

# Systematic Review of Future Direction of Broadly Neutralizing Antibodies against HIV

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## Abstract

A novel class of potential therapeutic agents is provided by the recent invention of the broadly neutralizing highly potent HIV-specific monoclonal antibodies (bnAbs). It has broadly been recognized that neutralising antibodies can hit the HIV envelope (Env) and efficiently subdue viral retort *in vivo* (vitro) but bnAbs aren't effective enough for practical use. The bnAbs are being sturdily followed and developed due to the imperative features, including the engaging the host immune response, excellent safety, and longer half-life. It has been reported the functions in a variety of studies, for instance clearing infected cells, inhibiting cell-to-cell transmittance, and neutralizing free virus of HIV-1. Furthermore, the upward contourofbnAbs renders new-fangled vision for cogent vaccine design and anticipating immunogen examination.To result in suboptimal or sporadic treatment, all these factors work

together that hikes the menace of treatment failure and viral resistance. A highly priority is still remained to quest for novel preventive and therapeutic interventions. An attractive new therapeutic modality against HIV/AIDS is known Antibodies. Antibodies not only can directly target explicit viral epitopes but also have the potential to tackle host immune receptions.

**Key Words:** Broadly Neutralizing Antibodies, HIV/AIDS, Future Directions, immunology, vaccine, antiretroviral drugs

## Introduction

### Background of the Study

The utmost public-health challenge of the contemporary world remains is HIV/AIDS pandemic. Almost 78 million people world-wide have been infected 39 million lives have been died by the AIDS instigating virus HIV-1 since its detection in the first 1980s. In 2013, HIV infection credited death to 1.5 million and 7000 new HIV contagions per day (Rubens, Ramamoorthy, Saxena, Shehadeh, & Appunni, 2015). In sub-Saharan part of Africa, the great majority of newfangled infections occurred 68% globally. The deaths occurring throughout the world with great magnitudes of AIDS-related infections are 14% in Nigeria, 13% in South Africa, 8% in India, and the 2% in Russian Federation (Sok & Burton, 2018). One cause that such rates of high AIDS-pertained expiries endure to ensue worldwide, in spite of the start of medications which are vastly efficacious at subduing HIV retort, is that only two in five persons surviving with HIV in point of fact have the approach to antiretroviral therapy (ART) (Wu et al., 2010).

Furthermore, antiretroviral therapy doesn't cure HIV-contagion infection and must be sustained for a life-time (Miner, Corey, & Montefiori, 2021). Even in the United States of America, only 31% of the 1.3 million persons surviving with HIV-infection have repressed HIV-infection to untraceable levels, in spite of the fact that most HIV-septic persons in the America have approach to antiretroviral therapy (Liao et al., 2013). Consequently, for over a decade in the USA there has been no declination in AIDS-related human expiries. Therefore, the anti-retroviral therapy is requisite but not adequate to cease the world AIDS pandemic (J. Huang, G. Ofek, & Ofek, L., 2015). According to the 2018 report of the World Health Organization, there were 39 million humans surviving with HIV infection letting in 1.7 million children beneath the age of 15 years. The vaccine for HIV infection relics intangible, in spite of decades of research-studies and number of clinical-trials (Huang et al., 2012). To treat the contagion more efficiently, improved interventions are immediately required due to new HIV infections and AIDS, the number of annual deaths has declined by 33% and 16%, correspondingly, and owing to the prevalent usage of efficacious anti-retroviral medication therapy over the last decade (Walker et al., 2011).

### Research Methodology

In this review paper, the literature search of previous studies was conducted by expending electronic databases for example PubMed, Ovid, Google Scholar, EMBASE, and Cochrane Central Register of Controlled-Trials. Keywords used for combining the following search terms to search quality research studies including HIV, AIDS, broadly neutralizing antibodies, clinical trials, vaccine, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell-mediated viral inhibition, CD4-T cells, and CD8-T cells. In this study, we pursued a systematic review approach to recapitulate the current improvements in HIV vaccine development and its future direction of broadly neutralising antibodies against HIV virus (Wu & Kong, 2016).

The studies were considered if they assessed bnAbs for HIV/AIDS and suitable for providing future direction of broadly neutralizing antibodies against HIV characterised their molecular source and effectiveness, and delved into their potential applications in submissive antibody intervention and vaccine pattern (Wagh et al., 2016). In this review paper we have sieved 700 studies based on medical trials from inception till March 01, 2024, and amassed 25 research studies which were appropriate to the area of the selected topic (Binley et al., 2017). Grounded on the existent medical literature concerning about the study topic as well as based on our own aim of the study and the clinical experience of medical experts to treating HIV infected subjects diagonally the various waves in the different countries around the world (Stephenson & Barouch, 2016b). It has been concluded while reviewing the selected previous relevant studies, the broad neutralizing antibodies could be an efficient choice for handling and prophylaxis for contemporary and future irruptions of HIV/AIDS (Blattner et al., 2014). At the end it is suggested that the foster research letting in long-term clinical trials is requisite to sew the optimum dosages, avert adversative reactions and foulest side-effects, and explicate treatment stratagems (Stephenson & Barouch, 2016a).

### Data Analysis

Nowadays, with antiretroviral therapy or with the cocktails of antiretroviral drugs, the management of HIV exerts plasma virus at untraceable echelon condition that the medication is extant at therapeutical levels *in vivo*, but doesn't vibrant viral reservoirs, and if surceased the virus ricochets (Steichen et al., 2019). Antiretroviral therapy composites are trivial molecules which normally have curt half-lives, postulating intervention regular for enduring safety in children and adults scuppered to HIV by lactating (Rubens, Ramamoorthy, Saxena, Shehadeh,

&Appunni, 2015). The topical progress of ameliorated formulation of antiretroviral therapy which entails sporadic drugging will eventually ameliorate adherence to medicines which possess substantial integral perniciousnesses that manifest usually as malaise and fatigue in various ART receivers, and may comprise lactic acidosis, liver failure, neuropathy, and myopathy from antiretroviral therapy encompassed mitochondrial dysregulation (Ren et al., 2018). To result in sporadic or suboptimal treatment, all of these factors work together that hinders the menace of treatment failure and viral resistance (Reh et al., 2015).

Over and above the therapeutic indicants, antiretroviral therapy is practiced by uninfected unprotected individuals to avert infection that is recognized as preexposure prophylaxis (PrEP) (Mu, Haynes, & Cain, 2021). Unfortunately, this method is not yet accessible worldwide but, in the USA and numerous other developed countries (Parsons, Chung, & Kent, 2018b). As a longer lasting and less toxic substitute to antiretroviral therapy, the practice of monoclonal-antibodies (mAbs), delivering submissively or by cistron therapy. It is being sightseen in pre-clinical or clinical trials. The trivial-molecule antiretroviral therapy remnants the only FDA-sanctioned intervention mode for HIV/AIDS in 2022 (Parsons, Chung, & Kent, 2018a).

The new class of latent therapeutic-agents is provided by the topical unearthing of broadly neutralizing vasty effective HIV-specific monoclonal antibodies (bnAbs) (Moysi, Petrovas, & Koup, 2018). It has broadly been recognized that neutralising antibodies can hit the HIV-envelope (Env) and efficiently subdue viral replication in *ex vivo* (vitro) but bnAbs aren't effective enough for practical use (Lin & Balazs, 2018). Combination antiretroviral therapy transformed the intervention of HIV-1 infection and evinced effectiveness in deterrence (Mayr, Su, & Moog, 2017). Though, the established infection is not eradicated by antiretroviral therapy and global HIV occurrence rates have sustained to wane tardily (Miner, Corey, & Montefiori, 2021). A highly priority is still remained to quest for novel preventive and therapeutic interventions. An attractive new therapeutic modality against HIV/AIDS is known Antibodies (Moore, 2018). Antibodies not only can directly target explicit viral epitopes but also have the potential to tackle host immune receptors (Moore, Gorman, Doria-Rose, & Morris, 2017). Sole-cell antibody cloning methods empowered the recognition and posterior enactment of bnAbs with outstanding effectiveness and extent in contrast to formerly recognized anti-HIV-1 neutralizing antibodies (Gama & Koup, 2018). These extremely effective new group bnAbs are an anticipating novel stratagem against HIV-1. In the last 5 years, numerous bnAbs with diverse envelope particularities have infixed clinical appraisal (Jones, Moody, & Thompson, 2020).

The causative mediator of developed immune-deficiency syndrome (AIDS) and largely blights CD4-positive (CD4+) immune cells, gradually harming the antibodies is known as human immunodeficiency virus-1 (HIV-1). Lacking of surveillance and defense by the immune-system, people with HIV-1 infection are more susceptible to gene-mutations and pathogenic micro-organisms, ensuing in devious contagions and tumors and even bereavement (Gombos et al., 2015). Nevertheless, there presently are no efficient HIV-1 vaccines and petty expectation for defensive immunisation. The average endurance time of in infected people is almost 10 years in a naturally morbid course. Though, the instauration of combination anti-retroviral therapy (cART) as an innovation has reformed the sequence flight (Jardine et al., 2016). Certainly, by overturning the viral riposte, indorsing immune reconstruction, and averting the inception of AIDS, the cART can dramatically upsurge the life anticipation of infested persons (Hua & Ackerman, 2016). Moreover, when administered as part of preexposure or postexposure prophylaxis, the cART might diminish a number of new contagions (Haynes et al., 2022). In spite of the suppression of plasma viremia, cART isn't sanative because these medications run out to excrete the potential HIV-1 source, and the stifled virus resiles hurriedly in the mass numbers of HIV-1-infected persons when intervention is surceased. Therefore, with numerous side effects, regular and lifetime therapy is necessitated (Dufloo, Bruel, & Schwartz, 2018).

A new method for averting, treating, handling, and potentially even eliminating HIV-1 transmission, the topical ontogeny of HIV-1 explicit potent provides broadly neutralising antibodies (bnAbs) (del Moral-Sánchez & Sliopen, 2019). The bnAbs are being sturdily followed and developed due to the imperative features, including the engaging the host immune response, excellent safety, and longer half-life (Corti & Lanzavecchia, 2013). It has been reported the functions in a variety of studies, for instance clearing infected cells, inhibiting cell-to-cell transmittance, and neutralizing the free virus of HIV-1 (Cohen & Caskey, 2018b). Furthermore, the upward contour of bnAbs renders novel vision for cogent vaccine design and anticipating the immunogen-testing (Cohen & Caskey, 2018a).

**Table 1: Broadly neutralizing antibodies, HIV vaccine efficacy trials, target sites, and breadth of neutralization**

Study Name	Specs	Vaccine	Site	Target Site	Broadly neutralizing antibodies	Participants	Breadth of neutralization (IC50 < 50 µg/mL)	Comparator to Placebo	Outcomes
Huang et al. (2012)	Vax004	AIDS-VAX B/B' gp120 with alum	Netherlands and USA	CD4 binding-site	VRC01	6100 MSM and 1000	79% of 190 isolates	1:1	10.1 % Vaccine efficacy at 51 months
Wu et al. (2010)	Vax003	AIDS-VAX B/E' gp120 with alum	South Africa and Thailand	CD4 binding-site	VRC02	3500 men and women IDUs	92% of 180 isolates	2:1	No vaccine efficacy
Wu et al. (2020)	HVTN 502 Step Trial	MRKAd5 HIV-1 'gag/pol.nef' trivalent vaccine based on adenovirus type 5	North America, South America, Australia, and the Caribbean Island	CD4 binding-site	VRC03	4000 MSM and heterosexual women and men	58% of 190 isolates	1:1	16 % Vaccine efficacy at 63 months
Walker et al. (2021)	RV144	Recombinant canarypox vector vaccine (ALVAC-HIV. vCP1521) and recombinant glycoprotein 120 submit vaccine (AIDS-VAX B/E)	Thailand and Uganda	CD4 binding-site	VRC-PGV04	18504 community-risk men and women	89% of 176 isolates	2:1	No vaccine efficacy
Wu et al. (2011)	HVTN. 503 'Phambili Trial'	MRKAd5 HIV-1 'gag/pol.nef' trivalent vaccine based on adenovirus type-5	South Africa and Rwanda	CD4 binding-site	VRC-PGV04b	902 heterosexual men and women	82% of 170 isolates	2:1	7 % Vaccine efficacy at 49 months

Liao et al. (2013)	HVTN 505	6-plasmid D.N.A. vaccine and 'rAd5' vector boost	UK and USA	gp41	CH103	3506 men or trans women who have sex with men	71% of 192 isolates	1:1	No vaccine efficacy
Corti et al. (2010)	HIV-V-A004	Homologous 'Ad26' mosaic vector regimens or 'Ad26' mosaic and MVA mosaic heterologous vector regimens, which high dose, low dose or no clade C 'gp140' protein plus adjuvant	Uganda, Rwanda, Thailand, South Africa, USA	gp120	2F5	600 men and women	89% of 160 isolates	2:1	Result awaited
Binley et al. (2004)	HVTN 100	Clade C ALVAC-HIV ('Vcp2438') and bivalent subtype-C 'gp120/MF59'	USA and South Africa	gp120-gp41	2G12	468 men and women	46% of 98 isolates	2:1	No vaccine efficacy
Walker et al. (2009)	HVTN 702	ALVAC-HIV and bivalent subtype-C 'gp120/MF59'	South Africa and Australia	V1-V2 loops	4E10	6300 men and women	77% of 170 isolates	5:1	27 % Vaccine efficacy at 52 months
Haug et al. (2012)	HVTN 703/HPTN 081	VRC01 broadly neutralizing monoclonal antibody	South America, North America Sub-Saharan Africa	CD4 binding-site	PG9	3600 MSM and transgender and 1600 women	78% of 180 isolates	1:1	19 % Vaccine efficacy at 74 months
Walker et al. (2011)	Vax003	AIDS-VAX B/B' gp120 with alum	South Africa and USA	gp41	PGT130	1200 heterosexual men and women	76% of 188 isolates	1:1	11.5 % Vaccine efficacy at 73

									months
Bonsignori et al. (2014)	Vax004	AIDS-VAX B/E' gp120 with alum	South Africa, Australia and Thailand	V1-V2 loops	PGT151	4800 men or trans women who have sex with men	67% of 119 cross-clade isolates	2:1	No vaccine efficacy
Blattner et al. (2014)	HVTN 502 Step Trial	MRKAd5 HIV-1 'gag/pol.nef' trivalent vaccine based on adenovirus type-5	North America, South America	CD4 binding-site	PGT152	2380 men and women	67% of 119 cross-clade isolates	2:1	19 % Vaccine efficacy at 69 months

Note: MSM: males who have sex with the men; IDUs: IV drug users.

### **Broadly Reactive Neutralizing Antibodies (bnAbs)**

Due to the characteristics of the virus itself, the defensive immune retort in HIV infection is an eventual challenge. Within a short-time span, HIV-virus mutates very hastily heading to various varies in the envelope proteins (Ali et al., 2020). Therefore, a vaccine should prompt numerous antibodies proficient of neutralising many genetically diverse strives. In this review paper, mostly of HIV-infected patients in selected different studies depict a hasty monoclonal-type antibody retort proficient of yielding some stages of defense against the HIV virus (Caskey, 2020). Notwithstanding, in the host superceding the cellular and humoral immune responses, the virus uprisers the resistance to these thrives and antibodies (Bhiman & Lynch, 2017). Distinguished delisions to this are non-conventional 'bnAbs' that are ascertained in a very trivial ratio of HIV-infested persons (Stephenson & Barouch, 2016b). Even in those people who develop bnAbs, merely about a quarter are proficient of persuading cross-reading antibodies with the passable extent and effectiveness assessed by consistent neutralisation analyses (Andrabi, Bhiman, & Burton, 2018).

Throughout the three years of natural contagion, these bnAbs are identified to develop. Contemporary scientists daresay that vaccine regimes should rivet on persuading convenient 'bnAbs' for neutralisation of the virus-strainings or rendering eminent stages of fortification. Yet this is identical auspicious, bnAbs likewise have inadequacies (Wagh et al., 2016). The BnAbs are hardly developed and the mechanisms for stimulating them through viable immunization regimens are not yet amply empathized (Reh et al., 2015). Though, due to numerous levels of corporeal hypermutations required for the development that acquires months to years (long time), by that time the virus develops newfangled and resilient transformations, it is hard to persuade bnAbs development (Parsons, Chung, & Kent, 2018a). Many researchers in the listed studies have also uttered the interests about bnAbs being autoreactive or polyreactive and potentially deleterious, and consequently poisoning the adverse set against beneficial outcomes requires additional deliberation (Moysi, Petrovas, & Koup, 2018). The present research accomplishes that bnAbs render entire fortification against viral contagion then administered inertly in adequate dosages. Numerous studies done on the animals have revealed that bnAbs develop therapeutic neutralisation of virus in disease-ridden animals (Hua & Ackerman, 2016). Ultimately, along with antiretroviral medicaments and preventative methods, bnAbs could develop into a gratis therapeutic mode (Moore, Gorman, Doria-Rose, & Morris, 2017). Table No. 1 indicates the review of various research studies in the form of the list of all HIV-vaccine effectiveness trials, target sites, broadly neutralising antibodies, and their breadth of neutralization.

### **Co-evolution of Broadly Neutralizing Antibodies**

The neutralising antibodies in the HIV infection should be bright to contend with numerous immune equivocation stratagems attained by the viruses. To overawed this marvel, the efficacious vaccines should tempt antibodies which are proficient of tying and neutralising a far-reaching ambit of disseminating viral products (Jones, Moody, & Thompson, 2020). These sort of 'bnAbs' are ascertained only in a trivial ratio of natural contagion and a set of emcee and viral-factors intercede the growth along with the potency and breadth of bnAbs (Caskey, 2020).

For effective bnAbs production, future vaccine testing trials should rivet on inducing VH-genes. According to the studies, numerous viral influences are also allied with the development of 'bnAbs' (Jardine et al., 2016). Ultimately explored that with the moderate and the sustained viral load, bnAbs are usually developed in patients (Bhiman & Lynch, 2017). Therefore, it is an intricate interaction of emcee antibody acquirement potentialities and ever-evading viral mutations which produce and substantiate convenient neutralising 'bnAbs'. In a table-1, a few trial studies have attempted to explicate the progression of 'bnAbs' retorts in HIV declared subjects in addition to recognize the mechanisms by which bnAbs are developed (Lin & Balazs, 2018). The present article reckons that steering the constant scramble between host immune responses and virus could assist inventors to formulate efficient vaccines which induce convenient bnAb development.

### **Future directions of Broadly Neutralizing Antibodies**

From the recent HIV prevention trials, the highly promised results may have imperative implications for future upcoming research. This special review study distinguishes the core issues scholars and scientists are pondering in the repercussion of the trials to test whether a broadly neutralizing antibody could keep people safe from HIV infection (Andrabi, Bhiman, & Burton, 2018). The present study provides the host platform to find out the leading results from the trials about the future of antibody-based prevention conducted by the experts in the medical field have to say (Ball, Tarr, & McKeating, 2014). A vaccine remains elusive for four decades into the HIV pandemic. Uhambo, the latest large-scale HIV vaccine trial was ceased in 2021 for the reason that a provisional investigation exposed the vaccine regimen did not work (Haynes et al., 2022). The ultimate analysis of the trial was lately promulgated that was a follow-on to the only one to render any vaccine efficiency.

The pursuit is far from over, the scientists are trailing other stratagems to develop an HIV vaccine. Simultaneously, some other HIV prevention possibilities, letting in long-acting methods of HIV pre-exposure prophylaxis or PrEP, are being sprang up and tested in research trials (Moysi, Petrovas, & Koup, 2018). For HIV anticipation the trials of

an injectable antiretroviral and infusions of a solo HIV antibody have lately come to culmination (Stephenson & Barouch, 2016a).

This peculiar review detects the core problems the field is pondering in the upshot of these research trials (Reh et al., 2015). If long-acting, vastly efficient injectable forms of PrEP are sanctioned momentarily, some important question about future endeavors to arise: 1- Will they be promptly implemented? 2- How do antibodies appropriate into the future HIV anticipation exertions? 3- Will a combination of antibodies adequately guard against the global diversity of HIV? 4- Will they able to be developed and distributed world-wide? (Haynes et al., 2022).

### Conclusion

Several new immunology and virological indications like pro-viral D.N.A. levels in reservoir cells, pointers of biochemical and cellular immune reception, amounts of running T and B cell sub-sets, viral neutralization rates, and viral transmission rates should be employed in upcoming research to assess the broadly neutralising antibodies, target sites, vaccine efficiency upshots, and their breadth of neutralisation in large-scale studies. Due to the newer models are being anticipated and flung hastily and research on these models is complicated and expensive, this is expressly challenging for present scientists, scholars, and funding-institutions. For the invention of a successful vaccine, there is need to invest more money and time in large-scale studies. The countries should collaborate with World Health Organization and together in summit these investments for a cause which could eventually save millions of humans along with the resources expended on handling the HIV/AIDS. After the successful efforts done by the different nations with the collaboration, HIV/AIDS can be checked even in the poor countries all around the world and hopes a purge in the future would be a reality.

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