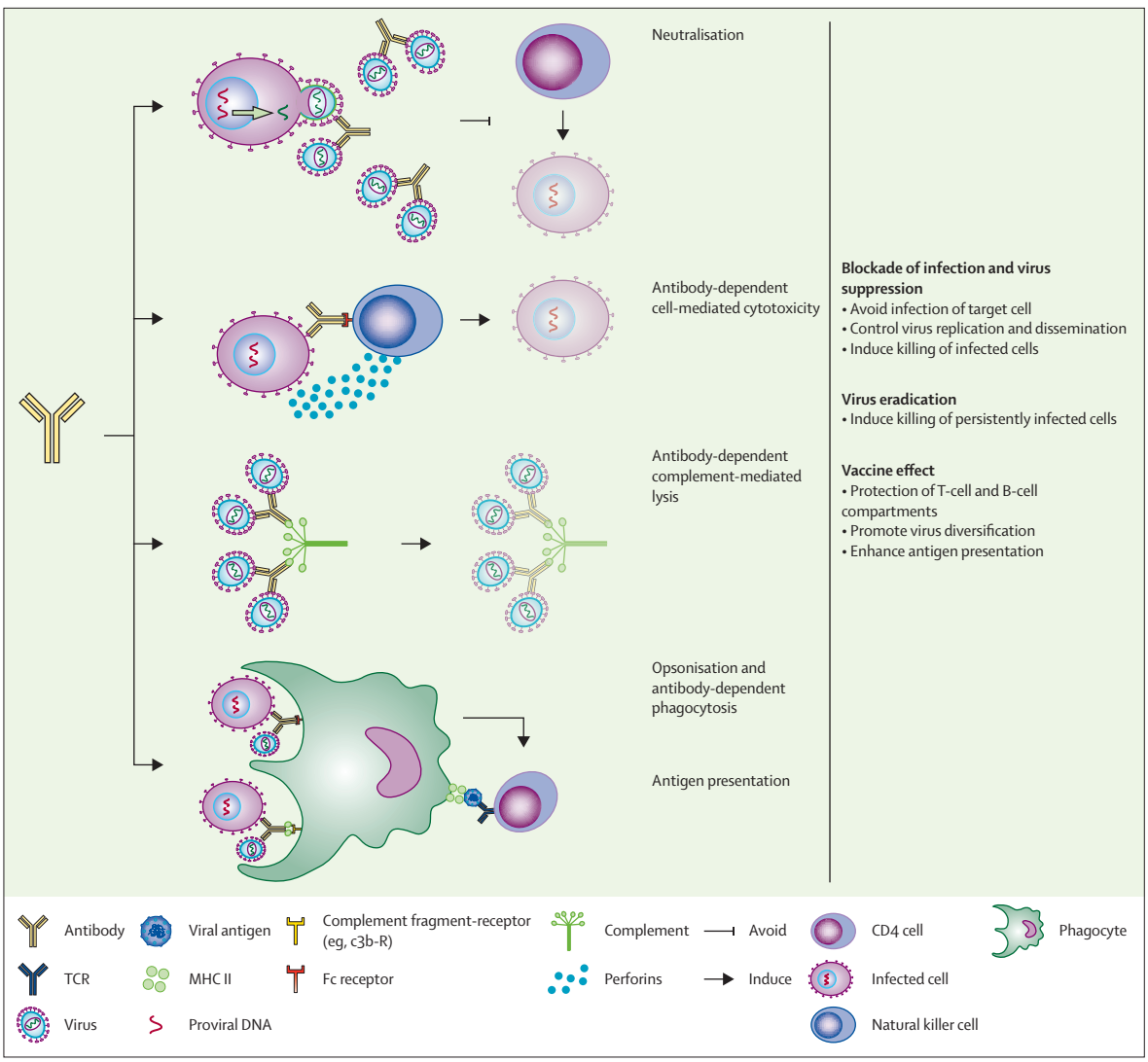

Figure: **Antibody mechanisms of action against viral infection**
Phagocytes include dendritic cells or macrophages. TCR=T-cell receptor.

pre-existing resistance and drove the emergence of VRC01 resistant virus.

In another series of studies, Caskey and colleagues[73] intravenously infused 3BNC117 antibody into 17 participants with HIV-1 who were untreated and viraemic with a dose range between 1 mg/kg and 30 mg/kg of antibody. A single infusion of 3BNC117 effectively reduced viraemia by 0·8–2·5 $\log_{10}$ in eight participants receiving the highest dose (30 mg/kg) of antibody and the reduction of viraemia remained statistically significant for an average of 28 days; by 56 days, three of eight individuals had not yet fully returned to baseline viral load. The authors observed the emergence of resistant viral strains in some individuals. However, in a subset of individuals rebound occurred only after 3BNC117 plasma concentration decreased.

A second study (phase 2a) with 3BNC117 assessed people with HIV-1 during analytic treatment interruption.[76] For this study, investigators enrolled participants with only 3BNC117 sensitive virus in their latent reservoir. From 63 individuals tested, 65% were sensitive to 3BNC117 (half maximal inhibitory concentration 2 µg per mL). 13 participants (<50 copies per mL for over 1 year) with neutralisation sensitive viruses received two or four intravenous infusions of 30 mg/kg of 3BNC117; ART was discontinued 2 days after the first infusion of antibody. The trial showed that 3BNC117 delayed HIV-1 rebound for an average of 6·7 weeks (two infusions) and 9·9 weeks (four infusions), and this result was statistically significantly different from matched historical controls (2·6 weeks). The authors noted that rebounding viruses were very closely related, consistent with the clonal expansion of a single recrudescent virus. In most cases, rebounding viruses showed increased resistance to 3BNC117, indicating strong selection pressure by this

antibody and escape by the recrudescent virus. In four (30%) individuals, suppression continued until the antibody concentrations decreased and emerging viruses showed no increase in resistance.

Overall, VRC01 and 3BNC117 (anti-CD4 binding site) antibodies have been shown to have antiviral activity when administered to people with HIV-1. However, viral rebound occurred without exception, even when there were high concentrations of antibody in plasma. Of note, these antibodies selected for the emergence of neutralisation resistant viruses, indicating a strong selection pressure by the antibody on the viral population present in the viral reservoir. The greater effectiveness of 3BNC117 compared with VRC01 might be a result of the greater neutralisation potency of 3BNC117. Alternatively, the prescreening of participants in the 3BNC117 trials for 3BNC117 sensitive viruses (participants were not prescreened in the VRC01 trials) might have influenced the frequency of pre-existing resistant variants within the viral reservoir, and consequently the efficacy of treatment.

To expand the arsenal of bnMAbs to fight HIV-1, Caskey and colleagues[77] tested the efficacy of 10-1074, a potent antibody that targets the V3 glycan supersite on Env. A single intravenous infusion of the antibody (30 mg/kg) was well tolerated and significantly reduced viraemia by a mean of 1·52 $\log_{10}$ copies per mL in 11 patients infected with neutralisation sensitive viral variants. However, as was seen with anti-CD4 binding site antibodies, viraemia returned to baseline amounts 1 month after infusion. At rebound, sequence and neutralisation analysis revealed rapid emergence of multiple independent 10-1074 resistant viruses. The simultaneous emergence of resistant variants could be explained by a single mutation at the nucleotide level, which is sufficient to drive viral escape from this antibody. Rebounding viruses were also resistant to PGT121 (which targets the V3 glycan supersite on Env), but remained sensitive to antibodies targeting non-overlapping epitopes, as is the case for VRC01 and 3BNC117. The finding that 10-1074 is safe, has a good pharmacokinetic profile, and is effective in decreasing viraemia extends previous observations to a novel non-overlapping target of vulnerability on Env.

Together, these clinical trials indicate that bnMAbs are safe and well tolerated. Furthermore, like preclinical studies in non-human primates, the infusion of heterologous bnMAbs during chronic infection can exert substantial effects on the virus (ie, reduction of plasma RNA concentrations and delayed viral rebound). Importantly, baseline viral load and sensitivity to the antibody can affect the degree to which an infused antibody reduces viraemia. In this regard, prescreening of participants for antibody sensitivity led to improved viraemia control. Additionally, these clinical trials have shown that virus selection and emergence of resistant viral variants occurs in single bnMAb therapy, emphasising the need for combinations of bnMAbs directed to different HIV-1-Env antigenic determinants in the future. It is probable that besides antibody pharmacokinetics, potency and breadth, for optimised treatment regimens clinicians will have to consider baseline viral load and neutralisation sensitivity of variants present in the patient's viral reservoir.

Ongoing clinical trials

Ongoing clinical trials will address the potential of the combination of bnMAbs targeting different Env epitopes in controlling viraemia. A series of clinical trials sponsored by the Rockefeller University (New York, NY, USA) is recruiting individuals with HIV-1 and healthy individuals to assess the co-administration of 3BNC117 and 10-1074 bnMAbs alone or in combination with ART (NCT02884536, NCT02825797, and NCT03526848). Additionally, two large-scale phase 2b clinical trials have been initiated to test the efficacy of VRC01 in preventing HIV-1 acquisition in high-risk populations.[79] These two trials are the first to test in humans whether bnMAbs can prevent HIV-1 infection. Both trials, sponsored by the HIV Prevention Trials Network and the HIV Vaccine Trials Network, are enrolling 4200 adults from several countries, including USA, Peru, Brazil, and Switzerland among others in sub-Saharan Africa. Protective efficacy in these trials will be assessed by comparing the number of breakthrough HIV-1 infections in the VRC01 groups with a placebo group. If effective, the trials will also help to define protective antibody titres and other correlates of protection. In this regard, the results could help to define target neutralisation amounts to be induced by experimental HIV-1 vaccines. Results from both trials are expected by 2020. Other clinical trials for VRC01 also include testing the efficacy of this antibody in children exposed to HIV-1 and the combination of VRC01 with ART to prevent mother-to-child transmission of HIV-1. A preliminary report from these trials has noted that VRC01 was well tolerated and showed good pharmacokinetics in children exposed to HIV-1.[80]

For **HIV Prevention Trials Network** see https://www.hptn.org/

For the **HIV Vaccine Trials Network** see https://www.hvtn.org/en.html

Potency, evasion, and resistance

Newly isolated bnMAbs show great promise; however, the vast diversity of HIV-1 circulating strains and the extreme plasticity of this virus demand constant and continuous improvements to increase the efficacy of immunotherapy and bnMAb-based prophylaxis. Since 2014, the identification of different bnMAbs such as N6, PGDM1400, and CAP256-VRC26.25, which are ten-times more potent than any other bnMAbs and account for an extended neutralisation breadth, might increase the efficacy of bnMAbs.[14,34,35] However, to date, no single bnMAb capable of neutralising all circulating viral strains has been identified, and for that reason, a combination of bnMAbs targeting distinct Env epitopes will be necessary to achieve effective protection in individuals without HIV-1 and sustained virus suppression without the emergence of resistant viral variants in individuals with HIV-1.

Different groups have done in-vitro studies to establish the optimal combination of bnMAbs for prevention and treatment of HIV-1.[27,81,82] Antibody combinations showed substantially improved neutralisation breadth compared with single bnMAbs.[81] The most promising bnMAb combinations were identified based not only on breadth and potency of neutralisation but also the extent of complete neutralisation and instantaneous inhibitory potential.[81] Overall, triple and quadruple combinations of bnMAbs were statistically significantly more effective than the best double combinations (98–100% for triple and quadruple *vs* 89–98% for double breadth). Additionally, bnMAb combinations further improved the probability of having multiple bnMAbs simultaneously active against a given virus, a requirement that could be essential for countering escape in vivo.[81]

As an alternative to bnMAb combination, engineered bivalent and trivalent antibodies targeting several independent antigenic determinants on HIV-1-Env have been developed. Initially, Bournazos and colleagues[83] combined 3BNC117 fragment antigen-binding (Fab) with either PGT135 or 10-1074 Fab, in two bispecific antibodies. While preserving normal architecture and pharmacokinetics of a regular IgG, these multivalent antibodies exhibited greater potency and breadth than any other single bnMAb described to date. More recently in 2017, Xu and colleagues[84] developed a series of tri-specific antibodies. One of these antibodies directed to the CD4 binding site (N6 Fab), MPER (10E8v4 Fab), and V1V2 glycan site (PGDM1400 Fab) had an impressive in-vitro performance. Most importantly, it conferred sterilising immunity against a mixture of SHIVs in a non-human primate model. Another set of bispecific antibodies was developed to link the Fab regions of 3BNC117 or 10E8v2 with a particular cell surface receptor (CCR5 or CD4). Huang and colleagues[85] were able to augment the antibody potency by anchoring it to either CD4 or CCR5 expressing cells.

Other challenges to clinical use

Apart from development of neutralisation resistance, other limitations to the clinical use of bnMAbs exist: production cost of bnMAbs is high compared with antiretroviral drugs; intravenous and frequent delivery might not be feasible on a population level; compartmentalisation and bio-distribution of bnMAbs, resistance of a well established and latent viral reservoir, and potential development of an immune response to bnMAbs used represent additional challenges that must be considered. These challenges prompted the rational design of different bioengineered bnMAbs with greater potency, enhanced Fc function, and extended half-life, as is the case of NIH45-46 derived NIH45-46^{Gly54Trp}, as well as VRC01-derived VRC07 and VRC01-LS.[26,28,86,87] In the case of VRC01, this antibody has an in-vivo half-life of 15 days. However, particular point-mutations (Met428Leu and Asn434Ser)[88] introduced into the Fc region of the VRC01-LS molecule increased binding to the neonatal Fc receptor, leading to a two-times to three-times higher in-vivo half-life and extended protection in macaques.[68] As antibody distribution to mucosal tissue is actively modulated by the neonatal Fc receptor, the Met428Leu and Asn434Ser point mutations also increased the persistence of antibody in the mucosal compartment leading to improved protection against mucosal SHIV challenge in macaques.[86] Results from a 2018 clinical trial with VRC01-LS emphasised that it would be possible to use bnMAbs as passive vaccines, given subcutaneously on a biannual basis to prevent and treat HIV-1 infection.[87] By contrast, the most effective long-lasting drugs might have to be administered once every 2 months for prevention or therapy. Apart from extending half-life, antibodies can be engineered to increase affinity to Fcγ receptor expressed on immune cells, enhance antibody-mediated effector functions, and stimulate endogenous immunity.[89,90] Of note, bioengineering can enhance several features of bnMAbs; however, engineering efforts can also result in antibody polyreactivity.[26] Although increased polyreactivity associated with bnMAb improvement might not necessarily be dangerous, it is associated with shortened plasma half-life and represents an indicator for further antibody optimisation.

The prophylactic and therapeutic efficacy of bnMAbs is associated with antibody potency, half-life, and breadth. Novel bioengineered antibodies, such as tri-mAbs, are effective at relatively low-doses and can decrease the risk of selecting neutralisation resistant variants. However, the chances of viral escape in the context of highly potent bnMAb combinations or multivalent bnMAbs, and the viral fitness cost associated with it, remain to be established. Furthermore, bnMAbs can be optimised for extended half-lives and enhanced effector functions (ie, ADCC). If bnMAbs exhibit strong ADCC in addition to broad coverage, such antibodies would be promising not only for pre-exposure and postexposure prophylaxis but also passive immunotherapy for established infection. The killing of infected cells might decrease the viral reservoir. Importantly, all these improvements will provoke a reduction in the required dose and the number of doses per year, leading to a considerable reduction in the treatment cost.

If substantial protection is achieved in the antibody mediated prevention trials, it is probable that bnMAbs will initially contribute to adjunctive therapy with currently available ART (pre-exposure or postexposure prophylaxis) in selected populations that are most at risk of acquiring infection, as might be the case for young women from high-prevalence regions or infants born to women with HIV-1. Although beyond the scope of this Review, the combination of bnMAbs with other therapeutic approaches (ie, ART, immunomodulatory proteins, and latency-reversing agents, among others), are currently being explored in preclinical and clinical settings. These trials will inform us of the potential

contribution of bnMAbs to the reduction of the viral reservoir and a potential functional cure for HIV-1.

As an alternative to passive immunisation, vector-mediated gene transfer has been proposed to secrete effective bnMAbs into circulation. This novel technique known as vectored immunoprophylaxis is based on a specialised adeno-associated virus vector optimised to produce a full-length antibody from muscle tissue. Studies showed that vectored immunoprophylaxis was capable of protecting humanised mice from HIV-1 and non-human primates from SHIV challenge.[91,92] Despite some limitations associated with vectored immunoprophylaxis (eg, pre-existing immunity against the vector, packaging limitation associated with adeno-associated virus, and safety uncertainties), this approach might represent an alternative to passive immunisation with bnMAbs. Two clinical trials are ongoing to test the safety of vectored immunoprophylaxis in a healthy human population (NCT01937455 and NCT03374202); the first of these trials is testing adeno-associated virus-1 expressing PG9 bnMAb and the second trial is testing adeno-associated virus-8 expressing VRC07 bnMAb.

Conclusion

ART roll-out has led to a massive reduction in AIDS-related deaths; however, even after several years of continued viral suppression, viral rebound after treatment interruption is to be expected in all cases, with few exceptions reported so far. The benefit of adding bnMAbs to ART has garnered interest in recent years. bnMAbs might enhance the effects of ART by augmenting antiviral immunity and clearing HIV-1 infected cells. These features of bnMAbs have the potential to control residual sources of viral replication and might lead to a gradual reduction of the viral reservoir. Moreover, the tissue distribution of bnMAbs could complement that of ART, with antibodies clearing persistently infected cells in tissue compartments receiving low levels of ART, as is the case of germinal centers in the lymph nodes. However, no single bnMAb can neutralise all HIV-1 circulating viral variants. Additionally, when single bnMAb treatments are administered to individuals chronically infected with HIV-1, they do not maintain viral suppression in the long term. Similar to what was described during the early days of ART, resistance to antibodies seems to arise from pre-existing variants present in the latent reservoir or de novo mutations, or both, because of HIV-1 plasticity and its high replication rate. A combination of multiple bnMAbs to cover all circulating viral strains will probably be needed to increase the prophylactic and therapeutic benefit of bnMAbs. By reducing the selection for pre-existing and emerging resistant viral variants, novel isolated and bioengineered antibodies with greater potency and breadth and longer half-life than the prototypic antibodies (eg, VRC01 and 3BNC117), will probably increase immunotherapy efficacy and reduce treatment costs. In the past decade, an arsenal of powerful bnMAbs has been identified. The challenge for the research field now is to optimise all available resources and design more effective treatment regimens while vaccine development efforts continue.

Search strategy and selection criteria

We searched PubMed with the search terms "HIV-1", "neutralizing antibodies", "therapy", "prophylaxis", and "antiretroviral therapy" from Jan 1, 2000 to March 31, 2018; only papers published in English were reviewed. The final references were selected based on relevance to the broad scope of this Review.

Contributors

JPJ designed and planned the work, did the literature search and interpretation, and wrote the manuscript. PC contributed to the literature search and analysis, and wrote and revised the manuscript.

Declaration of interests

We declare no competing interests.

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