TREATMENT ACTION GROUP
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Treatment Action Group

Broadly Neutralizing Antibodies (bNAbs) and HIV Cure-Related Research

Antibodies are Y-shaped proteins produced by immune system cells called B cells. The main task for antibodies is to bind to infectious agents like viruses, with the goal of neutralizing them (blocking their ability to infect cells) and promoting their elimination from the body. In some cases, antibodies also have the capacity to attach to cells infected with viruses or other pathogens, flagging the cell for destruction by the immune system.

HIV has evolved a variety of strategies for fending off antibody attacks. The virus is cloaked in a protective shroud of sugar molecules called glycans that serve as a shield against antibody-mediated neutralization. HIV also primarily infects and disrupts or destroys CD4+ T cells, an immune system cell that usually helps B cells make effective antibodies.

B cells produce many antibodies in response to HIV infection — they are used as the basis for the diagnostic HIV antibody test — but most are unable to inhibit the virus.

In recent years, technological advances have allowed researchers to sample vast numbers of B cells from people with HIV and identify rare B cells capable of producing antibodies that have strong anti-HIV activity. The genetic code of these rare B cells can be mapped and used as a blueprint for manufacturing the antibody in large quantities. These antibodies have been named broadly neutralizing antibodies (bNAbs) because, in laboratory tests, they can inhibit multiple different HIV variants from around the world.

In most cases, the bNAbs do not appear to benefit the sample donor because they are only present in small amounts and are essentially overwhelmed by the much larger amount of HIV present in the body. However, large-scale manufacturing has allowed bNAbs to be delivered as experimental therapies, most commonly by intravenous infusion or subcutaneous injection.

A GENE THERAPY APPROACH TO bNAb DELIVERY

Researchers are investigating whether a technique borrowed from gene therapy can generate bNAbs in the body on an ongoing basis. In this scenario, the genetic code for the bNAb is inserted into a specially engineered adeno-associated virus (AAV) vector that takes up residence in muscle tissue and acts as a factory for producing the bNAb. The aim is to give a single injection of the AAV vector. The challenge for this approach is that it's proving difficult to achieve high enough levels of the bNAb in the body to suppress HIV, but research is ongoing.

There is now a flourishing field of research investigating bNAbs for multiple purposes:

- In HIV cure research, bNAbs are being investigated primarily for their potential to promote clearance of HIV-infected cells and enhance the immune response against HIV (particularly CD8+ T cell responses).
- The therapeutic potential of bNAbs is being tested in studies in which they are combined with or substituted for antiretroviral therapy (ART).
- Prevention studies are investigating bNAbs in HIV-negative people to assess their capacity to block the acquisition of HIV.

THE NUMERICAL/ALPHABETICAL SOUP OF bNAbs

The discovery of increasing numbers of bNAbs has led to multiple candidates advancing into clinical trials. These candidates often have confusing codenames (or multiple names) that can be difficult to keep up with. Candidate bNAbs are sometimes classified based on the part of the HIV envelope they target; examples include the CD4 binding site and the V3 or V2 loops. For bNAb combination studies, researchers typically combine bNAbs that target different areas of the HIV envelope. Additionally, technical modifications can create long-acting bNAbs that require less frequent dosing; these versions are designated with an "LS" appended to the name.

These are some of the leading candidates currently under evaluation in HIV cure research:

10-1074-LS
3BNC117-LS

These two bNAbs, discovered by Rockefeller University, have been licensed by the pharmaceutical company Gilead Sciences and given additional names: 10-1074-LS is also known as GS-2872 or zinlirvimab, while 3BNC117-LS goes by GS-5423 or teropavimab. 10-1074-LS targets a part of the HIV envelope called the V3 loop; 3BNC117-LS targets the CD4 binding site. The pairing is currently the most frequently studied among bNAbs (see TAG's cure-related study listing).

VRC01

One of the first bNAbs to be identified by researchers at the Vaccine Research Center (VRC) at the US National Institutes of Health (NIH), VRC01 is no longer considered the most potent candidate but has been tested as a preventive agent in the large Antibody-Mediated Prevention (AMP) efficacy trials. A subset of AMP trial participants who acquired HIV and started ART have now enrolled in follow-up studies that involve an analytical treatment interruption (ATI). The goal is to assess whether the presence of VRC01 at the time of HIV acquisition led to the generation of anti-HIV immune responses capable of controlling viral load after ART interruption.

VRC07-523LS	**A bNAb discovered by researchers at the VRC with greater breadth and potency against HIV compared to VRC01, VRC07-523LS targets the CD4 binding site of the HIV envelope. A long-acting version is being tested in several studies (both adults and infants).**
PGT121.414.LS	**A long-acting version of the bNAb PGT121 that was originally isolated from a participant in an African cohort study conducted by researchers from IAVI, PGT121.414.LS targets the HIV envelope V3 loop.**
CAP256V2LS	**A long-acting version of the bNAb CAP256 that targets the V2 loop of the HIV envelope, CAP256V2LS was identified in samples from a participant in an acute HIV infection study conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA).**
PGDM1400/ PGDM1400LS	**First described by researchers affiliated with the International AIDS Vaccine Initiative (IAVI), PGDM1400 is a potent bNAb directed at the V2 loop of the HIV envelope.**
N6-LS	**The bNAb N6 was discovered by researchers at the NIH and subsequently licensed to GlaxoSmithKline and given the identifier GSK3810109A. N6 targets the CD4 binding site of the HIV envelope. Development of a long-acting version is being sponsored by ViiV Healthcare, primarily for treatment or prevention.**

RESISTANCE

While the activity of bNAbs is described as *broad* based on laboratory tests against multiple diverse HIV variants sampled from individuals in different geographic locations, this information does not tell researchers how well a bNAb will work in a larger population of people with HIV.

The part of HIV targeted by bNAbs — the outer envelope — mutates much more than the inner elements of the virus targeted by antiretroviral drugs (such as reverse transcriptase, integrase, and protease).

As a result, bNAbs are more vulnerable to the problem of HIV resistance in which mutations in the virus envelope reduce or block the activity of a given bNAb. These mutations can already exist in circulating HIV variants or be promoted when a person with HIV receives a bNAb.

The vulnerability of bNAbs to resistance is highlighted by the fact that a combination of three antiretroviral drugs is typically enough to block HIV replication and suppress viral load, whereas a study that administered three bNAbs was only able to demonstrate transient suppression of viral load because of the emergence of resistance mutations (see table).

Researchers are evaluating whether newly developed tests can measure the extent of HIV resistance against a particular bNAb. In some cases, these tests are being used to screen people interested in participating in studies of bNAbs, with those showing high levels of resistance excluded. But there is uncertainty regarding how well these tests may predict the anti-HIV activity of bNAbs, partly because only a fraction of the diverse copies of HIV present in the body can be sampled and assessed.

In several studies, a lack of evidence of bNAb resistance has been associated with stronger anti-HIV activity; however, other studies have found no association between outcomes and results of resistance testing, so this remains an area of active investigation.

RESULTS SO FAR

Initial studies have shown that bNAbs can have strong anti-HIV effects in both adults and children, but that resistance can be present at baseline or develop quite quickly when viral load is not fully suppressed. A few cases of extended control of HIV viral load to low levels after interruption of ART have been reported in studies of dual bNAbs or single bNAbs combined with other interventions. Evidence of enhanced CD8+ T cell responses against HIV after receipt of bNAbs has been observed among participants in at least two adult studies (see table).

The delivery of bNAbs by intravenous infusion or subcutaneous injection has generally been safe, with rare reports of transient infusion reactions that were managed without any complications. One candidate bNAb, 10E8, caused a severe injection site reaction in a participant in an initial study (a rash and inflammatory condition called panniculitis) and has not been investigated further.

SELECTED STUDY RESULTS

BNABS/ADDITIONAL INTERVENTIONS	KEY FINDINGS	CITATION(S)
3BNC117 + 10-1074	■ 76% (13/17) of study participants maintained HIV viral load suppression for at least 20 weeks after ATI. ■ There was no pre-screening for bNAb resistance, and post-trial analyses of resistance did not find an association with time to viral load rebound. ■ Two participants did not experience viral load rebound after 48 weeks; one was lost to follow-up after a year, while the other remained virally suppressed after two years in the absence of detectable ART. ■ Receipt of bNAbs was associated with increased HIV-specific CD4+ and CD8+ T cell responses. ■ There was a statistically nonsignificant trend for an average 46% reduction in the size of the intact HIV reservoir over six months.	Gaebler C, Nogueira L, Stoffel E, et al. Prolonged viral suppression with anti-HIV-1 antibody therapy. Nature. 2022 Jun;606(7913):368-374. Niessl J, Baxter AE, Mendoza P, et al. Combination anti-HIV-1 antibody therapy is associated with increased virus-specific T cell immunity. Nat Med. 2020 Feb;26(2):222-227.
3BNC117 + 10-1074	■ Nine participants with HIV sensitive to the bNAbs maintained viral load. suppression for an average of 21 weeks after ATI. ■ Two participants (13%) experienced extended (>30 weeks) control of viral load to undetectable levels.	Mendoza P, Gruell H, Nogueira L, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. Nature. 2018 Sep;561(7724):479-484. doi: 10.1038/s41586-018-0531-2.
3BNC117 +/- romidepsin	■ Administration of 3BNC117 at the time of ART initiation led to faster decline of HIV viral load and increased HIV-specific CD8+ T cell immunity compared to ART alone. ■ Study participants with HIV sensitive to 3BNC117 were significantly more likely to maintain ART-free control of HIV viral load after ATI compared to other participants. ■ One of the 16 participants in the 3BNC117 and romidepsin group remains off ART and has maintained undetectable HIV viral load for 3.7 years at time of last report.	Gunst JD, Pahus MH, Rosás-Umbert M, et al. Early intervention with 3BNC117 and romidepsin at antiretroviral treatment initiation in people with HIV-1: a phase 1b/2a, randomized trial. Nat Med. 2022 Nov;28(11):2424-2435. Rosás-Umbert M, Gunst JD, Pahus MH, et al. Administration of broadly neutralizing anti-HIV-1 antibodies at ART initiation maintains long-term CD8+ T cell immunity. Nat Commun. 2022 Oct 29;13(1):6473.

SELECTED STUDY RESULTS (CONTINUED)

BNABS/ADDITIONAL INTERVENTIONS	KEY FINDINGS	CITATION(S)
3BNC117 + 10-1074 +/- lefitolimod (TLR9 agonist)	■ Participants pre-screened for resistance and enrolled based on HIV samples being sensitive to the bNAbs. ■ Participants receiving bNAbs had significant longer time to loss of viral load suppression during ATI compared to placebo recipients. ■ Six participants (five of whom received bNAbs) did not meet ART restart criteria during the 24-week ATI.	Gunst JD, Reikvam DH, McMahon JH, et al. The Impact of 3BNC117, 10-1074, and Lefitolimod on HIV-1 Persistence: The TITAN Trial (Abstract 136). Paper presented at: Conference on Retroviruses and Opportunistic Infections; 2023 February 19–22; Seattle, WA.
10-1074 + VRC07-523LS + HIV Gag conserved element DNA/ IL-12 prime/ MVA boost vaccines + lefitolimod (TLR9 agonist)	■ Participants pre-screened for resistance to the bNAbs. ■ Five out of 10 participants had viral load set points <1,000 copies/ml after ATI. ■ One of the 10 participants has not experience viral load rebound for >18 months of follow up.	Peluso MJ, Deitchman A, Magombedze G, et al. Rebound Dynamics Following Immunotherapy with an HIV Vaccine, TLR9 Agonist, and bNAbs (Abstract 435). Paper presented at: Conference on Retroviruses and Opportunistic Infections; 2023 February 19–22; Seattle, WA.
3BNC117 + 10-1074 +/- peginterferon alfa-2b	■ Two of the 14 participants chose to discontinue study due to bNAbs infusion-related chills. ■ HIV viral load suppressed to <20 copies/ml for 26 weeks in 80% (10/12) of participants after ATI. ■ Two participants (14%) maintained viral load <50 copies/ml for >50 weeks. ■ Selection of bNAb resistance was observed in 75% of participants.	Tebas P, Azzoni L, Papasavvas E, et al. BEAT-2 primary trial outcomes: PEG-IFN- α2b +3BNC117 & 10-1074 in chronic HIV infection (Abstract 431). Paper presented at: Conference on Retroviruses and Opportunistic Infections; 2023 February 19–22; Seattle, WA.
PGDM1400 +/- PGT121 +/- VRC07-523LS	■ Single intravenous infusion of three bNAbs reduced viral load by an average of two logs, viral load rebound occurred an average of 20 days after reaching lowest point. ■ Rebounding HIV showed resistance to PGDM1400 and PGT121 in lab tests.	Julg B, Stephenson KE, Wagh K, et al. Safety and antiviral activity of triple combination broadly neutralizing monoclonal antibody therapy against HIV-1: a phase 1 clinical trial. Nat Med. 2022 Jun;28(6):1288-1296.

SELECTED STUDY RESULTS (CONTINUED)

BNABS/ADDITIONAL INTERVENTIONS	KEY FINDINGS	CITATION(S)
VRC01LS + 10-1074 in early-treated infants	■ Dual bNAb treatment maintained viral load suppression for 24 weeks in the absence of ART in 11 out of 25 (44%) of children and was well-tolerated. ■ No differences in HIV reservoir size observed after receipt of bNAbs.	Shapiro RL, Maswabi K, Ajibola G, et al. Treatment with broadly neutralizing antibodies in children with HIV in Botswana (Abstract 32). Paper presented at: Conference on Retroviruses and Opportunistic Infections; 2022 February 12–16; Virtual. Niesar A, Lian X, Hua R, et al. Viral reservoir landscape Of children with HIV in Botswana treated with dual bNAbs (Abstract 141). Paper presented at: Conference on Retroviruses and Opportunistic Infections; 2023 February 19–22; Seattle WA.
AAV8-VRC07 (bNAb delivered by AAV vector)	■ Measurable amounts of VRC07 observed in all eight study participants, but levels far lower than those associated with HIV suppression in other studies. ■ Three of eight participants (12.5%) developed antibody responses against VRC07.	Casazza JP, Cale EM, Narpala S, et al. Safety and tolerability of AAV8 delivery of a broadly neutralizing antibody in adults living with HIV: a phase 1, dose-escalation trial. Nat Med. 2022 May;28(5):1022-1030. doi: 10.1038/s41591-022-01762-x.

CURRENT STUDIES

Multiple ongoing clinical trials aim to build on the hints of promise that have emerged from completed bNAb studies. The three largest current studies all involve the dual combination of 10-1074-LS and 3BNC117-LS:

- **NCT05612178:** An unusually large phase I trial that plans to enroll 200 participants at the U.S. National Institutes of Health Clinical Center in Bethesda Maryland and Rockefeller University in New York City. The study will assess the effects of dual bNAbs on the HIV reservoir and does not include an ATI.
- **The RIO Trial/NCT04319367:** Enrolling 72 participants with primary HIV infection in the UK, the study will evaluate the capacity of dual bNAb administration to promote post-treatment control of viral load after ATI.
- **RHIVIERA-02/NCT05300035:** A similar study to RIO that aims to enroll 60 participants with primary HIV infection in France.

Information on additional HIV cure-related trials involving bNAbs can be found in **TAG's online listing of HIV cure-related clinical research.**

RELATED LINKS

TAG's regularly updated listing of clinical trials and observational studies related to the research effort to cure HIV infection: http://www.treatmentactiongroup.org/cure/trials

A related TAG resource is tracking the demographics of participation in HIV cure-related clinical research, including bNAb trials: https://www.treatmentactiongroup.org/cure/resource-on-the-demographics-of-participation-in-hiv-cure-related-clinical-research AVAC's infographic on HIV-Specific Neutralizing

Antibodies by Target: https://www.avac.org/resource/hiv-specific-neutralizing-antibodies-target

A resource page containing articles, reports, and links to other organizations and websites relevant to cure research: http://www.treatmentactiongroup.org/cure

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