Use of Broadly Neutralizing Antibodies as an Alternative Treatment for HIV-1, what the Clinical Trials Show: A review.

Uso de anticuerpos neutralizantes de amplio espectro como tratamiento alternativo para VIH-1, lo que los ensayos clínicos muestran: Una revisión

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Abstract

The human immunodeficiency virus (HIV) attacks the body's immune system, specifically CD4+ T-Lymphocytes. The virus gradually takes over the host's immune system, making it more susceptible to opportunistic infections and certain types of cancer. In recent years, the toxicity produced by antiretroviral therapy (ART) has become a problem due to risky adverse effects. Broadly neutralizing antibodies (bNAbs) have been studied as an alternative HIV-1 infection treatment. This article aims to review the state of the art of bNAbs that have entered or will soon enter clinical trials and provide information on their potential as a therapeutic agent against HIV-1 infection.

Key words: HIV-1, Broadly neutralizing antibodies, monoclonal antibodies, clinical trials, therapeutic.

Resumen.

El virus de la inmunodeficiencia humana (VIH) ataca el sistema inmunológico del cuerpo, específicamente los linfocitos T CD4+. El virus infecta gradualmente el sistema inmunológico del huésped, lo que lo hace más susceptible a las infecciones oportunistas y a desarrollar ciertos tipos de cáncer. En los últimos años, la toxicidad producida por la terapia antirretroviral (ART) se ha convertido en un problema debido a sus efectos adversos. Los anticuerpos neutralizantes de amplio espectro (bNAbs) están siendo estudiados como una alternativa para tratar la infección por VIH-1. El presente artículo tiene como objetivo revisar el estado del arte de los bNAbs que han entrado o pronto entrarán en ensayos clínicos y proveer información sobre su potencial como agente terapéutico frente a la infección por VIH-1.

Palabras clave: VIH-1, anticuerpos ampliamente neutralizantes, anticuerpos monoclonales, ensayos clínicos, terapéuticos.

Introduction

Acquired Immunodeficiency Syndrome (AIDS) is caused by the Human Immunodeficiency Virus (HIV) (Bhatti et al., 2016). This pathogen is known for having one of the most successful evasion mechanisms amongst viruses, due to its strain diversity, and its membrane dense sugar shield and conformational flexibility (Jaworski et al., 2017) HIV-1 usually infects CD4+ T-Lymphocytes (CD4+ cells), slowly taking over the host's immune system, allowing opportunistic infections and unusual cancers to arise (Bhatti et al., 2016).

In 2019, more than 38 million people around the world were HIV positive (UNAIDS DATA, 2020). However, the infection can be treated through antiretroviral therapy (ART), which has shown to slow down the progression of the disease, and reduce the risk of transmission (Bhatti et al., 2016).

Even though the use of ART has improved the life expectancy for HIV-1 positive patients, and reduced the number of AIDS related deaths, these have shown adverse effects, such as: nausea, diarrhea, hepatotoxicity, pancreatitis, vision problems, anemia, peripheral neuropathy, blood in the urine, among others (Bhatti et al., 2016; Chwiki et al., 2017).

In recent years, the use of broadly neutralizing antibodies (bNAbs) as a potential therapeutic agent against HIV-1 has been studied (Caskey et al., 2019). The present article aims to identify the state of the art on bNAbs that have entered, or will soon enter clinical trials, and evaluate their effect as a therapeutic agent against HIV infection.

Importance of antibodies as therapeutic molecules

In the late nineteenth century, Emil von Behring and Shibasaburo Kitasato developed and introduced serum treatment, establishing the beginning of antibody-based therapy. The latter consisted in the use of serum, better known as “antisera”, which contained polyclonal antibodies obtained from immunized animals to treat infectious diseases. The passive antibody therapy proved to be a successful antimicrobial agent, which introduced the use of antibodies (Santos et al., 2018).

During the 1940’s, information about antibody diversity, structure and production process was reported. These findings allowed the development of the hybridoma technology, which is based on the production of hybrid cells. These cells were acquired by the fusion of B cells - derived from immunized animals - with myeloma cells (Santos et al., 2018; Chen & Dimitrov, 2009). These techniques produce monospecific cells that secrete monoclonal antibodies (mAbs) capable of stimulating the immune system that had the potential to treat different diseases (Chen & Dimitrov, 2009).

At present, several mAbs have been approved by the FDA to treat multiple types of cancers, including melanoma, lung cancer and carcinomas, as well as multiple sclerosis, hemophilia A, asthma, psoriasis, Crohn's disease and rheumatoid arthritis. Because of their success, these antibodies started being evaluated in clinical trials to prevent, and treat different types of viruses, such as human cytomegalovirus (HCMV), influenza, respiratory syncytial virus (RSV), Ebola virus and rabies (Lu et al., 2020).

Since HIV-1 has been considered one of the most important public health challenges, the search for an effective and safe treatment is crucial. This led to the development of therapeutic antibodies, particularly the bNAbs. The first bNAbs used to treat HIV-1 were identified in the early 1990´s, proving to be far more powerful than any other antibody used before. The first bNAbs to be isolated by phage-display methods in 1991 were b12, leading to the possibility of treating HIV-1 by passive immunization. Since then, the quest for identifying new bNAbs has increased, creating a new hope to treat this infection (Awi & Teow, 2018; Burton et al., 1991).

bNAbs for HIV treatment

Current HIV-1 treatment includes ART to suppress the virus. Although this strategy has greatly reduced the global mortality rate, it can cause various side effects that may affect the patient's quality of life; these can include diarrhea, anemia, constipation, dizziness, insomnia, headache, fatigue, rashes, abdominal pain, emotional and mental

disturbance, nausea, and vomiting. ART can also cause more serious complications such as liver failure, lipodystrophy, and neurological and cardiovascular diseases (Awi & Teow, 2018; Koethe et al., 2020).

Antibody-mediated therapy has shown to possess several advantages over ART in various aspects, such as specificity and safety. bNAbs are a specific type of antibody that have shown promising results for treating HIV-1 because of their ability to bind onto conserved epitopes of the virus (Awi & Teow, 2018). Studies have shown that bNAbs are able to neutralize free viruses, clear infected cells and inhibit cell to cell transmission of HIV-1 (Liu et al., 2020; Sok & Burton, 2018).

bNAbs can be sorted into 2 groups: first- and second-generation antibodies. The difference between these groups lies in the method used to develop them and their functionalities. b12, 2G12, 4E10, and 2F5 were the first-generation bNAbs isolated during the 1990´s (Zhang et al., 2016). These were obtained using both Epstein Barr Virus Immortalized B-cells and phage-display methods. However, these first generation bNAbs had low neutralization efficacy. This led to the development of second generation bNAbs, which are known for having greater breadth and potency (Awi & Teow, 2018).

The second-generation bNAbs were identified until 2009, by using strategies like screening the sera from chronically infected HIV-1 patients containing high affinity and cross-reactive antibodies, implementing new approaches to B-cell selection and sorting, and developing high-throughput strategies for generating human mAbs (Shcherbakov et al., 2015). Second-generation bNAbs such as PG9, CH01, PGT145, PGT121, 10-1074, 10E8, VRC01 and 3BNC117 are currently being evaluated in clinical trials to determine their ability to treat HIV-1 infected patients (Awi & Teow, 2018).

Anti-HIV bNAbs in Clinical Trials

Passive immunization using bNAbs has become a promising approach for preventing, treating, reducing, and potentially eradicating HIV-1 infection (Mahomed et al., 2020). Due to their ability to enhance the host immune response, bNAbs are being greatly pursued and developed. As a result, bNAbs have been studied in clinical trials, in order to obtain an efficient treatment against the infection (Yubin et al., 2020).

A growing number of anti-HIV-1 bNAbs have been acknowledged in current scientific research, providing a potent activity, safety, and efficacy profiles for therapeutic applications in human clinical trials. The neutralizing activity of bNAbs on HIV-1 is achieved by blocking viral entry into the cells. Nevertheless, during an *in-vivo* infection, additional effector functions are likely at play, highlighting the importance of studying different bNAbs in clinical trials. These bNAbs can neutralize HIV-1 by recognizing the six “vulnerable sites” in the envelope glycoprotein gp160, which are: V1V2 apex, V3 glycan, CD4+ binding site (CD4bs), fusion peptide (FP), subunit interface, and membrane proximal external region (MPER) of gp41 (Figure 1) (Zhou et al., 2019).

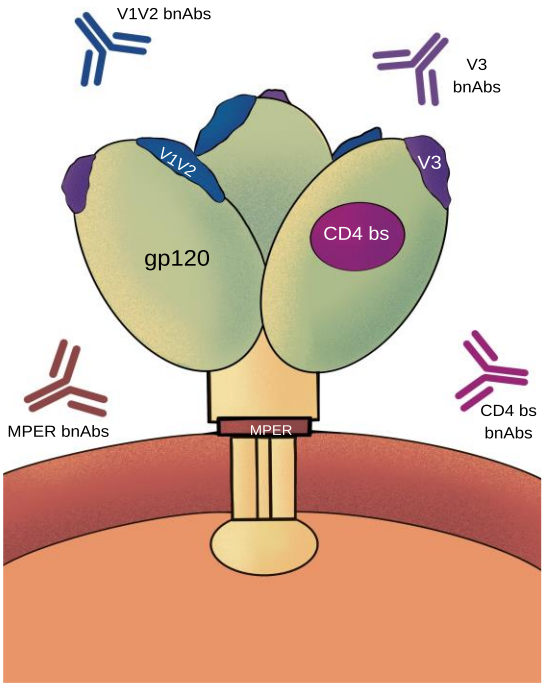

Figure 1. Vulnerable Binding Sites in the HIV-1 Membrane and their bNAbs (Modification of Kelsoe et al., 2012; Stefic et al., 2019)

First-generation bNAbs have shown the ability to neutralize diverse primary strains of HIV- 1, although their breadth and potency

have not been ideal. Clinical trials have shown that during ART interruption, the combination of 2G12, 2F5, and 4E10 neutralizing antibodies can suppress the viremia in HIV-1 infected individuals. However, 2F5 and 4E10 happen to be self-reactive, and variants resistant to 2G12 were observed in most of the patients, causing high titres (Yubin et al., 2020).

Through the development of unicellular antibody cloning techniques and high-throughput neutralization assays, it has been possible to isolate and characterize a new generation of bNAbs with significant breadth. These new generation bNAbs have shown more promising results than the first generation, displaying a 10-to-100-fold increase in potency, as well as new vulnerable sites to the neutralizing antibodies. Besides their tough *in vitro* activity, these agents have demonstrated effects for prevention and therapy *in vivo*. Studies in rhesus macaques have proven protection against both, high-dose viral and repeated low-dose challenges, due to the passive administration of bNAbs (Yubin et al., 2020).

The most promising new generation bNAbs from preclinical studies have progressed into clinical trials where they are currently being evaluated for treatment and prevention of HIV- 1 infection. Recently, antibodies against the V3 loop, such as 10-1074 and PGT121, and antibodies targeting the CD4+ binding site like VRC01, 3BNC117, VRC01-LS and VRC07-523LS, have been reported in humans trials (Yubin et al., 2020).

Methods and Inclusion Criteria

All the information about clinical trials was obtained through the International Clinic Trials Registry Platform Search Portal of the World Health Organization. The search focused on bNAbs that have advanced on the clinical development pipeline, such as: VRC01, 3BNC117, PGDM1400, 10-1074, PGT121, and VRC07-523LS. Completed trials with published data were searched through PubMed. The inclusion criteria consisted of clinical trials studying the effects of bNAbs on HIV-1 positive adults, with the aim of HIV-1 treatment.

CD4bs

The T-cell surface glycoprotein CD4+, is known for being the cellular receptor for HIV-1, which makes it crucial for the virus's entrance into the cell (Fisher et al., 1988). Due to its ability of disrupting the first and most crucial step of HIV-1 infection, CD4bs are one of the most abundant and studied bNAbs. More than twelve CD4bs bNAbs have been isolated, such as VRC01 and 3BNC117, just to name a few (Zhou et al., 2019).

VRC01 has been shown to neutralize approximately 90% of a broad panel of 190 group M HIV envelope viruses (Bar et al., 2016). A clinical study found that among six ART-treated volunteers with undetectable plasma viremia, two infusions of VRC01 did not reduce the peripheral blood cell–associated virus reservoir. In contrast, six out of eight ART-untreated, viremic subjects infused with a single dose of VRC01 experienced a 1.1 to 1.8 $\log^{10}$ reduction in plasma viremia. Results showed that a single infusion of VRC01 significantly decreased plasma viremia and preferentially suppressed neutralization-sensitive virus strains (Lynch et al., 2015).

In another clinical study, volunteers under ART were randomized to receive two infusions of VRC01. The first group involved a VRC01 infusion of 40 mg/kg at entry and week 3, with two infusions of placebo at weeks 6 and 9. Meanwhile, the second group received two infusions of placebo at entry and week 3, with two infusions of VRC01 at weeks 6 and 9. Results showed that VRC01 infusions were safe and well tolerated but did not affect plasma viremia, cellular HIV-1 RNA/DNA levels, or stimulated virus production from CD4+ T cells (Riddler et al., 2018).

On the other hand, in two open-label trials, twenty-four volunteers underwent ART interruption. Results showed that VRC01 slightly delayed plasma viral rebound but did not maintain viral suppression by week 8. Resistance to VRC01 was common in both trials, which might suggest that people with chronic infection may bear resistant virus to VRC01, which might be a considerable challenge (Bar et al., 2016).

Table 1. Number of published and unpublished clinical trials evaluating bNAbs in HIV-1 infected individuals (National Library of Medicine, 2020; EU Clinical Trials Register, 2020).

bNAbs	Target	Number of clinical trials with published results	Identifier of published clinical trials	Number of clinical trials with unpublished results	Identifier of unpublished clinical trials
VRC01	CD4+bs	5	NCT01950325, NCT02411539, NCT02463227, NCT02471326, NCT02664415.	3	NCT03729752, NCT03036709, NCT02591420.
3BNC117	CD4+bs	3	NCT02018510, NCT02446847, NCT02588586.	9	NCT04560569, NCT03719664, NCT03468582, NCT03254277, NCT03063788, NCT03041012, 2015-005238-23, 2015-002234-53, NCT02850016.
10-1074	V3 loop	1	NCT02511990.	1	NCT04340596.
PGT121	V3 loop	0	NA	1	NCT02960581.
3BNC117 and 10-1074	CD4+bs and V3 Loop	1	NCT02825797.	6	NCT03837756, 2018-001165-16, NCT03571204, NCT03554408, NCT03526848,NCT03588715.
3BNC117-LS and 10-1074-LS	CD4+bs and V3 Loop	0	NA	1	NCT04250636
VRC01 and 10-1074	CD4+bs and V3 Loop	0	NA	1	NCT03831945.
VRC07-523LS and PGT121	CD4+bs and V3 Loop	0	NA	1	NCT04144335.
PGT121, VRC07-523LS and PGDM1400	V3 loop, CD4+bs and V3 loop	0	NA	2	NCT03721510, NCT03205917.

In a trial also involving ART interruption, fourteen subjects were randomly assigned to a VRC01 group and five to a placebo group. VCR01 was administered at a dose of 40mg/kg intravenously every 3 weeks for up to 24 weeks. All volunteers underwent ART interruption except for one participant who experienced severe generalized urticaria during the first study infusion and did not complete the infusion. Final results showed that only one participant achieved viral suppression 24 weeks after ART interruption (Crowell et al., 2019). Beside the previously described clinical trials, as of October 28th, 2020, three more studies fit into the inclusion criteria that have yet to publish results (*Table 1*).

On the other hand, another broadly neutralizing HIV-1 antibody directed against the CD4+ binding site is 3BNC117. This bNAb has shown promising results because of its ability to neutralize 195 out of 237 HIV-1 strains. One study by The Rockefeller University reported that a single 30 mg/kg infusion of 3BNC117 reduced the viral load in days. Results showed that some individuals remained sensitive to 3BNC117 for a period of 28 days (Caskey et al., 2015).

An open label study involving 13 volunteers with 3BNC117-sensitive virus outgrowth cultures were studied in the setting of analytical treatment interruption. Results showed that two or four 30mg/kg infusions of 3BNC117, separated by 3 or 2 weeks respectively, were well tolerated. The infusions were associated with a delay in viral rebound for 5-9 weeks after two infusions, and up to 19 weeks after four infusions. 30% of volunteers remained suppressed until antibody concentrations decreased below 20µg/ml. In addition, only one individual showed resistance to 3BCN117 (Scheid et al., 2016).

A different clinical trial evaluated the effects of four infusions of 3BNC117 to prevent or delay viral load rebound during a brief ART interrupting treatment. Volunteers received 30 mg/kg of 3BNC117 on weeks 0, 12, 24, and 27. The circulating reservoir was determined by quantitative and qualitative viral outgrowth assay (Q2VOA) at entry and after 6 months.

Results showed that viruses emerging during interruption of antiretroviral therapy were not the dominant species found in the circulating latent reservoir but were recombinants of latent viruses (Cohen et al., 2018). As of October 28th, 2020, nine more studies fit into the inclusion criteria that have yet to publish results (*Table 1*).

V1/V2 Loop

gp120 is a glycoprotein found on the membrane of HIV, composed by five hypervariable regions (V1-V5). This molecule is indispensable for the virus's entry to the host's cell, and it is usually a target for the immune system (Yao et al., 2015). The first and second variable regions (V1-V2) of gp120 play a vital role in modulating the virus's ability to recognize the host´s cell receptors, as well as binding with the viral protein Tat (Yokoyama et al., 2016; Cardaci et al., 2013). The regions are also common targets for bNAbs like PGDM1400, CAP256 and PG9 (Stephenson & Barouch, 2016; Mahomed et al., 2020; Sok & Burton, 2018).

CAP256 is an bNAb isolated from an HIV-1 infected individual from South Africa and has demonstrated a high potency in neutralizing the viruses' C and A subtypes. On the other hand, PGDM1400 has displayed extraordinary breadth and potency, especially when combined with PGT121 (Stephenson & Barouch, 2016). Although research has been conducted to understand the effect of these V1/V2 dependent bNAbs in animals and healthy humans, there has not been any publications describing their effects on HIV-1 infected individuals (Priddy et al., 2019; van der Velden et al., 2018; Julg et al., 2017). Most clinical trials involving V1/V2 dependent bNAbs evaluate their effect by combining them with other antibodies.

V3 Loop

For HIV-1 to enter a cell, two regions of its glycoprotein gp120 must interact with proteins found in the host cell's surface: the CD4+ binding site, and the chemokine receptor binding site. The interaction between gp120 and the CD4+ receptor will expose the third variable region (V3) of the glycoprotein, allowing it to bind to the chemokine receptors CCR5 and CXCR4. (Tamamis & Floudas, 2014; Zolla-Pazner et al., 2016) Studies have shown that some strains of HIV-1 have developed strategies to infect a cell without binding to CD4+ receptors. However, the virus's binding to the chemokine receptors has proven to be indispensable for its infectivity (Zolla-Pazner et al., 2016).

Because of the V3 loop's importance for the entry to the cell, it is usually a target for antibodies produced by the infected individual (Zolla-Pazner et al., 2016). In recent years, several lineages have been discovered, such as 10-1074, PGT121, and PGT128 (Sok & Burton, 2018).

The 10-1074 is one of the most potent anti-HIV-1 neutralizing antibodies discovered to this day, and different studies are currently investigating its effect on HIV-1 infected individuals (Mendoza et al., 2018; Bar-On et al., 2018). A phase 1 clinical trial determined the safety and activity of 10-1074 in fourteen uninfected and nineteen infected individuals. The human subjects received a single intravenous infusion of the antibody at doses of 3, 10, or 30 mg/kg. The antibody proved to be generally safe and well-tolerated by all participants, and no serious adverse effects were observed during a follow-up period of 168 days. Thirteen of the HIV-1 positive individuals were administered the highest dose of 30 mg/kg; eleven of them showed a quick decline in viremia, by a mean of 1.52 $\log^{10}$ copies/ml (Caskey et al., 2017).

There are currently nineteen clinical trials studying the effects of 10-1074 in HIV-1. However, only one of them falls into the inclusion criteria described in this article. This study is a phase 1 clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) that aims to study the safety, tolerability, and efficacy of IL-15 Superagonist (N-803) with and without the combination of bNAbs to induce HIV-1 control during analytic treatment interruption (*Table 1*). As of October 28th, 2020, this study has not published any results.

PGT121 is a bNAb that was first isolated in 2011 from an African donor that targets the V3 Loop on the HIV-1 envelope. However, studies suggest that this antibody works differently from other V3 specific antibodies, since it inhibits the binding of CD4+ to gp120 (Stephenson & Barouch, 2016). PGT121 has shown successful results in trials

with humanized mice and none-human primates, but no data has been released describing its effect in humans infected with HIV-1 (Stephenson & Barouch, 2016; Mahomed et al., 2020; Sok & Burton, 2018; Kumar et al., 2018).

There are currently eight clinical trials studying PGT121, but only one that fits into the inclusion criteria previously described. This is a phase 1 clinical trial sponsored by International AIDS Vaccine Initiative that will study the safety and antiviral activity of PGT121 in both HIV-uninfected and HIV-infected adults (*Table 1*).

Combination of bNAbs

A combination of bNAbs that target different glycoprotein sites on the HIV envelope have shown promising results and have the potential to be considered as effective therapy and prevention agents. (Yubin et al., 2020) Two of the most combined bNAbs have been the V3 glycan dependent 10-1074 and the CD4+ binding antibody 3BNC117. Their combination has proven to be more successful than either antibody by itself (Bar-On et al., 2018).

One study revealed that the administration of a combination of the two antibodies resulted in the reduction of the viral load in most of its subjects. In this study, seven individuals received a single intravenous infusion of 3BNC117, and 10-1074 at a dose of 30 mg kg−1 per antibody, or three infusions of 30mgkg−1 per antibody every 2 weeks. These administrations were well tolerated by the individuals who received them. The combination of these antibodies also reduced the HIV-1 viral load in four of the individuals to a mean of 2.05 $\log^{10}$ copies per ml. Also, none of the individuals in this study developed resistance to either antibody (Bar-On et al., 2018).

As of October 28th, 2020, there are seven clinical trials that seek to evaluate the effect of combining 3BNC117, and 10-1074 on HIV-1 infected individuals. Furthermore, there are four clinical trials that are currently studying the effects of combining bNAbs that target different glycoprotein sites (*Table 1*).

bNAbs challenges in HIV-1 Therapy

Even though clinical trials have proven that bNAbs have the ability to reduce viremia and suppress the viral load (*Table 2)*, different challenges have emerged with this therapy. Clinical trials have shown that viremia can only be suppressed for a short period of time, mainly because bNAbs have shown an average half-life of 10 days, or even shorter in HIV-1 infected patients. However, increasing the potency and half-life of the bNAbs could result in a longer viremic suppression (Liu et al., 2020).

On the other hand, a complete immunization has not been successful due to the high genetic diversity of the target sites on the HIV-1 envelope glycoproteins, causing resistant strains (Harada & Yoshimura, 2017). Clinical studies have described that subjects with little to no response, carry resistant viruses as their dominant population pre-infusion. Nonetheless, some subjects with relatively sensitive viral variants, have shown viral rebound with resistant viruses post-infusion (Lynch et al., 2015; Liu et al., 2020). This could be the result of pre-existing resistant variants, or the development of mutations by the sensitive variants. Nevertheless, pre-clinical studies administering a cocktail of bNAbs with different target sites have proven to effectively interrupt viremia for two months as well as reducing viral resistance mutations (Liu et al., 2020).

Another complication involving bNAbs therapy involves the virus's ability to infect other cells via cell-to-cell transmission. Although studies have demonstrated that cell-to-cell dissemination is less sensitive to ART, the inhibiting effect of bNAbs is less clear. Studies have implied that the ability of bNAbs to reduce cell-to-cell transmission in HIV-1 varies, depending on their mechanism of action and virus strains (Liu et al., 2020).

As challenging as the last issues may seem, HIV´s main obstacle continues to be its latent reservoir integrated within the host´s cellular DNA. Although the reservoir has proven to be resistant to ART and to the host's immune system, there is some uncertainty about the effects bNAbs could have over it. Additional studies are needed to establish whether bNAbs could effectively target the reservoir (Churchill et., al, 2015 ;Liu et al., 2020).

Table 2. Clinical Trials with published results studying bNAbs to Treat HIV-1 infected individuals.

bNAbs	Target	Identifier	Scientific Title	Participants	Results
VRC01	CD4+bs	NCT01950325	VRC 601: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC HIVMAB060-00-AB (VRC01), With Broad HIV-1 Neutralizing Activity, Administered Intravenously or Subcutaneously to HIV-Infected Adults	27 HIV-1 infected adults, both male and female.	A single dose of VRC01 notably reduced plasma viremia and suppressed neutralization-sensitive virus strains. The infusion was well tolerated and long lasting in subjects on and off ART.Plasma virus load significantly reduced in subjects with circulating VRC01 sensitive strain. Although, it should be noted that VRC01 did not decrease cell associated virus load in subjects receiving ART. All together, viral loads returned to baseline as soon as VRC01 concentrations decreased (Lynch et al., 2015).
VRC01	CD4+bs	NCT02411539	A Phase I Study to Evaluate the Safety, Tolerability, and Effect of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), on Markers of HIV Persistence in ART-treated, HIV-infected Adults	40 HIV-1 infected adults, both male and female.	VRC01 infusions were safe and well tolerated but didn't alter plasma viremia, HIV-1 DNA/RNA levels or prompt virus production from CD4+ cells. It is important to note that two subjects developed grade 2 rash and grade 1 pruritus and three individuals experienced flu-like symptoms after the infusion (Riddler et al., 2018).
VRC01	CD4+bs	NCT02463227	A Phase I, Open-Label Study of the Safety, Pharmacokinetics, and Antiviral Activity of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), With Broad HIV-1 Neutralizing Activity, Administered Intravenously to HIV-Infected Adults Undergoing a Brief Analytical Treatment Interruption	14 HIV-1 infected male adults.	The administration of VRC01 generated high plasma concentrations of the bNAb, and did not show any safety concerns. However, the infusion did not produce a durable suppression of viremia. 12 of the individuals presented viral rebound before 8 weeks, with a medium time viral rebound of 4 weeks. Only one participant showed viral rebound until week 11. Viral resistance was detected, and viral sensitivity toVRC01 decreased significantly post-infusion (Bar et al., 2016)..
VRC01	CD4+bs	NCT02471326	An Exploratory, Open-Label Study of VRC-HIVMAB060-00-AB (VRC01) in Subjects With Chronic HIV Infection Undergoing Analytical Treatment Interruption	10 HIV-1 infected adults, both male and female.	The administration of VRC01 proved to be safe and well tolerated, and generated high plasma concentrations of the bNAb. Nevertheless, the infusion did not produce a durable suppression of viremia. All 10 individuals showed viral rebound, with a medium time at 5.6 weeks. Viral resistance was detected, and viral sensitivity toVRC01 decreased significantly post-infusion (Bar et al., 2016).
VRC01	CD4+bs	NCT02664415	Safety and Therapeutic Efficacy of the Broadly Neutralizing HIV-1 Specific Monoclonal Antibody VRC01 During Analytic Treatment Interruption in Patients Who Initiated Antiretroviral Therapy During Early Acute HIV Infection	23 HIV-1 infected male adults.	VRC01 infusion delayed viral rebound. This bNAb was found safe when administered during ART interruption but did not notably affect the proportion of individuals with viral suppression at 24 weeks after ART interruption. It is important to note that one subject experienced severe generalized urticaria after the first infusion (Crowell et al., 2019).
3BNC117	CD4+bs	NCT02018510	A Phase 1, Open Label, Dose-escalation Study of the Safety, Pharmacokinetics and Antiretroviral Activity of 3BNC117 Monoclonal Antibody in HIV-infected and HIV-uninfected Volunteers	49 HIV-1 infected and uninfected adults, both male and female.	An escalated dose of 3BNC117 up to a 30 mg/kg single infusion was well tolerated and demonstrated a viral load reduction for 28 days, without returning to pre-infusion levels during an observation period of 56 day. However, in some individuals HIV-1 develops higher resistance to this bNAb at 28 days after a single dose, while in others it does not. Also, it's important to mention that 3BNC117 has a higher decay rate in infected individuals than in uninfected individuals (Caskey et al., 2015).
3BNC117	CD4+bs	NCT02446847	A Phase 2, Open Label Study of the Safety, Antiretroviral Activity and Pharmacokinetics of 3BNC117 During a Short Analytical Treatment Interruption in HIV-infected Subjects	13 HIV-1 infected adults, both male and female.	Up to four 30 mg/kg infusions of 3BNC117 during analytical treatment interruption (ATI) proved to be safe and well tolerated. Some mild adverse effects such as rhinorrhea or cough, malaise, headache, diarrhea, myalgia, chills and feverishness (among others) were reported. All group A individuals maintained viral loads below 200 copies/ml, and showed viral rebound 5-9 weeks after ART interruption. Group B individuals showed viral rebound between 3-19 weeks after ATI. A majority of the participants (8/13) presented rebound viruses that were more resistant to 3BNC117. However, four of the participants did not show any change in viral sensitivity for 3BNC117 between pre-and post-infusion (Scheid et al., 2016).
3BNC117	CD4+bs	NCT02588586	An Open Label, Phase 2 Study of the Safety and Antiretroviral Activity of 3BNC117 in HIV-Infected Individuals on Combination Antiretroviral Therapy	15 HIV-1 infected adults, both male and female.	The infusion with 3BNC117 proved to be safe and well tolerated. However 29 adverse effects that were possibly related to 3BNC117, were reported. Although there was one report of a severe case of ecchymosis at the infusion site, most of the effects were mild cases of malaise, headache, diarrhea, chills, nausea, abdominal pain and dizziness (among others). The effects of 3BNC117 on the latent reservoir were examined, but it was concluded that two doses of the bNAb over 23 weeks in ART suppression does not reduce the size of the latent reservoir. Viral rebound was detected between 2-17 weeks after ART interruption, with a mean time of 5.5 weeks. Rebound viruses presented amino acid variants in the 3BNC117 binding site (Cohen et al., 2018).
10-1074	V3 loop	NCT02511990	A Phase 1, Open Label, Dose-escalation Study of the Safety, Pharmacokinetics and Antiretroviral Activity of 10-1074 Monoclonal Antibody in HIV-infected and HIV-uninfected Individuals	33 HIV-1 infected and uninfected adults, both male and female.	A single intravenous infusion of 10-1074 at doses 3, 10, and 30 mg/kg was safe and well tolerated without any adverse event. A half-life of 12.8 and 24 days was reported in infected and uninfected individuals, respectively. Individuals who received the 30 mg / kg dose showed a rapid decrease in HIV-1 RNA levels, especially in 10-1074-sensitive participants. Viremia decrease was significant from day 3 to day 27 post-infusion (Caskey et al., 2017).
3BNC117 + 10-1074	CD4+bs and V3 Loop	NCT02825797	A Phase 1b Study of the Safety, Pharmacokinetics and Antiretroviral Activity of the Combination of 3BNC117 and 10-1074 in HIV-infected Individuals	34 HIV-1 infected adults, both male and female.	Individuals received three infusions of 3BNC117 and 10-1074 (30 mg/kg per antibody) every two weeks, or a single intravenous infusion (30 mg/kg per antibody). Administration of both bNAbs was well tolerated, with no serious adverse events observed. Participants who have received either one or three infusions of the combination of both bNAbs revealed prolonged viral suppression, compared to a single infusion of each bNAb individually. The immunotherapy in four individuals who showed a dual antibody-sensitive virus remained viral load reduced for 3 months after the first infusion (Bar-On et al., 2018).

Lastly, production and distribution costs also pose an obstacle for bNAbs since biological molecules are far more expensive than chemical molecules such as ART. However, because of the exponential advances in science during the last years, new strategies are being investigated to reduce considerably the cost of production of bNAbs, with the expectation that they will one day be more accessible than other traditional therapies (Cohen & Caskey, 2018).

Even though different challenges have emerged with bNAbs therapy, they may offer several advantages over ART for both preventing and treating HIV-1 infected patients. These could also be a safer and less toxic alternative due to its pharmacokinetic profile. It is important to understand the obstacles faced by this therapy, in order to develop new strategies to improve its function. bNAbs´ should undergo certain engineering modifications in order to increase their breadth and potency. However, more studies need to be done on this matter (Cohen & Caskey, 2018).

Concluding remarks

There have been very few published papers describing the effect of bNAbs as an HIV-1 treatment. However, the few clinical studies have shown that these antibodies have both positive and negative results. The bNAbs have proven to be safe and well tolerated, but not as effective as hoped. Some of the challenges that have arisen involve transitory suppression of viremia, viral resistance, cell-to-cell transmission by the virus, the undetermined effect over the HIV-1 reservoir and high costs of bNAbs production. However, the development of new strategies such as the combination of bNAbs and engineered modifications could be possible solutions for these issues. Most of the clinical trials have focused on the combination of 3BNC117 and 10-1074, which have proven to be more effective when used together than by themselves. bNAbs have the potential to reshape the current HIV-1 treatment strategies, although more studies need to be done to ensure a safe and effective treatment.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Authors´ Contribution

Anapaula Gonzalez, Andrea Güemez and Ana Elena Hernández contributed equally to this work.

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