Immunotherapeutic approaches to HIV cure and remission

Lee MJ[1], Fidler S[1,2], Frater J[3,4]

1. Department of Infectious Disease, Imperial College London, London, UK
2. Imperial College NIHR BRC, London, UK
3. Peter Medawar School of Pathogen Research, Nuffield Department of Medicine, University of Oxford, Oxford, UK
4. Oxford NIHR BRC, Oxford, UK

Corresponding author:

Dr Ming J. Lee
Department of Infectious Disease, Imperial College Clinical Trials Centre, St Mary's Hospital, Praed Street, W2 1NY
Email: minglee@doctors.org.uk

Funding acknowledgement

This article is a discussion document and therefore represents the views of the co-authors, there is no specific funding associated with this work. MJL acknowledge the Bill and Melinda Gates Foundation, which supports his salary through the university. JF and SF acknowledge funding from Oxford and Imperial College NIHR BRC respectively, which support their salaries through their university.

Abstract (200 words)

Purpose of review

Despite improvements in the effectiveness of antiretroviral therapy, there are still unmet needs for people living with HIV which drive the search for a cure for HIV infection. The goal of this review is to discuss the challenges and recent immunotherapeutic advances towards developing a safe, effective and durable cure strategy for HIV.

Recent findings

In recent years, advances have been made in uncovering the mechanisms of persistence of latent HIV and in developing more accurate assays to measure the intact proviral reservoir. Broadly neutralising antibodies and modern techniques to enhance antibody responses have shown promising results. Other strategies including therapeutic vaccination, latency reversal agents, and immunomodulatory agents have shown limited success, but newer interventions including engineered T cells and other immunotherapies may be a potent and flexible strategy for achieving HIV cure.

Summary

Although progress with newer cure strategies may be encouraging, challenges remain and it is essential to achieve a high threshold of safety and effectiveness in the era of safe and effective antiretroviral therapy. It is likely that to achieve sustained HIV remission or cure, a multi-pronged approach involving a combination of enhancing both adaptive and innate immunity is required.

Keywords: HIV, cure, immunotherapies, bNAb, gene-editing

Introduction

Improvements in antiretroviral therapy (ART) have led to excellent prognosis for people living with HIV (PWH), preventing onward transmission and disease progression. Despite these advances, there are still unmet needs for people living with HIV which drive the search for a cure. Most ART is oral medication requiring daily adherence. Stigma and treatment fatigue associated with taking daily ART remains a concern for many people with HIV[1]. Although the development of long-acting ART may address some of these issues, nonadherence or delayed doses leading to treatment resistance remains an issue, and the costs of delivery may still prove prohibitive particularly in resource-limited settings [2]. Thus the search for a cure remains a priority. A cure may be 'functional', where there is long-term control of HIV replication without treatment, or 'sterilising', where there is complete elimination of HIV provirus from the body.

Cure strategies can be divided into two basic approaches - targeting the provirus directly, or enhancing HIV-specific immunity. The former approach which includes aiming to limit the size or characteristics of the HIV reservoir, preventing viral replication, and silencing of the HIV provirus ('block and lock'), is covered in a recent review by Vansant et al [3], and will not be covered further here.

In this review, we will discuss developments in immunotherapeutic approaches to enhance HIV-specific immune responses, as summarised in Figure 1.

The latent HIV reservoir

Over the past few years, progress has been made in understanding the mechanisms of persistent infection, and possible strategies towards cure. The HIV reservoir refers to a long-lived latently infected pool of CD4 positive cells which contain HIV DNA integrated into their genome. In the absence of expression of viral antigens these cells are invisible to effective immune responses and persist in a dormant state in the presence of ART. Figure 2 summarises the mechanisms of persistence and latency discussed in this section.

Memory CD4 T cells form the majority of the latently infected cell population [4]. The transition from an effector to quiescent memory phenotype may allow the establishment of HIV latency, through temporary up-regulation of CCR5 expression and rapid downregulation of HIV gene transcription, while allowing completion of the HIV life cycle through integration [5]. Clonal proliferation also plays a significant role in reservoir persistence [6], which needs to be addressed in cure strategies. Immune checkpoint molecules (e.g. PD-1, CTLA-4, LAG3, TIGIT) dampen T cell activation, and may be associated with HIV latency [7]. Other cellular reservoirs have been described, including myeloid cells such as monocytes, tissue-resident macrophages, and follicular dendritic cells [8], but there is on-going discussion around their significance, with most cure approaches still directed towards the CD4+ T-cell reservoir.

Other mechanisms of persistence include avoidance of cytotoxic T lymphocyte (CTL) mediated cell death; latently-infected cells that survive ART initiation may as a result have a greater ability to persist after peak viraemia[9]. Cellular resistance mechanisms may include upregulation of Fas Ligand on infected cells leading to apoptotic cell death of uninfected CTLs [10], the up-regulation of BCL-2, an inhibitor of apoptosis [11], or distraction of CTL through defective virion 'decoys' [12]. The vast majority (~98%) of HIV proviral DNA is defective [13] with fatal defects such as deletions or

hypermutations. Although these defective proviruses are unlikely to contribute to the replication-competent latent HIV reservoir, they may be transcriptionally active, and express proteins that may distract and reduce CTL-mediated cytotoxicity of cells containing replication-competent virus [12]. The ability to find and measure replication-competent virus amongst the vast amount of defective proviral genome has implications for evaluating cure strategies. Recently, novel PCR assays such as the high-throughput intact proviral DNA assay [14] have replaced the previous gold standard quantitative viral outgrowth assay due to advantages over turnover, cost, and labour requirements. Whilst multiple assays are available to characterise and quantify the HIV reservoir, none to date have been able to accurately predict viral control (to < 50 copies HIV RNA/ml) after interruption of ART.

After treatment interruption, recrudescence of rebound plasma viraemia from activation of the latent reservoir is expected in the absence of viral control. Rebounding viral populations are diverse and have been found in multiple tissue compartments [15]. Analytical treatment interruption (ATI) is currently the only effective way to test the efficacy of HIV therapeutic interventions for post-treatment virological control as there are no validated predictive biomarkers [16]. Consensus recommendations for conducting ATI in HIV research trials have been reported to minimise risk to research participants [16], and further risk mitigation strategies should be considered when designing ATI studies to address the challenges brought by the COVID-19 pandemic [17].

Clinical strategies for HIV cure

Broadly neutralising antibodies

Neutralising antibodies prevent HIV from infecting host cells - blocking virus entry through disrupting virus-receptor interactions - and facilitate antibody-dependent cell mediated cytotoxicity. Due to genetic diversity and error-prone viral replication allowing viral escape from antibody neutralisation, high levels of somatic hypermutation are required to generate broadly neutralising antibodies (bNAbs) [18][16][17]. Development of high-throughput neutralisation assays and single-cell antibody cloning techniques has led to the possibility of generating potent bNAbs with greater neutralisation breadth to viral strains [19].

The target of all bNAbs is the HIV envelope glycoprotein (Env), which is heavily glycosylated, forming a 'glycan shield' that protects the virus against humoral responses which recognises glycans as 'self'[20]. Recent studies have confirmed the concept of 'glycan holes or the absence of particular proteins in env, which may offer exposed proteins as a relatively easier target [21]. For example, the use of an immunogen with a filled glycan hole at residue 241, and removal of surrounding glycans was found to redirect neutralising antibody responses to the newly unmasked epitopes [22]. The C3/465 glycan hole cluster has also been shown to be a major neutralising target in prevention of SHIV mucosal infection [23].

bNAbs with different HIV Env targets, including long-acting antibody variants ('LS' variants) have been reported to be well tolerated with infrequent adverse events [24–27]. However, studies of bNAb monotherapy, using 3BNC117 [28], VRC01 [26] , and 10-1074 [23], have shown viral rebound, and development of resistance through the selection of pre-existing resistant viral populations after bNAb levels wane. A combination of 3BNC117 and 10-1074 administered with an ATI in nine individuals with latent reservoirs sensitive to both bNAbs maintained viral suppression for a median of 21 weeks [28]. Resistance to both bNAbs did not arise in any participants, supporting the use of combination bNAbs

for greater effectiveness against HIV compared to monotherapy. Bispecific bNAbs, able to target V2, and V3 glycan regions using the same antibody, were more potent compared to the individual parent antibodies *in vitro* [27] and these multi-specific antibodies may further improve the effectiveness of bNAbs. Planned or ongoing trials of combination bNAbs registered on clinicaltrials.gov are summarised in Table 1[31].

A subset of human [28] and macaques [29] receiving combination bNAbs have demonstrated unexpectedly long-term viral remission, greater than 30 months and 4 years respectively, raising the possibility of antibody-mediated CD8 T-cell responses contributing to prolonged control. This effect may be due to increased HIV *gag*-directed T-cell immunity, and MIP1-β-expressing CD8 T cells [30]. BNAbs may also enhance antibody-directed cellular cytotoxicity (ADCC) in a synergistic mechanism - binding to different viral Env trimer epitopes exposes CD4-induced epitopes for further host antibody-ADCC responses [31]. There is still debate around the existence of this bNAb-induced 'vaccinal' response, and results from ongoing randomised placebo-controlled trials of combination bNAbs may provide further insight to determine if these immunological changes are indeed bNAb driven.

When investigating the effect of bNAbs on the HIV reservoir in the gut, where the largest HIV reservoir is present, antibodies may not achieve concentrations as high as in serum. In HIV-negative individuals, VRC01 antibodies in rectal and vaginal tissue were measured to be 10-fold lower compared to serum [32]. It needs to be determined if this will be the case in HIV-positive individuals; the tissue concentrations of bNAbs in PWH may achieve even lower concentrations due to viral antigen present in tissue providing an antigen sink effect. However for VRC01, the lower tissue antibody concentration compared to plasma, still maintained HIV neutralisation when tissue form VRC01 recipients were challenged with HIV *ex vivo* compared to controls not receiving VRC01.

For immune-privileged anatomical sites such as the central nervous system (CNS), intravenously infused antibodies may penetrate the blood brain barrier (BBB) poorly, as seen in non-human primate models [32]. However, data from human trials are lacking [33]. The use of modified Fc bNAbs containing 2 amino acids substitution M428L/N434S (commonly shortened to LS), increases bNAb half-life *in vivo* by increasing affinity for the neonatal Fc receptor [34], leading to higher serum levels, and hypothetically may also allow accumulation to higher concentrations in tissue. The use of nanocapsules may improve CNS delivery of bNAbs in non-human primates [33] and may provide better CNS penetration options.

The development of an accurate, simplified assay with rapid turnaround to predict viral resistance to bNAb would be essential to determine the utility of bNAbs in clinical practice. The use of quantitative viral outgrowth assays and TZM-bl neutralisation assays are time consuming and expensive, and may miss replication-competent provirus that remains latent during stimulation [35]. Novel machine learning algorithms used to predict bNAb susceptibility based on *Env* sequences have achieved high overall prediction accuracies of bNAb resistance [36–39] and may allow prediction of bNAb therapy efficacy similar to resistance testing for antiretroviral therapy.

Recent advances in the delivery of bNAbs may provide promising ways to elicit high long-term bNAb concentrations *in vivo*, such as the use of CRISPR/Cas9 to edit mice or human B cells to express mature bNAbs [40,41]. Another approach is the use of viral vectors such as adeno-associated virus (AAV) delivery of anti-HIV monoclonal antibodies, which generated sustained viral control in 4 monkeys, however anti-drug antibodies (ADA) limited the delivery of these bNAbs [42]. In human trials, 5 out of

8 HIV-positive individuals produced functional VRC07 4-6 weeks after AAV administration which remained at, or above, the 4-6 week peak at 1 year in 3 out of 5 individuals [43].

Therapeutic vaccination

Rapid rates of error-prone HIV replication can result in immune escape mutations to both T cells and antibody responses, through escape mutations resulting in avoidance of antigen recognition [44] and processing [45] potentially challenging bNAb efficacy and the therapeutic vaccines. Various therapeutic vaccine classes aim to boost HIV-specific T-cell responses in terms of magnitude or breadth of antigen specificity, with the aim of targeting and killing cells containing HIV, including potentially those in the reservoir. These include inactivated virus, subunit vaccines with recombinant envelope glycoprotein rgp160, DNA vaccines, viral vectors (modified vaccinia Ankara (MVA), adenovirus, vesicular stomatitis virus, canary pox virus), RNA vaccines, lentiviral vectors and dendritic cell vehicles [46]. These vaccine efforts, while safe, have predominantly proven to induce only limited effect on viral control. For example, the use of a therapeutic vaccine regimen comprising a multi-antigen plasmid DNA vaccine, followed by an attenuated live viral vector containing HIV *gag* gene had no effect on the kinetics of viral rebound or HIV reservoir size after ATI [47]. However, recent promising results from the AELIX-002 trial using HIVACAT T cell immunogen vaccines (HTI) reported safe and highly immunogenic responses following administration of a combination of DNA.HTI, MVA.HTI, and ChAdOx1.HTI vaccines in early treated people living with HIV, with 40% of vaccine-recipients compared to 8% of placebo-recipients remaining off ART for 22 weeks [48]. The novel HTI design approach uses T cell response data from more than 1000 individuals with HIV, to direct the T cell response to the most vulnerable sites of HIV[54].

Progress in mRNA technology for therapeutic HIV vaccination may re-energise the therapeutic vaccine field. The improved safety, efficacy, and ease of manufacturing compared with previous vaccine technology make them attractive vaccine candidates, as reviewed by Mu et al [49]. One advantage may be that the constant production of mRNA-encoded immunogens leads to a slow but prolonged antigen delivery *in vivo*, with the potential to improve germinal centre and neutralising antibody responses *in vivo* [50].

Latency reversal agents (LRAs) & 'Kick and Kill' approaches

One of the challenges to immune elimination of the HIV reservoir is the lack of expression of target antigens by latently infected cells. To address this, the 'kick and kill' or 'shock and kill' strategy aims to activate latent cells to express HIV antigen using LRAs, allowing CTL or NK cells to identify and eradicate HIV-containing reservoir cells. Early LRAs included global T-cell activators such as OKT3 and interleukin 2 [51], but were limited by severe toxicities [52]. Subsequent classes of LRA include epigenetic LRAs such as histone deacetylase inhibitors (HDACi) (vorinostat, panobinostat and romidepsin); signal agonist LRAs including activators of protein kinase C (PKCa), Bryostatin-1; IL-15 superagonists (e.g. N803); toll-like receptor agonists; molecules which mimic second mitochondrial activator of caspases (SMAC mimetics or SMACm) and recently, stimulator of interferon genes (STING) agonists.

The RIVER study, a randomised trial of vorinostat, a histone deacetylase inhibitor LRA, and a therapeutic HIV vaccine (ChAdV63. HIVconsv and MVA.HIVconsv) did not show any difference in measures of the HIV reservoir despite evidence of augmented HIV-specific CD4 and CD8 T cell responses [53]. Participants did not interrupt ART, and although the lack of any impact on reservoir

size using different assays is circumstantial evidence, an impact on time to viral rebound cannot be proven. Similarly, trials of other LRAs including romidepsin, panobinostat and valproic acid have not shown significant or meaningful changes in the size of the viral reservoir [54].

Potential explanations for the lack of success with LRAs include an insufficiently robust 'kick', as even the most potent LRAs are not able to activate more than a fraction of the latent reservoir containing cells *ex vivo* [55], and LRAs used in clinical trials are often used at lower doses to avoid the systemic inflammation and off-target toxicities associated with these compounds [56]. Some LRAs also impair NK [57] and CTL function [58], and there is also evidence that latent reservoir cells exhibit inherent resistance to CD8-mediated killing even in the presence of functional cellular immunity [59].

The search for safer but adequately potent LRA candidates is ongoing. TLR-7 agonists [60–63], TLR-9 agonists [64], TLR-3 agonists (Poly-ICLC) [65], Protein Kinase C agonists (bryostatin-1) [66] have all been unable to consistently and significantly reverse latency. STING agonists were shown to activate latently infected cells, increasing SIV RNA and decreasing SIV DNA levels *ex vivo* in macaque peripheral blood mononuclear cells (PBMCs) [67].

The SMACm AZD5582 was shown to induce latency reversal in two animal models with minimal side effects and better HIV-specificity [68]. Depletion of CD8+ lymphocytes to remove CD8-mediated viral suppression has been investigated in combination with N-803, leading to a synergistically greater effect leading to more robust viral reactivation in macaques compared to CD8 depletion or N-803 administration alone [69]. Similarly, CD8 lymphocyte depletion augmented the efficacy of the SMACm AZD5582 in SIV-infected rhesus macaques [70], suggesting that antagonising the CD8-mediated mechanisms of viral suppression may boost the effects of LRAs. Should SMAC mimetics be combined with a potent cytotoxic reservoir targeting agent, one might envisage the increasingly ineffective 'kick and kill' approach being replaced with a new 'SMAC and whack' strategy.

Immune modulation for enhanced T-cell function

CD8 T cell exhaustion, characterised by cellular markers such as PD-1, CTLA-4, LAG-3, TIGIT or Tim-3, likely leads to the immune dysregulation associated with HIV [71]. These inhibitory markers contribute to latency, and may be amenable to therapeutic targeting to achieve latency reversal. Treatment of rhesus macaques with anti-PD-1 and anti-CTLA-4 antibodies appeared to induce reactivation and subsequent reduction of the reservoir including decreased intact proviral measurements [72]. However, autoimmune adverse effects may limit use of ICBs in future trials [73], and there is increasing evidence for some irreversibility of immune exhaustion based on epigenetic approaches[74,75].

Engineering enhanced T responses

Two individuals have achieved sustained HIV remission and likely 'cure' following haematopoietic stem cell transplant (HSCT) from donors with homozygous CCR5Δ32 mutations [76,77]. However, the high one year mortality rate (41-44%) and complication rate [78] suggest HSCT is not a viable treatment option for most people living with HIV, without another clinical indication for HSCT. But these cases lend support to engineered T-cell approaches through gene therapy approaches, including removal of CCR5 receptors to prevent HIV cell entry, or modifying chimeric antigen receptors (CAR) in CAR-T cells for augmented HIV-specific CTL responses.

Developments in CAR-T cell technology have been directed to increased potency and overcoming viral antigen escape. BNAb-based chimeric antigen receptors recognise a breadth of HIV strains (over 95%) through targeting conserved sites in the Env protein [79], and bispecific chimeric antigen receptors improve targeting of conserved epitopes exposed through simultaneous binding of CD4 and gp120 [80]. The use of a universal CAR-T cell platform (*convertible*CAR-T cells), able to bind to a multitude of bNAbs, allows a single CAR-T cell infusion to be paired with different antibodies for greater breadth of activity. They may be introduced in an inert state with the ability to be turned 'on' with the appropriate activation and proliferation signals [81]. Another development is the use of stem cell-derived CAR T-cells, which can produce CAR T-cells that physiologically expand without the need for *ex vivo* expansion. They have been shown to persist in tissue-associated viral reservoirs for nearly 2 years in macaque models, and may provide an effective long-lasting scalable solution for CAR-T cell delivery [82].

Defining the ideal cure

A cure or remission strategy should be safe and portable. It should achieve long-term viral suppression (at least 6 months after stopping ART), negate any risk of onward viral transmission, and ideally protect against re-infection. Finally, the cure must be affordable to allow access to those with the highest need, often living with HIV in low resource settings with multiple challenges to sustain ART drug stocks [83].

Limitations and challenges for future therapies

While the goal is to achieve a safe, effective, and durable cure for HIV, ART is safe, relatively cheap and with fewer barriers for implementation compared to current cure strategies. Therefore, it is imperative that a cure strategy meets a high threshold of safety and efficacy to provide a viable alternative to currently available ART, which may provide a barrier for future research. In the example of CAR-T cells, these thresholds may differ from their use in oncology treatment where alternatives have a greater toxicity profile, and the presence of moderate or severe adverse events may not be tolerable for PWH in the presence of safer alternatives. Other challenges towards HIV cure remain, such as the search for improved markers or assays of latency to reduce the need for treatment interruptions as well as a robust marker for effective HIV-specific immune responses.

Conclusion

It is likely that to achieve sustained HIV remission or cure, a multi-pronged approach involving a combination of enhancing both adaptive and innate immunity is required. Although this review is not exhaustive of all current immunotherapeutic approaches, it provides an overview of promising developments within the field towards a safe, effective, and durable HIV cure.

Figure 1. Diagram summarising immunotherapeutic strategies targeting the latent HIV reservoir.

Figure 2. The latent HIV reservoir and mechanisms of persistence.

Table 1. Summary of current or future clinical trials involving combination bNAbs registered on clinicaltrials.gov [31]

Trial registration number	Intervention	Study design	PI, Sponsor	Start date	Primary endpoint
Trials assessing viral control as the primary outcome					
NCT03837756 TITAN	bNAbs: 3BNC117, 10-1074 TLR9 agonist: Lefitolimod,	Phase II randomised placebo-controlled double blinded study n = 48	PI: Søgaard, Aarhus University Hospital, Denmark	May 2019	Time to HIV viral load >10 000 copies/ml x3 or end of ATI
NCT03707977	bNAbs: VRC01-LS, 10-1074	Phase I/II open label non-randomised trial in children n = 40	PI: Shapiro, Kuritzkes, Licterfield, National Institute of Allergy and Infectious Diseases, USA (Study in Botswana)	Jun 2019	Safety Proportion with HIV viral load <400 copies/ml Proportion with HIV viral load <40 copies/ml
NCT03588715 BEAT-2	bNAbs: 3BNC117, 10-1074 Peg-IFN-a2b,	Phase I randomised open-label trial n = 21	PI: Montaner, University of Pennsylvania, USA	Jun 2020	Safety Frequency of HIV viral load < 50 copies/ml at week 8 after ATI Innate activation
NCT04250636	bNAbs: 3BNC117-LS, 10-1074-LS	Phase I open label single arm study n = 10	PI: Caskey, Rockefeller University, USA	Aug 2020	Safety Pharmacokinetics Decline in HIV viral load through week 4
NCT04357821	bNAbs: VRC07-523LS, 10-1074, Vaccines: IL-12 adjuvanted p24CE DNA prime, IL-12 adjuvanted DNA boost, MVA/HIV62B boost, TLR9 agonist: Lefitolimod	Phase I/II Single group open label combination intervention trial n = 20	PI: Deeks, University of California, USA	Aug 2020	Safety Proportion achieving post treatment control
NCT04319367	bNAbs: 10-1074-LS 3BNC117-LS	Phase II randomised placebo controlled double blinded study n = 72	Fidler, Imperial College London, UK	May 2021	Time to HIV viral rebound within 36 weeks of analytical treatment interruption.

NCT04340596	bNAbs: VRC07-523LS 10-1074 Il-15 superagonist: N-803	Phase I randomised open-label trial. n = 46	Wilkin, National Institute of Allergy and Infectious Disease, USA	May 2021	Safety, number of N-803 doses completed, proportion of participants with suppressed HIV viral load
NCT04983030	bNAbs: PGT121, PGDM1400, VRC07-523LS Vaccines: Ad26.Mos4.HIV MVA-BN-HIV	Phase I/II randomised double blinded study n = 36	PI: Juelg, Beth Israel Deaconess Medical Centre, USA	Aug 2021	Safety, T-cell and antibody responses, Proportion with HIV viral load <1000 copies/ml
Trials assessing safety as the primary outcome					
NCT03571204	bNAbs: 3BNC117, 10-1074	Phase I triple-blinded randomised placebo-controlled trial n = 50	PI: Sneller, National Institutes of Health Clinical Centre, Maryland, USA	Sep 2018	Safety Tolerability
NCT03554408	bNAbs: 10-1074-LS, 3BNC-117-LS	Phase I, dose escalation, first in man in HIV-negative and HIV-positive individuals. n = 75	Caskey, Rockefeller University, USA	Jun 2018	Safety and tolerability
NCT04173819	bNAbs: 3BNC117-LS 10-1074-LS	Phase I/II Randomised double-blinded placebo controlled trial n = 225	PI: Caskey, Rockefeller University, USA	Jan 2019	Safety Pharmacokinetics
NCT03705169	Trispecific bNAb SAR441236	Phase I randomised, double blinded study n = 84	PI: Tsibris, Kuritzkes, Tebas, National Institute of Allergy and Infectious Diseases, USA	Apr 2019	Safety, pharmacokinetics
NCT03875209	Bispecific bNAb: 10E8.4/iMab	Phase I randomised triple blinded study n = 63	PI: Ho, Bill and Melinda Gates Foundation, International AIDS Vaccine Initiative, USA, The Emmes Company, LLC	Apr 2019	Safety
NCT04811040	bNAbs: 3BNC117-LS (GS-5423) 10-1074-LS (GS-2872) Capsid inhibitor: Lenacapavir	Phase I randomised double blinded study n = 50	PI: Gilead Sciences	Apr 2021	Safety, Efficacy

Key points:

- A cure should be safe, affordable, portable, achieve long-term viral remission, negate any risk of onward viral transmission, and ideally protect against re-infection.
- Developments in the field of immunotherapeutics for HIV cure and remission include broadly neutralising antibodies with promising results.
- Other strategies including therapeutic vaccination, latency reversal agents, and immunomodulatory agents have shown limited success, but newer interventions including engineered T cells may be a potent and flexible strategy for achieving HIV cure.

Acknowledgements:

Financial support and sponsorship: This article is a discussion document and therefore represents the views of the co-authors, there is no specific funding associated with this work. MJL acknowledge the Bill and Melinda Gates Foundation, which supports his salary through the university. JF and SF acknowledge funding from Oxford and Imperial College NIHR BRC respectively, which support their salaries through their university.

Conflicts of interest:

MJL has received travel grants and honoraria from Gilead Sciences and Viiv Healthcare not related to this work.

References

1. Katz IT, Ryu AE, Onuegbu AG, et al: **Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis.** *Journal of the International AIDS Society* 2013, **16**.

2. *Thornhill J, Orkin C: **Long-acting injectable HIV therapies: the next frontier:** *Current opinion in HIV and AIDS* 2021, **16**:98–105.

   Comprehensive review of current and future long-acting injectable HIV therapies including the use of broadly neutralising antibodies.

3. *Vansant G, Bruggemans A, Janssens J, Debyser Z: **Block-And-Lock Strategies to Cure HIV Infection**. *Viruses* 2020, **12**.

   Recent review covering block and lock strategies for HIV cure.

4. Finzi D, Hermankova M, Pierson T, et al.: **Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy**. *Science (New York, NY)* 1997, **278**:1295–1300.

5. Shan L, Deng K, Gao H, et al.: **Transcriptional Reprogramming during Effector-to-Memory Transition Renders CD4+ T Cells Permissive for Latent HIV-1 Infection**. *Immunity* 2017, **47**:766.

6. Reeves DB, Duke ER, Wagner TA, Palmer SE, Spivak AM, Schiffer JT: **A majority of HIV persistence during antiretroviral therapy is due to infected cell proliferation**. *Nature Communications 2018 9:1* 2018, **9**:1–16.

7. Fromentin R, Bakeman W, Lawani M, et al.: **CD4+ T Cells Expressing PD-1, TIGIT and LAG-3 Contribute to HIV Persistence during ART**. *PLoS pathogens* 2016, **12**.

8. Wong ME, Jaworowski A, Hearps AC: **The HIV Reservoir in Monocytes and Macrophages**. *Frontiers in Immunology* 2019, **10**:1435.

9. * Leyre L, Kroon E, Vandergeeten C, et al.: **Abundant HIV-infected cells in blood and tissues are rapidly cleared upon ART initiation during acute HIV infection**. *Science translational medicine* 2020, **12**.

   Study reporting most infected cells during acute HIV infection are rapidly cleared after antiretroviral therapy initiation, and remaining infected cells present after peak viraemia have a greater ability to persist.

10. Xu X-N, Screaton GR, Gotch FM, Dong T, Tan R, Almond N, Walker B, Stebbings R, Kent K, Nagata S, et al.: **Evasion of Cytotoxic T Lymphocyte (CTL) Responses by Nef-dependent Induction of Fas Ligand (CD95L) Expression on Simian Immunodeficiency Virus–infected Cells**. *Journal of Experimental Medicine* 1997, **186**:7–16.

11. Ren Y, Huang SH, Patel S, et al.: **BCL-2 antagonism sensitizes cytotoxic T cell–resistant HIV reservoirs to elimination ex vivo**. *The Journal of Clinical Investigation* 2020, **130**:2542–2559.

    This study show overexpression of BCL-2 associated with CD4 T cells which survive CTL killing, and the use of BCL-2 antagonists with a combination of LRAs, T-cells was able to deplete viral reservoirs *ex vivo*.

12. Imamichi H, Smith M, Adelsberger J, et al.: **Defective HIV-1 proviruses produce viral proteins**. *Proceedings of the National Academy of Sciences of the United States of America* 2020, **117**:3704–3710.

This paper reports the mechanism of defective proviruses, although not replication competent, are still able to express proteins that may distract and reduce efficacy of CTL-mediated responses.

13. Bruner KM, Murray AJ, Pollack RA, et al.: **Defective proviruses rapidly accumulate during acute HIV-1 infection**. *Nature Medicine* 2016, **22**:1043–1049.

14. Bruner KM, Wang Z, Simonetti FR, et al.: **A quantitative approach for measuring the reservoir of latent HIV-1 proviruses**. *Nature* 2019, **566**:120–125.

15. **Chaillon A, Gianella S, Dellicour S, et al.: **HIV persists throughout deep tissues with repopulation from multiple anatomical sources**. *Journal of Clinical Investigation* 2020, **130**:1699–1712.

A unique study of multiple anatomical sites exploring the location of the HIV latent reservoir in tissue compartments, and the emergence of clonal HIV populations in the blood after cessation of therapy.

16. Julg B, Dee L, Ananworanich J, et al.: **Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting**. In *The Lancet HIV*. . Elsevier Ltd; 2019:e259–e268.

17. * Fidler S, Lewin S, Deeks S, et al.: **HIV cure research in the time of COVID-19 - Antiretroviral therapy treatment interruption trials: A discussion paper**. *Journal of virus eradication* 2021, **7**.

This paper discusses the challenges, ethical and practical considerations of conducting HIV cure trials involving treatment interruptions in the context of the SARS-Cov-2 pandemic.

18. Bhiman JN, Anthony C, Doria-Rose NA, et al.: **Viral variants that initiate and drive maturation of V1V2-directed HIV-1 broadly neutralizing antibodies**. *Nature medicine* 2015, **21**:1332.

19. Sok D, Burton DR: **Recent progress in broadly neutralizing antibodies to HIV**. *Nature Immunology* 2018, **19**:1179–1188.

20. Stewart-Jones G, Soto C, Lemmin T, et al.: **Trimeric HIV-1-Env Structures Define Glycan Shields from Clades A, B, and G**. *Cell* 2016, **165**:813–826.

21. McCoy L, van Gils M, Ozorowski G, et al.: **Holes in the Glycan Shield of the Native HIV Envelope Are a Target of Trimer-Elicited Neutralizing Antibodies**. *Cell reports* 2016, **16**:2327–2338.

22. Ringe R, Pugach P, Cottrell C, et al.: **Closing and Opening Holes in the Glycan Shield of HIV-1 Envelope Glycoprotein SOSIP Trimers Can Redirect the Neutralizing Antibody Response to the Newly Unmasked Epitopes**. *Journal of virology* 2019, **93**.

23. * Charles T, Burton S, Arunachalam P, et al.: **The C3/465 glycan hole cluster in BG505 HIV-1 envelope is the major neutralizing target involved in preventing mucosal SHIV infection**. *PLoS pathogens* 2021, **17**.

This paper demonstrates the immunisation of rhesus macaques with the immunogen BG505 SOSIP.664 elicited a high titre, protective neutralising antibody response targeting a glycan hole proximal to residue 465.

24. Caskey M, Klein F, Lorenzi JCC, et al.: **Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117**. *Nature* 2015, **522**:487–491.

25. Ledgerwood JE, Coates EE, Yamshchikov G, et al.: **Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults**. *Clinical & Experimental Immunology* 2015, **182**:289–301.

26. Caskey M, Schoofs T, Gruell H, et al.: **Antibody 10-1074 suppresses viremia in HIV-1-infected individuals**. *Nature medicine* 2017, **23**:185.

27. *Gaudinski M, Houser K, Doria-Rose N, et al.: **Safety and pharmacokinetics of broadly neutralising human monoclonal antibody VRC07-523LS in healthy adults: a phase 1 dose-escalation clinical trial**. *The lancet HIV* 2019, **6**:e667–e679.

Demonstration of the improved pharmacokinetic properties (longer elimination half-lives) of the engineered VRC07-523LS, a variant of VRC07 with the amino acid substitutions M428L/N434S.

28. Cohen YZ, Lorenzi JCC, Krassnig L, et al.: **Relationship between latent and rebound viruses in a clinical trial of anti-HIV-1 antibody 3BNC117**. *Journal of Experimental Medicine* 2018, **215**:2311–2324.

29. Bar KJ, Sneller MC, Harrison LJ, , et al.: **Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption**. *https://doi.org/101056/NEJMoa1608243* 2016, **375**:2037–2050.

30. Davis-Gardner M, Alfant B, Weber J, Gardner M, Farzan M: **A Bispecific Antibody That Simultaneously Recognizes the V2- and V3-Glycan Epitopes of the HIV-1 Envelope Glycoprotein Is Broader and More Potent than Its Parental Antibodies**. *mBio* 2020, **11**.

31. National Institute of Health. **ClinicalTrials.gov**. [Website] Available from https://clinicaltrials.gov/. [Last accessed 18th Oct 2021]

32. Mendoza P, Gruell H, Nogueira L, et al.: **Combination therapy with anti-HIV-1 antibodies maintains viral suppression**. *Nature* 2018, **561**:479–484.

33. **Nishimura Y, Donau O, Dias J, et al.: **Immunotherapy during the acute SHIV infection of macaques confers long-term suppression of viremia**. *The Journal of experimental medicine* 2021, **218**.

This study describes a subset of macaques who demonstrate long-term viral remission up to 4 years after receiving combination bNAbs with evidence of induction of cd8 T cell immunity, suggestive of a 'vaccinal effect' following bNAb administration.

34. **Niessl J, Baxter AE, Mendoza P, et al.: **Combination anti-HIV-1 antibody therapy is associated with increased virus-specific T cell immunity**. *Nature Medicine* 2020, **26**:222.

Study suggesting combination bNAb therapy is associated with virus specific T cell immunity.

35. Anand SP, Prévost J, Baril S, et al.: **Two Families of Env Antibodies Efficiently Engage Fc-Gamma Receptors and Eliminate HIV-1-Infected Cells**. *Journal of Virology* 2019, **93**.

36. **Astronomo RD, Lemos MP, Narpala SR, et al.: **Rectal and vaginal tissue from intravenous VRC01 recipients show protection against ex vivo HIV-1 challenge**. *Journal of Clinical Investigation* 2021, doi:10.1172/JCI146975.

This study measured bNAb levels in tissue, suggesting that bNAb levels accumulate to levels 10-fold less in tissue compared to blood, however the lower tissue concentrations still was associated with HIV neutralisation in ex vivo challenge experiments.

37. Hessell AJ, Jaworski JP, Epson E, et al.: **Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques**. *Nature Medicine* 2016, **22**:362–368.

38. Zalevsky J, Chamberlain AK, Horton HM,et al.: **Enhanced antibody half-life improves in vivo activity**. *Nature biotechnology* 2010, **28**:157.

39. * Wen J, Cheever T, Wang L, et al.: **Improved delivery of broadly neutralizing antibodies by nanocapsules suppresses SHIV infection in the CNS of infant rhesus macaques**. *PLoS Pathogens* 2021, **17**.

Study reporting the use of nanocapsules technology to improve bNAb delivery in the CNS in infant rhesus macaques.

40. **Abdel-Mohsen M, Richman D, Siliciano RF, et al.: **Recommendations for measuring HIV reservoir size in cure-directed clinical trials**. *Nature Medicine 2020 26:9* 2020, **26**:1339–1350.

A comprehensive overview of the various methods of measuring the latent HIV reservoir, including advantages and challenges of each method.

41. *Rawi R, Mall R, Shen C-H, et al.: **Accurate Prediction for Antibody Resistance of Clinical HIV-1 Isolates**. *Scientific Reports* 2019, **9**.

This paper reports the use of machine learning to identify and predict bNAb antibody resistance and sensitivity, with an overall prediction accuracy of 96%.

42. Magaret CA, Benkeser DC, Williamson BD, et al.: **Prediction of VRC01 neutralization sensitivity by HIV-1 gp160 sequence features**. *PLoS Computational Biology* 2019, **15**:1–35.

43. *Yu W-H, Su D, Torabi J, et al.: **Predicting the broadly neutralizing antibody susceptibility of the HIV reservoir**. *JCI Insight* 2019, **4**.

This paper reports the use of a baesian machine-learning model to predict ideal bNAb combinations to achieve neutralisation.

44. **Moldt B, Parvangada A, Martin R, et al.: **Evaluation of Broadly Neutralizing Antibody Sensitivity by Genotyping and Phenotyping for Qualifying Participants to HIV Clinical Trials**. *Journal of acquired immune deficiency syndromes (1999)* 2021, **88**:61–69.

This paper reports the use of a genotypic assessment to be as predictive as direct measurement of bNAb sensitivity by phenotyping, and may provide a more rapid and accurate method of assessing individuals suitable for receiving bNAb combinations.

45. Hartweger H, McGuire AT, Horning M, et al.: **HIV-specific humoral immune responses by CRISPR/Cas9-edited B cells**. *Journal of Experimental Medicine* 2019, **216**:1301–1310.

46. **Huang D, Tran JT, Olson A, et al.: **Vaccine elicitation of HIV broadly neutralizing antibodies from engineered B cells**. *Nature Communications 2020 11:1* 2020, **11**:1–10.

Proof of concept study showing HIV bNAb-engineered mice B cells successfully transferred and vaccinated in immunocompetent mice resulting in the expansion of bNAb memory and plasma cells.

47. Martinez-Navio JM, Fuchs SP, et al.: **Adeno-Associated Virus Delivery of Anti-HIV Monoclonal Antibodies Can Drive Long-Term Virologic Suppression**. *Immunity* 2019, **50**:567-575.e5.

48. *Casazza J, Narpala S, Novik L, et al.: **Durable HIV-1 Antibody production in humans after AAV8-mediated gene transfer**. In *Conference on Retroviruses and Opportunistic Infections*. 2020.

This conference report demonstrates proof of concept for the use of AAV to produce functional bNAb VRC07 up to 1 year in 3 out of 5 individuals.

49. Kawashima Y, Pfafferott K, Frater J, et al.: **Adaptation of HIV-1 to human leukocyte antigen class I**. *Nature* 2009, **458**:641.

50. Zimbwa P, Milicic A, Frater J, et al.: **Precise Identification of a Human Immunodeficiency Virus Type 1 Antigen Processing Mutant**. *JOURNAL OF VIROLOGY* 2007, **81**:2031–2038.

51. Chen Z, Julg B: **Therapeutic Vaccines for the Treatment of HIV**. *Translational research : the journal of laboratory and clinical medicine* 2020, **223**:61–75.

52. Sneller M, Justement J, Gittens K, et al.: **A randomized controlled safety/efficacy trial of therapeutic vaccination in HIV-infected individuals who initiated antiretroviral therapy early in infection**. *Science translational medicine* 2017, **9**.

53. *Bailon L, Llano A, Cedeño S, et al.: **A PLACEBO-CONTROLLED ATI TRIAL OF HTI VACCINES IN EARLY TREATED HIV INFECTION**. In *Conference of Retroviruses and Opportunistic Infections*. 2021.

54. Mothe B, Hu X, Llano A, et al.: **A human immune data-informed vaccine concept elicits strong and broad T-cell specificities associated with HIV-1 control in mice and macaques**. *Journal of translational medicine* 2015, **13**.

55. *Mu Z, Haynes B, Cain D: **HIV mRNA Vaccines-Progress and Future Paths**. *Vaccines* 2021, **9**:1–22.

This review summarises the progress and development of mRNA vaccine thecnology for therapeutic HIV vaccination strategies.

56. Cirelli KM, Carnathan DG, Nogal B, et al.: **Slow delivery immunization enhances HIV neutralizing antibody and germinal center responses via modulation of immunodominance**. *Cell* 2019, **177**:1153.

57. Prins J, Jurriaans S, van Praag R, et al.: **Immuno-activation with anti-CD3 and recombinant human IL-2 in HIV-1-infected patients on potent antiretroviral therapy**. *AIDS* 1999, **13**:2405–2410.

58. van Praag R, Prins J, Roos M, et al.: **OKT3 and IL-2 treatment for purging of the latent HIV-1 reservoir in vivo results in selective long-lasting CD4+ T cell depletion**. *Journal of clinical immunology* 2001, **21**:218–226.

59. **Fidler S, Stöhr W, Pace M, et al.: **Antiretroviral therapy alone versus antiretroviral therapy with a kick and kill approach, on measures of the HIV reservoir in participants with recent HIV infection (the RIVER trial): a phase 2, randomised trial**. *The Lancet* 2020, **395**:888–898.

The first placebo-controlled randomised trial of a latency reversal agent Vorinostat, and therapeutic vaccine, which ddid not show any difference in measures of the HIV reservoir.

60. Singh V, Dashti A, Mavigner M, Chahroudi A: **Latency Reversal 2.0: Giving the Immune System a Seat at the Table**. *Current HIV/AIDS Reports* 2021, **18**:117.

61. Cillo A, Sobolewski MD, Bosch R, et al.: **Quantification of HIV-1 latency reversal in resting CD4+ T cells from patients on suppressive antiretroviral therapy**. *Proceedings of the National Academy of Sciences of the United States of America* 2014, **111**:7078–7083.

62. *Ward AR, Mota TM, Jones RB: **Immunological approaches to HIV cure**. *Seminars in Immunology* 2020, doi:10.1016/J.SMIM.2020.101412.

Comprehensive review of the immunological approaches to HIV cure strategies, including an overview of other trials of LRAs which have yielded limited results.

63. Pace M, Williams J, Kurioka A, et al.: **Histone Deacetylase Inhibitors Enhance CD4 T Cell Susceptibility to NK Cell Killing but Reduce NK Cell Function**. *PLoS pathogens* 2016, **12**.

64. Jones R, Ndhlovu L, Barbour J, et al.: **Tim-3 expression defines a novel population of dysfunctional T cells with highly elevated frequencies in progressive HIV-1 infection**. *The Journal of experimental medicine* 2008, **205**:2763–2779.

65. Huang S-H, Ren Y, Thomas AS, et al.: **Latent HIV reservoirs exhibit inherent resistance to elimination by CD8+ T cells**. *The Journal of Clinical Investigation* 2018, **128**:876.

66. del Prete G, Alvord W, Li Y, et al.: **TLR7 agonist administration to SIV-infected macaques receiving early initiated cART does not induce plasma viremia**. *JCI insight* 2019, **4**.

67. Bekerman E, Hesselgesser J, Carr B, et al.: **PD-1 Blockade and TLR7 Activation Lack Therapeutic Benefit in Chronic Simian Immunodeficiency Virus-Infected Macaques on Antiretroviral Therapy**. *Antimicrobial agents and chemotherapy* 2019, **63**.

68. Bricker K, Obregon-Perko V, Uddin F, et al.: **Therapeutic vaccination of SIV-infected, ART-treated infant rhesus macaques using Ad48/MVA in combination with TLR-7 stimulation**. *PLoS pathogens* 2020, **16**.

Study of therapeutic ad48-SIV prime, MVA-SIV boost vaccine in combination with tLR-7 agonist GS-986 in rhesus macaques. Despite greater SIV-specific T cell responses, there was no difference in SIV reservoir measurements.

69. Borducchi EN, Liu J, Nkolola JP, et al.: **Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys**. *Nature* 2018, **563**:360–364.

70. Vibholm LK, Konrad C., Schleimann MH, et al.: **Effects of 24-week Toll-like receptor 9 agonist treatment in HIV type 1+ individuals**. *AIDS* 2019, **33**:1315–1325.

71. Saxena M, Sabado RL, Mar M la, et al.: **Poly-ICLC, a TLR3 Agonist, Induces Transient Innate Immune Responses in Patients With Treated HIV-Infection: A Randomized Double-Blinded Placebo Controlled Trial**. *Frontiers in Immunology* 2019, **10**.

72. Gutiérrez C, Serrano-Villar S, Madrid-Elena N, et al.: **Bryostatin-1 for latent virus reactivation in HIV-infected patients on antiretroviral therapy**. *AIDS* 2016, **30**:1385–1392.

73. Yamamoto T, Kanuma T, Takahama S, et al.: **STING agonists activate latently infected cells and enhance SIV-specific responses ex vivo in naturally SIV controlled cynomolgus macaques**. *Scientific Reports* 2019, **9**.

74. Nixon CC, Mavigner M, Sampey GC, et al.: **Systemic HIV and SIV latency reversal via non-canonical NF-κB signalling in vivo**. *Nature 2020 578:7793* 2020, **578**:160–165.

This paper show the activation of the non-canonical NF-kB signalling pathway by the SMAC mimetic AZD5582 induced HIV and SIV RNA expression in humanized mice and rhesus macaques.

75. McBrien JB, Mavigner M, Franchitti L, et al.: **Robust and persistent reactivation of SIV and HIV by N-803 and depletion of CD8+ cells**. *Nature 2020 578:7793* 2020, **578**:154–159.

This study showed CD8-lymphocyte depletion in ART treated macaques, followed by N-803 administration, induced robust viral reactivation.

76. Mavigner M, Liao LE, Brooks AD, et al.: **CD8 Lymphocyte Depletion Enhances the Latency Reversal Activity of the SMAC Mimetic AZD5582 in ART-Suppressed Simian Immunodeficiency Virus-Infected Rhesus Macaques**. *Journal of Virology* 2021, **95**.

This study showed the use of the SMAC mimetic AZD5582 with CD8 depletion augmented viral reactivation compared to AZD5582 or CD8 depletion alone.

77. Pardons M, Fromentin R, Pagliuzza A, Routy J, Chomont N: **Latency-Reversing Agents Induce Differential Responses in Distinct Memory CD4 T Cell Subsets in Individuals on Antiretroviral Therapy**. *Cell reports* 2019, **29**:2783-2795.e5.

78. **Harper J, Gordon S, Chan CN, et al.: **CTLA-4 and PD-1 dual blockade induces SIV reactivation without control of rebound after antiretroviral therapy interruption**. *Nature Medicine 2020 26:4* 2020, **26**:519–528.

This study demonstrated the use of PD-1 and CTLA-4 blockade appeared to induce robust viral reactivation, and decreased the total and intact SIV DNA measurements in macaques receiving ART.

79. Gay CL, Bosch RJ, Ritz J, et al.: **Clinical Trial of the Anti-PD-L1 Antibody BMS-936559 in HIV-1 Infected Participants on Suppressive Antiretroviral Therapy**. *The Journal of Infectious Diseases* 2017, **215**:1725.

80. Yates KB, Tonnerre P, Martin GE, et al.: **Epigenetic scars of CD8+ T cell exhaustion persist after cure of chronic infection in humans**. *Nature Immunology 2021 22:8* 2021, **22**:1020–1029.

This study show CD8 T cell exhaustion markers persist in chronic viral infections, and is driven by epigenetic super enhancers near the genes *TOX* and *HIF1A.*

81. **Martin G, Sen D, Pace M, Robinson N, Meyerowitz J, Adland E, Thornhill J, Jones M, Ogbe A, Parolini L, et al.: **Epigenetic Features of HIV-Induced T-Cell Exhaustion Persist Despite Early Antiretroviral Therapy**. *Frontiers in immunology* 2021, **12**.

This study demonstrates CD4 and CD8 markers of exhaustion, with epigenetic features of exhaustion typically seen in chronic HIV infection, are increased and did not completely normalise despite 3 years of ART in people treated early in primary HIV infection.

82. Allers K, Hütter G, Hofmann J, et al.: **Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation**. *Blood* 2011, **117**:2791–2799.

83. **Gupta RK, Peppa D, Hill AL, et al.: **Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report**. *The Lancet HIV* 2020, **7**:e340.

This is the second case report of an individual who experienced a sterilising HIV cure following CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation.

84. Arslan S, Litzow MR, Cummins NW, et al.: **Risks and Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies in Patients with HIV Infection**. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2019, **25**:e260.

85. Huang J, Kang BH, Ishida E, Zhou T, et al.: **Identification of a CD4-Binding-Site Antibody to HIV that Evolved Near-Pan Neutralization Breadth**. *Immunity* 2016, **45**:1108–1121.

86. Anthony-Gonda K, Bardhi A, Ray A, et al.: **Multispecific anti-HIV duoCAR-T cells display broad in vitro antiviral activity and potent in vivo elimination of HIV-infected cells in a humanized mouse model**. *Science Translational Medicine* 2019, **11**.

87. * Herzig E, Kim KC, Packard TA, Vardi N, et al.: **Attacking Latent HIV with convertibleCAR-T Cells, a Highly Adaptable Killing Platform**. *Cell* 2019, **179**:880.

This study show the platform of an adaptable CAR-T cell platform engineered to bind to a variety of bNAbs, for greater breadth and flexibility.

88. **Barber-Axthelm IM, Barber-Axthelm V, et al.: **Stem cell–derived CAR T cells traffic to HIV reservoirs in macaques**. *JCI Insight* 2021, **6**.

This study shows the use of stem cell derived CAR-T cells which can physiologically expand without the need for *ex-vivo* expansion, and may persist for nearly 2 years in macaque models.

89. Kiem H-P: **Setting the stage for the use of cell and gene therapy to enhance control or eradication of HIV**. In *11th IAS Conference on HIV Science, Keynote session SY14*. 2021.