Utilizing immunotherapy towards achieving a functional cure for HIV-1

Fabrícia Heloisa Cavicchioli Sugiyama[a,b,c], *Lisa Loksø Dietz*[b,c] *and Ole Schmeltz Søgaard*[b,c]

Purpose of review
Advancements in antiretroviral therapy (ART) have positively impacted the life expectancy and possibility of living a normal life for people with HIV-1. However, lifelong daily medication is necessary to prevent disease progression. To this end, immunotherapeutic strategies are being tested with the aim of developing a functional cure in which the immune system effectively controls HIV-1 in the absence of ART.

Recent findings
The most promising advances in achieving sustained HIV-1 remission or cure include broadly neutralizing antibodies (bNAbs) that are administered alone or in combination with other agents. Newer and more innovative approaches redirecting T cells or natural killer cells to kill HIV-1 infected cells have also shown promising results. Finally, multiple ongoing trials focus on combining bNAbs with other immune-directed therapies to enhance both innate and adaptive immunity.

Summary
While immunotherapies as an alternative to conventional ART have generally proven to be well tolerated, these therapeutic approaches have largely been unsuccessful in inducing ART-free control of HIV-1. However, promising results from recent trials involving bNAbs that have reported durable HIV-1 control among a subset of participants, provide reason for cautious optimism that we with further optimization of these treatment strategies may be able to achieve functional cure for HIV-1.

Keywords
clinical trials, functional cure, HIV-1, immunotherapy

INTRODUCTION

Since the approval of the first antiretroviral therapy (ART) drug in 1987 [1], massive improvements in treatment strategies have been made, leading to a great improvement in the prognosis for people living with HIV-1 (PLWH) [2]. However, ART is not capable of eliminating the integrated proviruses, which persist in a latent state within infected cells. Consequently, life-long adherence to ART is required as discontinuation of treatment leads to the re-emergence of plasma viremia within weeks [3]. In this way, adherence is a critical determinant of health outcomes and preventing antiretroviral drug resistance development [3–7].

The latent HIV-1 reservoir is defined as a pool of long-lived cells harboring replication-competent but transcriptionally inactive HIV-1 proviruses. Although memory $CD4^+$ T cells are the major cellular reservoir, other immune cells may also contribute to HIV-1 persistence, such as monocytes, macrophages, and dendritic cells [8]. Initiation of ART early in the infection has been shown to limit the size of the HIV-1 reservoir. Early ART initiation and a smaller reservoir have been associated with achieving posttreatment control among PLWH who subsequently interrupt ART [9,10]. In light of this, most functional cure approaches aim at both reducing viral reservoirs and boosting antiviral immunity. Here, we review and discuss the most recent advances of immunotherapy in the clinic to enhance HIV-specific immunity leading to a functional cure for HIV-1.

[a]Department of Clinical, Toxicological and Bromatological Analysis, University of São Paulo, Ribeirão Preto, Brazil, [b]Department of Infectious Diseases, Aarhus University Hospital and [c]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Correspondence to Ole Schmeltz Søgaard, PhD, MD, Aarhus University Hospital, Aarhus 8200, Denmark. Tel: +45 2721 5985; e-mail: olesoega@rm.dk

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KEY POINTS

- Immunotherapeutic approaches have been explored with the goal of enhancing immune responses to effectively control HIV-1 without ART and its potential side effects.
- Newer and innovative strategies for an HIV-1 cure include clinical interventions used in the treatment of hematological malignancies (such as immune checkpoint inhibitors and tyrosine kinase inhibitors).
- The advancement of bNAbs and the development of bi-specific and tri-specific antibodies represent a promising immunotherapeutic strategy in the pursuit of a functional cure for HIV-1.
- Some people treated with bNAbs maintain suppressed plasma viremia after ART is stopped and bNAb plasma concentrations have dropped to sub-therapeutic levels.
- The integration of multiple strategies that target both the innate and adaptive immunity emerges as a promising avenue toward achieving success in a functional cure.

IMMUNOTHERAPEUTIC STRATEGIES

Broadly neutralizing antibodies

Highly potent anti-HIV-1 broadly neutralizing antibodies (bNAbs) neutralize a broad range of different strains of HIV-1 and are the main novel class of therapeutic interventions in ongoing and recent HIV-1 trials. Beyond neutralizing the virus through their Fab domains, a critical function of bNAbs is their ability to exert effector functions mediated through their Fc domains, mediating the clearance of viral particles and infected cells [11]. Several bNAbs are currently in clinical development (summarized in Table 1). These bNAbs differ in their potency, breath, pharmacokinetics, and antiviral activity. Moreover, bNAbs that target different nonoverlapping binding-sites on the HIV-1, including membrane proximal external region (MPER), CD4-binding site, the V1/V2 and V3 loop, and epitopes on gp41 and gp120 have been identified and developed for clinical testing. In addition, bi-specific and tri-specific antibodies have been evaluated.

Monotherapy with a single bNAb generally leads to rapid selection of viral escape variants and subsequent resistance, which can at least be partially prevented by using combinations of bNAbs with different binding-sites or by combining bNAbs with (small molecule) antiretroviral drugs [12,13,14]. Indeed, following three infusions of the two bNAbs 3BNC117 and 10-1074, 76% (13 out of 17) of participants maintained virologic suppression for at least 20 weeks during antiretroviral treatment interruption (ATI) [15▪]. Similarly, Sneller *et al.* [16] demonstrated that up to eight infusions of the same combination of bNAbs (3BNC117 and 10–1074) administered over a period of 24 weeks effectively maintained suppression of plasma viremia in absence of ART (for five out of seven participants) for up to 43 weeks.

One of the limitations of bNAbs is their relatively short *in vivo* half-life. Rapid viral rebound and the emergence of variants are associated with the decay of bNAbs. In light of this, sustaining high and stable concentrations appears crucial for maintaining therapeutic efficacy. To prolong their plasma half-life, long-acting bNAb variants with a LS mutation in their Fc-region have been developed and are now in clinical trials (NCT04250636, NCT04319367, NCT05612178, NCT05300035, NCT05719441, and NCT06031272).

To cover a wider range of HIV-1 variants, and thereby potentially preventing viral escape and the emergence of new resistances, studies are assessing triple combinations of bNAbs that each target distinct epitopes. The first trial of a triple antibody combination in humans evaluated the administration of PGDM1400, PGT121, and VRC07–523-LS. The authors reported that triple bNAb combination was safe and well tolerated. However, despite a rapid decrease in the viral load with the triple bNAb therapy, they observed viral rebound possibly due to preferential replication of viruses harboring resistance mutations against PGDM1400 and PGT121 among viremic individuals not on ART [17▪▪].

In addition to neutralizing free virions and preventing infection of new cells, recent findings suggest that bNAbs may play a crucial role in modulating the immune system by enhancing adaptive HIV-1-specific immune responses (known as a vaccine-like effect). Schoofs *et al.* [18] observed an increase in humoral immunity after the administration of 3BNC117 among viremic individuals. The vaccinal effect was also noted by Niessl *et al.* [19] after concurrent administration of 3BNC117 and 10–1074 in PLWH undergoing ATI. Among all participants in the study (nine out of nine), increases in $CD8^+$ Gag-specific T cell responses were observed, with eight individuals also exhibiting an augmentation in $CD4^+$ T cell responses [19]. Further, in a randomized trial, individuals who received two infusions of 3BNC117 at ART initiation also displayed elevated HIV-1 specific T cell responses compared to individuals who only received ART. Specifically, elevated frequencies of $CD8^+$ Pol- and Gag-specific T cells, along with an enhanced Gag-induced IFN-γ secretion, were demonstrated [20].

The perhaps most surprising finding in many of these bNAb trials is the observation that a minority of trial participants maintain suppressed plasma viremia

Table 1. Summary of current trials of immunotherapy

Clinicaltrials.gov number	Intervention	Status (as of 10 January 2024)	Sponsor/ Collaborators	Phase	Primary endpoint
Broadly neutralizing antibodies (bNAbs)					
NCT03571204	3BNC117 + 10-1074	Completed	NIAID	Phase I	Safety and efficacy
NCT03526848	3BNC117 + 10-1074	Completed	Rockefeller University	Phase I	Safety and antiretroviral activity
NCT04250636	3BNC117-LS + 10-1074-LS	Completed	Rockefeller University	Phase I	Safety, pharmacokinetics and antiviral activity
NCT04871113 (BANNER)	GSK3810109A (formerly N6-LS)	Completed	ViiV Healthcare	Phase IIa	Plasma HIV-1 RNA maximum change from baseline during monotherapy and safety
NCT03205917	PGDM1400 +/−PGT121 +/− VRC07-523LS	Completed	International AIDS Vaccine Initiative	Phase I	Safety, tolerability, pharmacokinetics and antiviral efficacy
GS-US-420–3902	Elipovimab (PGT121-derived)	Completed	Gilead	Phase Ib	Safety and tolerability; pharmacokinetics
NCT02591420	VRC01	Completed	NIAID	Phase I	Safety and virologic effect
NCT04319367 (RIO)	3BNC117-LS + 10-1074-LS	Recruiting	Imperial College London	Phase II	Efficacy
NCT05300035	3BNC117-LS + 10-1074-LS	Not yet recruiting	French National Agency for Research on AIDS and Viral Hepatitis (ANRS)	Phase II	Virological activity
NCT06031272	3BNC117-LS-J + 10-1074-LS-J	Not yet recruiting	ACTG	Phase I	Safety and virologic activity
NCT05612178	3BNC117-LS + 10-1074-LS	Recruiting	NIAID	Phase I	Safety and virologic activity
NCT05719441	VRC07–523LS + PGT121.414.LS	Not yet recruiting	NIAID	Phase II	Safety and virologic activity
NCT03374202	AAV8-VRC07	Enrollment closed	NIAID	Phase I	Safety and Tolerability
NCT03705169	SAR441236	Enrollment closed	NIAID	Phase I	Pharmacokinetics and Safety
Bispecific T cell engagers (BiTEs)					
2021–002008-11	IMC-M113V	Recruiting	Immunocore	Phase I/II	Safety, pharmacokinetics and antiviral activity
IMC-M113V-101 (STRIVE)	IMC-M113V	Completed	Immunocore	Phase I/II	Safety and tolerability
Immune checkpoint inhibitors (ICIs)					
NCT04554966	ABBV-382	Completed	AbbVie	Phase I	Safety and adverse events
NCT06032546	ABBV-382	Recruiting	AbbVie	Phase II	Safety and changes in disease
NCT04223804	ABBV-181 (budigalimab)	Completed	AbbVie	Phase I	Safety, pharmacokinetic and pharmacodynamic
NCT04799353	ABBV-181 (budigalimab)	Completed	AbbVie	Phase I	Safety and administration
NCT05330143	ASC22 (envafolimab)	Recruiting	Ascletis Pharmaceuticals Co., Ltd	Phase II	Safety, tolerance and efficacy
NCT05129189	ASC22 (envafolimab)+ Chidamide	Recruiting	Shanghai Public Health Clinical Center	Phase II	Functional cure
NCT05187429	Nivolumab	Recruiting	University of Melbourne	Phase I/II	Safety, immunogenicity and efficacy
Combinations					
NCT03837756	Lefitolimod + 3BNC117 + 10-1074	Completed	University of Aarhus	Phase IIa	Safety and efficacy
TLR agonist					
NCT02443935	MGN1703 (TLR-9 agonist)	Completed	University of Aarhus	Phase I/II	Safety, tolerability and size of HIV-1 reservoir
NCT02071095	Poly-ICLC (TLR-3)	Completed	The Campbell Foundation, Oncovir, Inc, NIH, NIAID	Phase I/II	Safety and tolerability
NCT03060447	Vesatolimod (TLR-7 agonist)	Completed	Gilead Sciences	Phase I	Safety and efficacy
Cytokines					
NCT04505501	N-803 (IL-15)	Recruiting	Thai Red Cross AIDS Research Centre	Phase II	Safety, tolerability and immunomodulation effect
NCT04340596	N-803 + bNAb (VRC07–523LS and 10–1074)	Recruiting	NIAID	Phase I	Safety, tolerability, and efficacy of N-803 with and without bNAbs
NCT05245292	N-803 + bNAb (3BNC117-LS and 10–1074-LS)	Recruiting	Rockefeller University	Phase I	Safety and antiretroviral activity

Table 1 (*Continued*)

Clinicaltrials.gov number	Intervention	Status (as of 10 January 2024)	Sponsor/ Collaborators	Phase	Primary endpoint
Tyrosine kinase					
NCT05527418	Desatinib	Not yet recruiting	Eva Bonfill	Phase II	Safety, tolerability and antiretroviral activity
NCT05780073	Desatinib	Recruiting	Fundaci Institut Germans Trias i Pujol	Phase II	Safety, tolerability and impact of low-dose Dasatinib

ACTG, AIDS Clinical Trials Group; NIAID, National Institute of Allergy and Infectious Diseases.

after ART is stopped and bNAb plasma concentrations have dropped to sub-therapeutic levels [15▪,21–23]. While posttreatment control has been reported to occur at a low frequency (~3–6%) among people who stop ART [10], the frequency of "postbNAb control" appear to be closer to 15–20% in trials were bNAbs are dosed at ART initiation or into an ATI.

These encouraging findings may suggest that HIV-1 cure strategies involving bNAbs could be further optimized to increase the proportion of individuals experiencing long-lasting ART-free control. In addition, more work is needed to elucidate and harness the potential beneficial effects of bNAbs beyond their ability to neutralize and maintain viral suppression in the absence of ART.

T CELL AND NATURAL KILLER CELL ENGAGERS

As the T cell response appears to be critical in spontaneous control of HIV-1 infection, an attempt to improve cellular responses against HIV-1 has emerged as a promising cure strategy. The bispecific T cell-engaging (BiTE) technology redirects effector T cells to kill HIV-1 infected cells. The BiTE approach was originally developed for the treatment of malignancies and has successfully been applied in patients with non-Hodgkin's lymphoma and B-cell lymphoblastic leukemia [24,25].

Given the success of the BiTE technology in treatment of hematological malignancies, a next generation of bispecific reagents, the immune-mobilizing monoclonal T-cell receptors against viruses (ImmTAVs) have been developed against HIV-1 [26]. ImmTAVs are epitope-specific soluble TCRs linked to an scFv specific for a cytotoxic cell, which, in turn, is redirected to specifically lyse infected cells expressing the target virus-derived epitope presented by human leukocyte antigen (HLA). The first and, so far, only in-human clinical trial investigated a HIV-1 Gag x CD3 soluble TCR ImmTAV (IMC-M113 V; Immunocore Holding plc, Oxfordshire, UK). IMC-M113 V was designed to redirect effector T cells to kill HIV-1 Gag-expressing infected cells [27]. The single-dose component of the study IMC-M113 V was reported to be well tolerated with no reported cytokine release syndrome, neurotoxicity, or SAEs [28]. Following the single-dose step, the trial will proceed to evaluate safety and impact on HIV-1 reservoirs as well as posttreatment control following repeating dosing of IMC-M113 V (EU CT: 2021–002008–11).

Another type of cell engagers referred to as bi-specific killer cell engagers (BiKEs) [29,30] and tri-functional NK cell engager (NKCE) [31], which redirect NK cells to the target cell of interest are also in development. Preclinical results show that the NKCEs are more potent *in vitro* than clinical therapeutic antibodies targeting the same tumor antigens, show no off-target effects, and efficiently control tumor growth in mouse models of solid and invasive tumors. The findings support clinical development of NK cell engagers for next-generation cancer treatment and possibly HIV-1 cure immunotherapy.

PD-1 INHIBITORS

Chronic HIV-1 infection has been linked to exhausted and dysfunctional T cell responses potentially caused by increased expression of immune checkpoints on $CD4^+$ and $CD8^+$ T cells [32,33]. mAbs against immune checkpoints – immune checkpoint inhibitors (ICIs) – have successfully been used in the treatment of cancers [34,35] including in PLWH [36–39]. The safety and efficacy of ABBV-181 (budigalimab), a PD-1 inhibitor, are currently being investigated (NCT04223804 and NCT04799353), and preliminary results indicate good tolerance and immune-mediated viral suppression during ATI in a subgroup of study participants [40]. Another clinical trial will be assessing the combined use of budigalimab and the anti-α4β7 antibody ABBV-382 (NCT06032546).

ICIs have also been combined with other potential HIV-1 curative interventions, like latency reversing agents (LRAs) or therapeutic HIV-1 vaccines. In a clinical trial evaluating the effect of ASC22 (envafolimab, anti-PD-L1 antibody; NCT05129189) and chidamide (an LRA) on the viral reservoir in PLWH, preliminary findings have indicated that the drug combination was well tolerated and led to latency reversal, as evidenced by transient increases in cell-

associated HIV-1 RNA to HIV-1 DNA ratios [41]. Collectively, the current data suggest that the treatment combination holds promise for activating latent HIV-1 reservoir.

TOLL-LIKE RECEPTOR AGONIST

Toll-like receptors (TLRs) are membrane proteins expressed in various immune cells that play an important role in innate and adaptive immunity [42]. TLR7 and 9 are intracellular receptors that recognize viral and bacterial nucleic acids. TLR7/9 signaling rapidly induces the release of cytokines such as IFN-1 and other antiviral factors [43,44]. This, in turn, triggers the activation of various cell types, including NK cells and myeloid dendritic cells (mDCs) [45]. In HIV-1 research, TLR agonists have been investigated for their potential dual effect as LRAs and immune-enhancing agents [46]. Despite promising preclinical results, TLR agonist treatment has not had a significant impact on the size of the viral reservoir in clinical trials [47,48]. Considering the multifactorial challenges of HIV-1 infection, employing a combination of strategies reversing viral latency and enhancing antiviral immune responses may increase the likelihood of achieving a functional cure. In a trial combining AELIX HTI vaccine (HIVACAT T-cell immunogen) with vesatolimod (TLR-7 agonist), vesatolimod was found to significantly enhance plasma cytokines and chemokines [49]. While 33% of participants who received the combination treatment were able to remain without ART for 24 weeks, 24% in the placebo group also did not restart ART for 24 weeks (nonsignificant). Thus, whether the combination of an HIV-1 vaccine with vesatolimod provides a clinical benefit is still unclear.

Finally, Lefitolimod (MGN1703), a TLR-9 agonist was recently investigated in a phase 2a clinical trial designed to evaluate the effectiveness of lefitolimod in combination with two bNAbs (3BNC117 and 10–1074) on time to viral rebound during ATI. Although HIV-1-specific $CD8^+$ T cell responses increased among those who received bNAb and maintained viral suppression, the administration of lefitolimod either alone or in combination with bNAb did not impact time to viral rebound or the HIV-1 reservoir [21]. However, individuals who received bNAbs demonstrated prolonged ART-free virologic control during the ATI, suggesting that bNAbs may be an important component in HIV-1 cure strategies.

CYTOKINE THERAPY

In addition to TLR agonists, various recombinant cytokines have been studied alone or in conjunction with other interventions, for their impact on immune functions and the viral reservoir size. N-803, a superagonist of IL-15, has been shown to reverse latency *in vitro* and promote the survival, proliferation, and function of T and NK cells [50,51]. Results from a clinical trial showed that N-803 led to enhanced proliferation and activation of NK and T cells, along with a modest increase in plasma HIV-1 RNA [52]. Combination interventions with N-803 are now on-going. In a single arm study (NCT05245292), participants receive two bNAbs (3BNC117-LS and 10–1074-LS) at week 0 and then N-803 at week 1 and every 3 weeks (eight doses in total). In addition, a two-arm study (NCT04340596) will compare N-803 alone to N-803 plus two bNAbs (VRC07–523LS and 10–1074).

Initially, it was observed that IL-7 induces proviral reactivation in $CD4^+$ T cells [53]. However, this effect was associated with the expansion of infected cells, thereby contributing to the persistence of HIV-1 without impacting latency reversal [54,55]. Although IL-7 has failed to reverse viral latency, it possesses immunomodulatory properties by enhancing the recognition and killing of $CD8^+$ T cells.

Indeed, a plasmid DNA vaccine formulation containing HIV-1 Gag with IL-7 or IL-15 increased central Gag-specific memory and effector function of $CD8^+$ T cells. A single-arm 5 stage study evaluated 10 individuals on ART who sequentially received IL-12 adjuvanted p24CE DNA prime, IL-12 adjuvanted DNA boost (p24CE plus p55gag), MVA/HIV62B, single dose of two bNAbs (VRC07–523LS and 10–1074) and lefitolimod before receiving a second dose of two bNAbs the day prior to ATI (NCT04357821). Preliminary findings from revealed an average of 15 weeks until viral rebound after the last bNAb administration which is in line with previous studies. Seven of the 10 participants were reported to have some degree of virological control with one of the 10 individuals having less than 20 HIV-1 RNA copies/ml for more than 1 year [56].

Finding the optimal balance between activating the immune system to target HIV-1 and avoid excessive inflammation is critical. It is worth noting that while a multitherapy approach may be a promising strategy for achieving functional HIV-1 cure, it may also introduce complexities in terms of safety and the potential for drug-drug interactions.

TYROSINE KINASE

Tyrosine kinase inhibitors are used in the treatment of chronic myeloid leukemia (CML), but they are also being evaluated as an adjunct therapy to ART as a means to reduce the viral reservoir [57–59]. Preliminary findings indicate that dasatinib may

reduce HIV-1 replication *in vitro*, possibly by inhibiting the activation and proliferation of $CD4^+$ T cells, the major target of HIV-1 [60]. This inhibition, in turn, can hinder the spread of the virus and preserve the number and function of T cells. SAMHD1, one of the targets of dasatinib and induced by HIV-1, is an essential cellular factor for viral replication. Unphosphorylated SAMHD1 (active form) decreases the availability of intracellular dNTPs, preventing cDNA synthesis through reverse transcription and subsequent integration into the host cell genome [59,61]. Therefore, the use of a tyrosine kinase inhibitor in combination with ART could be a way to reduce the viral reservoir [62]. There are two ongoing clinical trials aimed at investigating dasatinib in combination with ART. The single-center, randomized, clinical trial (NCT05780073) focuses on the impact of dasatinib on inflammation, immune activation, and size of the HIV-1 reservoir during 24 weeks of adjunctive treatment (whist continuing ART). In the trial (NCT05527418), individuals with recent HIV-1 infection who are ART-naive will receive dasatinib for 4 weeks prior to starting ART. Subsequently, concurrent initiation of ART with dasatinib will continue until week 12. The study will assess safety and tolerance, as well as the level of inflammation and changes in the size of the HIV-1 reservoir. The advancement of innovative strategies aimed at reducing the reservoir in the early stages of infection could aid in the development of a functional cure.

CONCLUSION

The safety and efficacy of bNAbs, immunomodulators, latency-reversing agents, and immune adjuvants alone or in combinations are increasingly being evaluated in clinical trials. Very encouraging signals have been picked in recent trials, in particular related to bNAb treatment but several challenges still persist on the path towards a functional cure. These challenges include the identification of the optimal dosage and the timing to intervention initiation, addressing the diversity of HIV-1 strains, reducing the size of the HIV-1 reservoir, and safety of novel drug combinations. Addressing these complexities remains crucial for ongoing research to find a functional cure for HIV-1.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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