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Research Toward a Cure and Immune-Based Therapies

TAG
Treatment Action Group

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By Richard Jefferys

Introduction

The number of new HIV cure-related clinical trials and observational studies ticked up again over the past year as the COVID-19 pandemic waned slightly and the research enterprise adapted to the new environment. A total of 31 new studies have been initiated since the 2021 Pipeline Report (compared with 19 during the previous year), 22 involving interventions and nine observational in nature (see Table 1).

On August 17, 2021, the U.S. National Institutes of Health announced a significant expansion of their cornerstone program, the Martin Delaney Collaboratories for HIV Cure Research.[1] Initiated in 2010 and named after the activist and founder of the community-based advocacy organization Project Inform, the first round of five-year awards supported three large collaborations between academic researchers, industry representatives, and other stakeholders. The second round, in 2016, expanded the number to six such collaboratories. The latest iteration is funding ten collaboratories, including the first to specifically focus on pediatric HIV cure research. Funding support has concomitantly increased, from $70 million initially to approximately $269 million over the next five years.[2]

In February of 2022, significant news emerged from the Conference on Retroviruses and Opportunistic Infections (CROI). Yvonne Bryson from the University of California at Los Angeles described another possible case of an HIV cure achieved by stem cell transplantation, this time in a woman of mixed race in the New York City area.[3] Three similar cases have previously been reported (see box), but all involved men.

Prior Stem Cell Transplantation HIV Cure Cases

Timothy Ray Brown, initially referred to as "the Berlin patient," was the first person to receive a stem cell transplant from an adult donor homozygous for the CCR5Δ32 mutation, which renders immune cells resistant to most HIV strains. The transplant was required to treat acute myelogenous leukemia (AML). HIV viral load did not rebound after the procedure, despite the cessation of combination antiretroviral therapy (ART).[4] After more than 3.5 years of follow-up off ART, the doctors responsible for Brown's treatment declared he was likely cured of HIV infection.[5] There was no sign of a return of HIV for more than 13 years after the transplant, but sadly the cancer eventually recurred, and he died on September 29, 2020.[6]

Adam Castillejo, also known as "the London patient," represents the second case of a successful HIV cure after receipt of a stem cell transplant from an adult donor homozygous for the CCR5Δ32 mutation (the transplant was needed to treat lymphoma). Several preceding attempts to recapitulate the cure achieved in Timothy Ray Brown by providing stem cells from CCR5Δ32 homozygote donors to people with HIV and cancers had failed

due to either cancer recurrence or complications of the procedure.[7] Castillejo's case was first reported at CROI 2019,[8] with a paper published simultaneously in the scientific journal *Nature*.[9] In early 2020, after 2.5 years of follow-up, the researchers proposed that Castillejo was likely cured,[10] and he remains without evidence of HIV infection (or cancer) nearly five years after stopping ART.

The Düsseldorf patient, who remains anonymous, was described in a poster presentation at CROI 2019.[11] His stem cell transplant was indicated due to a diagnosis of AML and, as with Brown and Castillejo, the cells were sourced from an adult donor homozygous for CCR5Δ32. At the time of the first CROI presentation he had only been off ART for around three months, so the case drew less media attention. But a follow-up poster at CROI 2020 reported that HIV viral load remained undetectable off ART after 14 months, with no intact virus detectable using sensitive tests.[12] Most recently, in February 2022, the lead researcher Björn Jensen gave an interview to NBC News in which he disclosed that the Düsseldorf patient is still off ART after more than three years and is now "almost definitely" cured of HIV.[13]

Information on the new case was first presented as an abstract at the American Society for Hematology's 2018 annual meeting.[14] The woman was diagnosed with HIV infection in June 2013 and successfully treated with ART. In March of 2017, she was diagnosed with a potentially life-threatening cancer, AML. The cancer ultimately required treatment with stem cell transplantation, a procedure that aims to eliminate the cancerous cells and generate a new immune system from donated stem cells.

As part of a research protocol undertaken by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network, a source of stem cells was identified from a donor homozygous for the CCR5Δ32 mutation. The mutation causes immune cells to be resistant to most strains of HIV by preventing the expression of a particular external receptor, CCR5, which the virus uses as a foothold to gain entry. The stem cells were derived from umbilical cord blood units that were stored for the purpose of providing a source for transplantation.

The cord blood stem cells were administered together with adult stem cells lacking the CCR5Δ32 mutation, which were donated by a relative. This combination approach was used because there is evidence that cord blood stem cells can take longer to generate new immune system cells after transplantation compared with adult cells.

As was hoped, the stem cells from the adult donor were the source of initial immune reconstitution post-transplant, but then cells derived from the cord blood units (which had the CCR5Δ32 mutation) took over. From 55 days of follow-up onwards 100% of immune cells were derived from the cord blood donor.

ART was eventually interrupted three years after the transplant, after tests showed the cancer was in remission and HIV was undetectable. At the time of Bryson's presentation at CROI 2022, the woman had been off ART for more than 14 months with persistently undetectable HIV viral load. During this time a COVID-19 vaccine was administered without any untoward effect.

Tests for HIV DNA, a surrogate measure of the HIV reservoir, have been negative except one detection of trace amounts at an early timepoint after ART cessation. Antibody and T-cell responses against HIV are no longer detectable. The absence of ART has been confirmed by measuring drug levels in blood. The researchers have also tested the woman's cells in the laboratory and found them to be resistant to HIV.

At the current time, the researchers are being cautious and referring to the outcome as "remission" rather than cure. In prior cases, a period off ART of around 2.5-3 years without the return of detectable virus has been the threshold for proposing that an individual has been cured of HIV infection.

The case potentially offers additional encouragement that an HIV cure is achievable and demonstrates that, for people with HIV and certain life-threatening cancers, stem cell transplantation from donors homozygous for the CCR5Δ32 mutation can work in women as well as men.

Yvonne Bryson and colleagues have also noted that the novel approach of combining adult stem cells with cord blood units should increase the chances of finding appropriate donors homozygous for CCR5Δ32. There are less stringent requirements for genetically matching cord blood stem cells to recipients, which has been reported to increase the possibility of identifying suitable donors for people of diverse racial and ethnic backgrounds.[15]

It can be difficult to keep count of HIV cure cases because there is uncertainty regarding how long people should be followed off ART before being considered cured. Hence media stories often provide differing numbers, which is confusing. To summarize, there are two widely accepted cases resulting from stem cell transplantation: Timothy Ray Brown and Adam Castillejo. The Düsseldorf patient likely also belongs to this group but is sometimes omitted because there isn't a formal report in a scientific journal yet. The New York patient is considered too early in follow-up to be included as a proven cure, but hopefully this will eventually change and bring the total to four.

Outside of the realm of stem cell transplantation, there is strong evidence that two women have cleared all the viable HIV from their bodies thanks to unusually vigorous immune responses against the virus. Both belonged to the rare category of "elite controllers," a term for people who can control HIV viral load to undetectable levels without ART (estimated to represent 1% or less of all people with HIV). Careful studies involving very large numbers of cells indicate that, over time, any HIV capable of replicating has been eliminated. To use a gardening metaphor, it is as if the immune system slowly pruned away all the cells containing HIV that was intact and capable of replicating.

Loreen Willenberg was the first case to be reported,[16] followed by the Esperanza Patient, a woman in Argentina who has chosen to remain anonymous.[17] These are sometimes referred to as natural cures, which is accurate but also potentially misleading—the evidence indicates that rare traits of the women's immune systems played a key role, and these traits cannot be replicated by the type of herbal "natural cures" you might see falsely promoted on the internet.

The stem cell transplant and elite controller cure cases can't be directly translated into interventions that might work for all people with HIV, but the cure research field is working to take lessons from these examples and apply them to potential cure strategies. For example, gene therapies are attempting to create HIV-resistant immune cells in a less risky and invasive way than stem cell transplantation from CCR5Δ32 homozygotes. In some studies, this approach is being combined with another gene therapies designed to

enhance the immune response to HIV using chimeric antigen receptors (CARs), which have shown success when targeted against cancers.[18] Broadly neutralizing antibodies (bNAbs) have also emerged as attractive candidates for bolstering the immune response against HIV and are increasingly being administered in combination with other modalities such as therapeutic vaccines.

A simple but perhaps long-shot idea inspired by data from elite controllers[19] is that some people on very long-term ART may also eventually clear all the viable HIV from their body. Several studies have found that levels of intact HIV decline at a faster rate in people on ART compared with virus that is defective and unable to replicate.[20,21,22] These findings suggests that immune responses are preferentially targeting intact and functional HIV for elimination.

Similarly, the research group that studied Loreen Willenberg and the Esperanza Patient have shown that the HIV reservoir in people on long-term ART is more likely to consist of viruses that are trapped inside cells because they've landed in a spot that's inhospitable to viral replication.[23] These areas within the cell's genetic code are referred to as "gene deserts."

The researchers, led by Xu Yu at the Ragon Institute in Boston, are now conducting an amfAR-sponsored study to identify people on long-term ART who might be candidates for an analytical treatment interruption (ATI) to assess any viable HIV remains in their bodies.[24,25] Importantly, the criteria for participating will involve very careful technical analysis of the HIV reservoir, and the researchers are emphasizing that people on long-term ART shouldn't try an ATI on their own.

In late 2021, the International AIDS Society published an update to their "Towards an HIV Cure Global Scientific Strategy," authored by multiple stakeholders,[26] along with a community Q&A provided by Simon Collins at HIV i-Base in the United Kingdom.[27] The documents offer a comprehensive overview of the state of the field and the strategies being pursued.

A critical consideration as HIV cure-related research continues to expand is the diversity of study participants. Regardless of whether a particular investigation is studying an intervention or is intending to better understand parameters involved in HIV persistence in the body, if the results are generated in a homogenous group, the applicability to the diverse global population of people with HIV will be unknown.

Several analyses of HIV cure-related studies have reported on the underrepresentation of women, people of non-white race/ethnicity, and transgender people.[28,29,30,31] A review of publications from the Martin Delaney Collaboratories during 2019 found that only about half of the studies involving human participants or samples included any demographic information.[32] The authors state: "This review is a call to action for attention to diversity of participants when conducting HIV cure research as well as reporting on diversity."

In parallel with the biomedical research pipeline, social science can make an important contribution to understanding the perspectives of potential participants toward cure-related studies. The past year has seen the publication of multiple studies exploring attitudes toward key aspects of the research, including ATIs, gene therapies, and combination approaches.[33,34,35,36,37]

Efforts to develop immune-based therapies as adjuncts to ART for people who experience suboptimal CD4+ T-cell recovery despite viral load suppression remain limited, although there has been a slight uptick in activity over the past year, with four new clinical trials initiated (see Table 2).

Table 1. Research Toward a Cure 2022: Current Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
ADOPTIVE IMMUNOTHERAPY					
AutoRESIST: HIV antigen-specific T cells targeting conserved epitopes for treatment of HIV-associated lymphoma		NCT04975698	Children's Research Institute	United States	Phase II
AlloRESIST: Evaluate the safety, immunologic, and virologic responses of donor-derived HIV-specific T cells in HIV+ individuals following allogeneic bone marrow transplantation		NCT04248192	Children's Research Institute	United States	Phase I
HIV-1–specific T cells for HIV+ individuals	HIV-specific T cells with non-escaped epitope targeting (HST-NEETs)	NCT03485963 (closed to enrollment)	Children's Research Institute	United States	Phase I
ANALYTICAL TREATMENT INTERRUPTION					
SCOPE-ATI	**ATI**	NCT04359186	The University of California, San Francisco (UCSF)	United States	N/A
TESOVIR	Tracking and exploring the source of viral rebound, **ATI**	NCT03117985	Centre Hospitalier Régional d'Orléans	France	N/A
Imaging and biopsy of HIV+ individuals undergoing ATI	**ATI**	NCT05419024	National Cancer Institute (NCI)	United States	Phase II
ANTIBODIES					
VRC01	Analytical treatment interruption in HVTN 703/HPTN 081 AMP trial participants, **ATI**	NCT04860323	HIV Vaccine Trials Network (HVTN)	Botswana, Malawi, South Africa, Zimbabwe	N/A
VRC01	Analytical treatment interruption in HVTN 704/HPTN 085 AMP trial participants, **ATI**	NCT04801758	HVTN	Brazil, Peru, United States	N/A
GSK3810109A	Long-acting broadly neutralizing antibody formerly named N6-LS	NCT04871113	ViiV Healthcare	Europe, United States	Phase IIa

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
10-1074-LS + 3BNC117-LS	Long-acting broadly neutralizing antibodies in primary infection, **ATI**	NCT04319367	Imperial College London	United Kingdom	Phase II
3BNC117-LS + 10-1074-LS	Long-acting broadly neutralizing antibodies in primary infection, **ATI**	NCT05300035 (not yet open for enrollment)	French National Agency for Research on AIDS and Viral Hepatitis (ANRS)	France	Phase II
UB-421	Antibody inhibitor of HIV binding to CD4 receptors	NCT04404049 (not yet open for enrollment)	UBP Greater China (Shanghai) Co., Ltd	China	Phase II
Vedolizumab	Anti-α4β7 integrin antibody, **ATI**	NCT03147859	Ottawa Hospital Research Institute	Canada	Phase II
ABBV-382	Anti-α4β7 integrin antibody	NCT04554966	AbbVie	United States	Phase Ib
3BNC117-LS + 10-1074-LS	Long-acting broadly neutralizing antibodies, **ATI**	NCT05079451 (not yet open for enrollment)	NIAID	United States	Phase I
AAV8-VRC07	Broadly neutralizing antibody delivered by adeno-associated virus (AAV) vector	NCT03374202 (closed to enrollment)	NIAID	United States	Phase I
SAR441236	Tri-specific broadly neutralizing antibody	NCT03705169	NIAID	United States	Phase I
ANTI-CYTOMEGALOVIRUS THERAPY					
Letermovir (Prevymis)	Anti-cytomegalovirus drug	NCT04840199	NIAID	United States	Phase II
ANTI-INFLAMMATORY					
Canakinumab	IL-1β inhibitor	NCT02272946 (closed to enrollment)	UCSF	United States	Phase II
Camu (*Myrciaria dubia*)	Brazilian fruit extract	NCT04058392	McGill University Health Centre	Canada	Phase I
ANTIRETROVIRAL THERAPY					
IDOLTIB: Impact of dolutegravir + lamivudine simplification on HIV-1 reservoirs	Integrase inhibitor + nucleoside reverse transcriptase inhibitor	NCT04034862 (closed to enrollment)	University of Liège	Belgium	Phase III

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
CANNABINOIDS					
GALIG-CBD	Effects of cannabidiol on the activation of autophagy and inflammation genes	NCT05306249 (not yet open for enrollment)	Centre Hospitalier Régional d'Orléans	France	Phase II
TN-CT11LM, TN-TC19LM	Oral capsules containing Δ9-tetrahydrocannabinol and cannabidiol in two different ratios	NCT03550352 (not yet open for enrollment)	McGill University Health Center	Canada	Phase II
COMBINATIONS					
Perturbing of HIV reservoir with immune stimulation: Fluarix, Pneumovax vaccines	Influenza and pneumococcus vaccines	NCT02707692 (closed to enrollment)	University of California, San Diego (UCSD)	United States	Not listed
MVA.HTI + ChAdOx1.HTI ± vesatolimod	Therapeutic vaccines + TLR7 agonist, **ATI**	NCT04364035	Aelix Therapeutics	Spain	Phase IIa
TITAN: lefitolimod ± 3BNC117 + 10-1074	TLR9 agonist ± broadly neutralizing antibodies, **ATI**	NCT03837756	Aarhus University	Australia, Denmark, United States	Phase IIa
VRC07-523LS, CAP256V2LS, vesatolimod	Long-acting broadly neutralizing antibodies + TLR7 agonist, **ATI**	NCT05281510	Gilead Sciences	South Africa	Phase IIa
Albuvirtide + 3BNC117	Fusion inhibitor + broadly neutralizing antibody, **ATI**	NCT04819347 (not yet open for enrollment)	Frontier Biotechnologies Inc.	China	Phase II
ASC22 + chidamide	Anti–PD-L1 antibody + HDAC inhibitor	NCT05129189	Shanghai Public Health Clinical Center	China	Phase II
MVA HIV-B ± vedolizumab	Viral vector vaccine ± anti-$\alpha_4\beta_7$ integrin antibody, **ATI**	NCT04120415	ANRS	France, Germany, Italy, Netherlands, Spain, Switzerland, United Kingdom	Phase II
Research in viral eradication of HIV reservoirs (RIVER): ART, ChAdV63. HIVconsv, and MVA.HIVconsv vaccines, vorinostat	Therapeutic vaccines + HDAC inhibitor	NCT02336074 U.K. CPMS18010 (closed to enrollment)	Imperial College London	United Kingdom	Phase II
UB-421 + chidamide	Antibody inhibitor of HIV binding to CD4 receptors + HDAC inhibitor, **ATI**	NCT04985890 (not yet open for enrollment)	UBP Greater China (Shanghai) Co., Ltd	Taiwan	Phase II
UB-421 + chidamide	Antibody inhibitor of HIV binding to CD4 receptors + HDAC inhibitor, **ATI**	NCT05056974	United BioPharma	Taiwan	Phase II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
Vorinostat ± tamoxifen in postmenopausal women	HDAC inhibitor + estrogen receptor modulator	NCT03382834 (closed to enrollment)	NIAID	United States	Phase II
Ad26.Mos4.HIV, MVA-BN-HIV, PGT121, PGDM1400, VRC07-523LS	Therapeutic vaccines, broadly neutralizing antibodies, **ATI**	NCT04983030	Boris Juelg, MD, PhD	United States	Phase I/IIa
HIVARNA01.3, MVA vector HIV vaccine, 10-1074, romidepsin, HIVACAR01	Therapeutic vaccines, broadly neutralizing antibody, HDAC inhibitor, **ATI**	NCT03619278 (not yet open for enrollment)	David Garcia Cinca	Spain	Phase I/IIa
IMPAACT P1115 v2.0: very early intensive treatment of HIV-infected infants to achieve HIV remission (ART ± VRC01)	Combination antiretroviral therapy, VRC01 broadly neutralizing antibody, **ATI**	NCT02140255	IMPAACT/NIAID/ NICHD	Argentina, Brazil, Haiti, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, United States, Zambia, Zimbabwe	Phase I/II
Panobinostat + pegylated interferon-α2a	HDAC inhibitor + cytokine	NCT02471430 (closed to enrollment)	Massachusetts General Hospital	United States	Phase I/II
IL-12 adjuvanted p24CE DNA vaccine, MVA/HIV62B vaccine, lefitolimod, VRC07-523LS, 10-1074	Therapeutic conserved element DNA vaccine, MVA vaccine boost, TLR9 agonist, broadly neutralizing antibodies, **ATI**	NCT04357821	UCSF	United States	Phase I/II
Elipovimab (formerly GS-9722) ± vesatolimod	Broadly neutralizing antibody + TLR7 agonist	GS-US-420-3902 (no clinicaltrials.gov entry)	Gilead Sciences	United States	Phase Ib
CD4ζ ± interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	United States	Phase I
HVRRICANE: HIVIS DNA + MVA-CMDR vaccines ± Cervarix (TLR4 agonist)	Therapeutic vaccines + TLR4 agonist	NCT04301154	PENTA Foundation	Italy, South Africa, Thailand	Phase I
N-803 ± VRC07-523LS + 10-1074	Recombinant human super agonist IL-15 complex, broadly neutralizing antibodies, **ATI**	NCT04340596	NIAID	United States	Phase I
N-803, 3BNC117-LS, 10-1074-LS	Recombinant human super agonist IL-15 complex, long-acting broadly neutralizing antibodies, **ATI**	NCT05245292 (not yet open for enrollment)	Rockefeller University	United States	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
Peginterferon-α2b + 3BNC117 + 10-1074	Cytokine, broadly neutralizing antibodies, **ATI**	NCT03588715	Wistar Institute	United States	Phase I
Vorinostat + HXTC: HIV-1 antigen expanded specific T-cell therapy	HDAC inhibitor + adoptive immunotherapy	NCT03212989	University of North Carolina, Chapel Hill	United States	Phase I
CYTOKINES					
N-803	Recombinant human super agonist IL-15 complex in acute HIV infection	NCT04505501	Thai Red Cross AIDS Research Centre	Thailand	Phase II
N-803	Effect of a recombinant human super agonist IL-15 complex on B-cell follicles	NCT04808908 (closed to enrollment)	University of Minnesota	United States	Phase I
DUAL-AFFINITY RE-TARGETING (DART) MOLECULES					
MGD020 ± MGD014	Bispecific DART molecules targeting the HIV envelope gp41 and gp120 proteins and CD3-expressing T cells	NCT05261191 (not yet open for enrollment)	MacroGenics	United States	Phase I
GENE THERAPIES					
EBT-101	AAV9 vector delivering CRISPR/ Cas9 gene-editing tool targeting HIV provirus, **ATI**	NCT05144386	Excision BioTherapeutics	United States	Phase I/IIa
LVgp120duoCAR-T cells	Autologous T cells gene-modified to express chimeric antigen receptors (CARs) targeting HIV	NCT04648046	Steven Deeks, UCSF	United States	Phase I/IIa
Cal-1: Dual anti-HIV gene transfer construct	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 and a fusion inhibitor (C46)	NCT02390297 (long-term safety phase; closed to enrollment)	Calimmune	United States	Phase I/II
SB-728-T	Autologous CD4+ T cells modified to inhibit CCR5 expression	NCT03666871 (closed to enrollment)	Case Western Reserve University	United States	Phase I/II
AGT103-T	Gene-modified HIV-specific CD4+ T cells	NCT04561258	American Gene Technologies International	United States	Phase I
CD4 CAR + SB-728mR modified T cells	Autologous CD4+ T cells gene-modified to inhibit CCR5 expression and CAR T cells, **ATI**	NCT03617198 (closed to enrollment)	University of Pennsylvania	United States	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
CAR T-cell therapy	Autologous T cells gene-modified to express a CAR targeting HIV	NCT03240328	Guangzhou 8th People's Hospital	China	Phase I
EBT-101	Long-term follow-up study	NCT05143307 (enrolling by invitation)	Excision BioTherapeutics	United States	Phase I
Long-term follow-up of HIV+ participants exposed to SB-728-T or SB-728mR-T	Autologous CD4+ T cells gene-modified to inhibit CCR5 expression	NCT04201782 (enrolling by invitation only)	Sangamo Therapeutics	United States	Phase I
SB-728mR-HSPC	Autologous hematopoietic stem/ progenitor cells gene-modified to inhibit CCR5 expression, **ATI**	NCT02500849 (closed to enrollment)	City of Hope Medical Center	United States	Phase I
Third-generation CAR T-cell therapy	Autologous T cells gene-modified to express CARs targeting HIV	NCT04863066 (not yet open for enrollment)	Beijing 302 Hospital	China	Phase I
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS					
Stem cells gene-modified with Cal-1 in HIV-1–related high-risk lymphoma	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 and a fusion inhibitor (C46), **ATI**	NCT03593187	Assistance Publique - Hôpitaux de Paris	France	Phase I/II
Gene therapy in treating patients with HIV-related lymphoma receiving stem cell transplant	Stem cells gene-modified with CCR5 shRNA/ TRIM5α/TAR decoy	NCT02797470	AIDS Malignancy Consortium	United States	Phase I/II
Gene therapy and combination chemotherapy in treating patients with AIDS-related non-Hodgkin's lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (rHIV7-shI-TAR-CCR5RZ), **ATI**	NCT02337985 (closed to enrollment)	City of Hope Medical Center	United States	Phase I
Busulfan and gene therapy after frontline chemotherapy in patients with AIDS-related non-Hodgkin's lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (rHIV7-shI-TAR-CCR5RZ) + cyclophosphamide conditioning, **ATI**	NCT01961063 (closed to enrollment)	City of Hope Medical Center	United States	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
GONADOTROPIN-RELEASING HORMONE (GnRH) AGONISTS					
Triptorelin acetate depot		NCT03536234	Immune System Regulation AB	Sweden	Phase II
IMAGING STUDIES					
Imaging immune activation in HIV by PET-MR		NCT03684655	UCSF	United States	Phase I
Radiolabeled VRC01	Radiolabeled broadly neutralizing antibody	NCT03729752	UCSF	United States	Phase I
IMMUNE CHECKPOINT INHIBITORS					
ASC22	Anti–PD-L1 antibody	NCT05330143	Ascletis Pharmaceuticals Co., Ltd.	China	Phase II
NIVO-LD: Low dose nivolumab in adults living with HIV on antiretroviral therapy	Anti–PD-1 antibody, **ATI**	NCT05187429 (not yet open for enrollment)	University of Melbourne	Australia	Phase I/II
Budigalimab	Anti–PD-1 antibody, **ATI**	NCT04223804	AbbVie	Australia, Canada, France, United States	Phase Ib
Budigalimab	Anti–PD-1 antibody	NCT04799353 (closed to enrollment)	AbbVie	Puerto Rico, United States	Phase I
Nivolumab + ipilimumab	Anti–PD-1 antibody + anti–CTLA-4 antibody in people with advanced HIV-associated solid tumors	NCT02408861	National Cancer Institute	Australia, United States	Phase I
Pembrolizumab	Anti–PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms	NCT02595866	National Cancer Institute	United States	Phase I
Pembrolizumab	Anti–PD-1 antibody, single dose	NCT03239899	National Institute of Neurological Disorders and Stroke	United States	Phase I
LATENCY-REVERSING AGENTS					
Arsenic trioxide	Chemotherapy	NCT03980665	Guangzhou 8th People's Hospital	China	Phase I
decitabine, romidepsin	Chemotherapy, HDAC inhibitor	NCT05230368 (not yet open for enrollment)	ANRS	France	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
Euphorbia kansui	Traditional Chinese medicine containing ingenols	NCT04503928 (not yet open for enrollment)	Shanghai Public Health Clinical Center	China	Phase I
Euphorbia kansui	Traditional Chinese medicine containing ingenols	NCT02531295 (temporarily suspended)	UCSF	United States	Phase I
mTOR INHIBITORS					
Metformin		NCT04500678	University of Hawaii	United States	Phase II/III
OBSERVATIONAL STUDIES					
2000 HIV Human Functional Genomics Partnership Program (2000HIV)		NCT03994835	Radboud University	Netherlands	N/A
2000HIVTrained	HIV trained innate immunity in HIV elite controllers	NCT04968717 (closed to enrollment)	Radboud University	Netherlands	N/A
Accurate staging of immuno-virological dynamics during acute HIV infection (ACS)		NCT03449706	University Hospital, Ghent	Belgium	N/A
Analytic treatment interruption to assess HIV cure	**ATI**	NCT02437526 (enrolling by invitation only)	Mayo Clinic	United States	N/A
ANRS CO24 OncoVIHAC: Immune checkpoint inhibitors in HIV+ individuals with cancers		NCT03354936	Inserm-ANRS	France	N/A
ATGALIG-HIV: Study of autophagy and the effects of GALIG gene products in HIV-1+ patients on ART since primary infection, chronic phase, or never treated		NCT04160455	Centre Hospitalier Régional d'Orléans	France	N/A
BICTEVOIR: Study to determine the cartography of virologic reservoir related to antiretroviral concentrations in HIV-1+ patients on first-line treatment containing bictegravir, emtricitabine, and tenofovir alafenamide		NCT05222945 (not yet open for enrollment)	ANRS	France	N/A
CHRONO: Prospective cohort for ex vivo cure studies with chronic HIV+ patients in the Netherlands		NCT04888754 (not yet open for enrollment)	Erasmus Medical Center	Netherlands	N/A
CODEX (the 'Extreme' cohort)	Long-term non-progressors and HIV controllers	NCT01520844	Inserm-ANRS	France	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
Developing a functional cure for HIV disease: clinical specimen collection from HIV+ individuals	Determination of levels of HIV-reactive CD4+ T cells, possible leukapheresis	NCT03215004	American Gene Technologies International	United States	N/A
DOLUVOIR: Cartography of virologic reservoir related to antiretroviral concentrations in people with HIV on first-line treatment containing dolutegravir and nucleoside/nucleotide reverse transcriptase inhibitors		NCT04133012	Inserm-ANRS	France	N/A
Establish and characterize an acute HIV infection cohort in a high-risk population		NCT00796146	South East Asia Research Collaboration with Hawaii	Thailand	N/A
Evaluation of the role of HIV-1 Tat protein and anti-Tat immune response in HIV reservoir (ISS OBS T-005)		NCT04263207	Barbara Ensoli, MD, PhD, Istituto Superiore di Sanità	Italy	N/A
Expectation, motivation, and experience of HIV+ patients regarding participation to an HIV cure-related clinical trial (AMEP-EHVA T02)		NCT05280392 (not yet open for enrollment)	ANRS	France	N/A
EX VIVO: Ex vivo characterization and targeting of the latent HIV-infected reservoir to cure HIV		NCT05215704	Erasmus Medical Center	Netherlands	N/A
FRESH (females rising through education, support, and health)	Early diagnosis, treatment, and support for women at high risk for HIV infection	No clinicaltrials.gov entry	Ragon Institute of MGH, MIT, and Harvard	South Africa	N/A
FXR#2: Selection of farnesoid X receptor (FXR) ligands on the reactivation of latent HIV proviruses		NCT05219916 (not yet open for enrollment)	Hospices Civils de Lyon	France	N/A
HIV-Mercuri: HIV study on measuring the reservoir on cellular level to cure infection		NCT04305665 (not yet open for enrollment)	University Hospital, Ghent	Belgium	N/A
HUSH restriction in HIV+ patients		NCT04172480	Inserm-ANRS	France	N/A
iCHIP: Effect of immune checkpoint inhibitors on HIV persistence		No clinicaltrials.gov entry	University of Melbourne	Australia	N/A
IciStem: Collaborative project to guide and investigate the potential for HIV cure in HIV+ patients requiring allogeneic stem cell transplantation for hematological disorders	**ATI**	No clinicaltrials.gov entry	amfAR	International	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
Identification and quantification of HIV CNS latency biomarkers		NCT02989285	St Vincent's Hospital, Sydney	Australia	N/A
Investigation of the impact of inducible, replication-competent latent HIV-1 as an impediment to HIV/AIDS cure in the context of sustained viral suppression		NCT04938518	Kenya Medical Research Institute	Kenya	N/A
LAMIVIH: Evolution of HIV reservoir, inflammation, and microbiota footprint of PLWH switching to long-acting injectable treatment		NCT05303337 (not yet open for enrollment)	Hôpital Européen Marseille	France	N/A
Long-term clinical, immunologic, and virologic profiles of children who received early treatment for HIV		NCT05154513	IMPAACT	Botswana, Brazil, Haiti, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, United States, Zimbabwe	N/A
Measurement for viral reservoir and immune function in HIV-1–infected patients under antiretroviral therapy		NCT04068441	National Taiwan University Hospital	Taiwan	N/A
Post-analytic treatment interruption study		NCT02761200	South East Asia Research Collaboration with Hawaii	Thailand	N/A
Primary infection cohort (PRIMO)		NCT03148964	Inserm-ANRS	France	N/A
Quantification of antisense HIV RNA		NCT05381844 (not yet open for enrollment)	Institut National de la Santé et de la Recherche Médicale, France	France	N/A
RESERVIH32: Bioclinical evaluation of two biomarkers of aviremic HIV-1 in CD4+ T cells of adults undergoing treatment		NCT03940521	Centre Hospitalier Universitaire de Nîmes	France	N/A
Role of the IL-33/ amphiregulin pathway as a potential therapeutic target in HIV infection		NCT03622177	Inserm-ANRS	France	N/A
Saturne-HIV: Sequential analysis before and after treatment initiation to unravel the role of naturally occurring extracellular vesicles in HIV infection		NCT04653610	University Hospital, Ghent	Belgium	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
The Gemini Study: Safety and survival of genetically modified white blood cells in HIV+ twins		NCT04799483 (closed to enrollment)	NIAID	United States	N/A
The Last Gift Study (for people with HIV and less than 6 months life expectancy due to terminal illness)		No clinicaltrials.gov entry	UCSD	United States	N/A
The use of leukapheresis to support HIV pathogenesis studies		NCT01161199	UCSF	United States	N/A
Thinking and memory problems in people with HIV		NCT01875588	National Institute of Neurological Disorders and Stroke	United States	N/A
TRESAX: T follicular helper reservoir in axillary lymph nodes study		No clinicaltrials.gov entry	Kirby Institute	Australia	N/A
STEM CELL TRANSPLANTATION					
IMPAACT P1107	Cord blood transplantation using CCR5Δ32 donor cells for the treatment of HIV and underlying disease	NCT02140944 (closed to enrollment)	IMPAACT/NIAID/ Eunice Kennedy Shriver National Institute of Child Health and Human Development	United States	N/A
Cord blood transplant with OTS for the treatment of HIV+ hematologic cancers		NCT04083170	Fred Hutchinson Cancer Research Center	United States	Phase II
STIMULANTS					
EMRLHD: Effect of methamphetamine on residual latent HIV disease study		NCT03825536	UCSF	United States	Phase IV
THERAPEUTIC VACCINES					
BELIEVE: BCG vaccination	BCG vaccination effect on latent reservoir size in treated HIV-1 infection	NCT05004038	University of Zurich	Switzerland	Phase IIa
ChAdOx1.HTI, MVA.HTI, ConM SOSIP.v7 gp140	Viral vector vaccines + HIV envelope protein, **ATI**	NCT05208125 (not yet open for enrollment)	IrsiCaixa	Spain	Phase I
DC-HIV04: a1DC + inactivated whole autologous HIV, a1DC + conserved HIV peptides	Autologous dendritic cell vaccine variants loaded with either autologous inactivated HIV or conserved HIV peptides	NCT03758625	Sharon Riddler, University of Pittsburgh	United States	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
MVA.tHIVconsv3 ± MVA.tHIVconsv4	Viral vector vaccines	NCT03844386	University of North Carolina, Chapel Hill	United States	Phase I
NETI: Trimer 4571 therapeutic vaccination	HIV envelope protein vaccine	NCT04985760	NIAID	United States	Phase I
TREATMENT INTENSIFICATION/EARLY TREATMENT					
Antiretroviral regime for viral eradication in newborns	Combination ART	NCT02712801 (closed to enrollment)	National Center for Women and Children's Health, China CDC	China	Phase IV
DGVTAF: Immediate initiation of antiretroviral therapy during 'hyperacute' HIV infection	Combination ART	NCT02656511 (closed to enrollment)	UCSF	United States	Phase IV
AAHIV: Antiretroviral therapy for acute HIV infection	Combination ART	NCT00796263	South East Asia Research Collaboration with Hawaii	Thailand	Phase III
EIT: Early infant HIV treatment in Botswana	Combination ART	NCT02369406 (closed to enrollment)	Harvard School of Public Health	Botswana	Phase II/III
EARLIER: early ART to limit infection and establishment of reservoir	Combination ART	NCT02859558 (closed to enrollment)	AIDS Clinical Trials Group	Brazil, Malawi, Peru, South Africa, Thailand, United States, Zimbabwe	Phase II
EDIT: Effect of dolutegravir intensification on HIV-1 reservoirs	Combination ART	NCT05351684	University of Liege	Belgium	Phase II

ATI = analytical treatment interruption. In some cases (particularly in trials of gene therapies for HIV-positive people with cancers), ATIs will be conducted only if study participants meet certain criteria.

N/A = not applicable.

Shaded entries represent additions since the 2021 Pipeline Report.

For the complete listing, including completed trials related to cure research and links to published and presented results where available, see TAG's Research Toward a Cure clinical trials web page at http://www.treatmentactiongroup.org/cure/trials.

Analytical Treatment Interruptions (ATIs)

Three studies are specifically analyzing the effects of ATIs in the absence of interventions, with a particular focus on identifying the sources of HIV viral load rebound. A newly initiated project sponsored by the National Cancer Institute is marrying tissue sampling with imaging technology to assess both viral reemergence and the resulting immune activation.

An ATI study at the University of California at San Francisco is pursuing similar goals, but it plans to offer a different imaging approach that uses a radiolabeled bNAb, VRC01, to track HIV rebound. The first data on this technique were published in early 2022, indicating that the approach has promise for visualizing HIV activity in the body.[38]

Broadly Neutralizing Antibodies (bNAbs)

The cure research field maintains a strong interest in the potential role of bNAbs in enhancing immune control of HIV replication, driven by hints of extended post-ATI viral load control among a few study participants. Preclinical research suggests that bNAbs can have a "vaccinal effect" that improves the function of HIV-specific immune responses, in addition to exerting direct antiviral activity.[39]

The combination of the bNAbs 10-1074 and 3BNC-117 has shown particular promise in multiple trials. Two recently published papers continue that theme. Christian Gaebler and colleagues from Rockefeller University conducted an open-label study in which 26 participants received up to seven infusions of the bNAbs.[40] ART was interrupted either two days after the first infusion (group one) or 26 weeks later (group two).

The dual bNAbs were able to maintain suppression for more than 20 weeks in most of the group one participants (13 out of 17; 76%). Echoing a prior trial that administered three infusions,[41] two participants displayed extended viral load control after all infusions ended; one was lost to follow-up after a year, and the second has displayed viral load suppression for two years (with tests confirming the absence of ART in blood samples). There were no cases of extended control in group two, who interrupted ART 13 weeks after the last bNAb infusion, but viral load rebound was delayed for a median of seven weeks.

A placebo-controlled investigation of the same bNAb combination undertaken by scientists at the National Institute of Allergy and Infectious Diseases (NIAID) also produced encouraging results. The majority of participants had started ART during the acute/early phase of infection and interrupted ART shortly after the first bNAb infusion, with up to eight doses given subsequently (every two weeks initially and then every four weeks). At week 28, six out of seven participants in the placebo arm met criteria for restarting ART, compared with none of the seven bNAb recipients. In the latter group, the average duration off ART was nearly 40 weeks.

As reported in the Gaebler paper, a combined analysis of participants in both these studies uncovered evidence that receipt of bNAbs was associated with an accelerated decline in levels of intact (but not defective) HIV in the body, hinting that this approach has the potential to promote immune clearance of cells containing viable copies of the virus.

A key issue for bNAbs is the prevalence of resistant HIV variants, which are relatively common due to the high variability of their target on the virus envelope. Several participants in the studies displayed resistance to one or both bNAbs, which was associated with a lack of sustained viral load suppression. Gaebler and colleagues note that assays designed to predict the sensitivity of HIV to bNAbs are suboptimal and didn't correlate with outcomes in their study "in part because the depth of the reservoir makes it difficult to obtain fully representative samples." Ongoing work is aiming to improve the accuracy of these technologies and better predict whether the HIV in a given individual will respond to a particular bNAb.

The vulnerability of bNAbs to HIV resistance was also emphasized by the results of a triple bNAb trial in five people who were not receiving ART.[42] Researchers led by Boris Juelg at the Ragon Institute administered infusions of the bNAbs PGT121, VRC07-523LS, and PGDM1400. While the combination led to a decline in viral load of a maximum of approximately two logs on average, all participants experienced a rebound within a median of 20 days. The rebounding HIV demonstrated resistance to both PGDM1400 and PGT121 in laboratory assays. The results show that bNAbs cannot be considered

equivalent to antiretroviral drugs, because the latter target internal components of HIV that are far less mutable than the viral envelope.

Three new trials of long-acting formulations of 10-1074 and 3BNC-117 (designated by an appended -LS) have been initiated over the past year. In the United Kingdom, the placebo-controlled RIO trial will investigate the ability of the bNAbs to maintain HIV suppression in 72 participants who initiated ART during primary infection and have received treatment for at least 12 months.[43] In France, the RHIVIERA-02 study will employ a different design, comparing therapy with ART plus the bNAbs to ART alone in people with primary HIV infection, with an ATI occurring after 52 weeks of follow-up.

NIAID and Rockefeller University are collaborating on a smaller assessment of 10-1074-LS and 3BNC-117-LS in 30 participants with chronic HIV infection, in which ART will be interrupted two days after the first bNAb infusions.

Combinations

Results from a combination trial involving the bNAb antibody 3BNC117 and a candidate latency-reversing agent, romidepsin, were presented by Ole Søgaard from Aarhus University at CROI 2022.[44] The primary aim was to assess whether administering these interventions at the time of ART initiation could accelerate clearance of the HIV reservoir and promote control of HIV viral load after an ATI. The timing of administration was novel compared with most previous cure-related research, which has generally focused on giving candidate therapies to people with long-term viral load suppression on ART. The rationale derives from research suggesting that the bulk of the HIV reservoir is formed at, or close to, the time that ART is started.[45]

The study enrolled 60 participants, approximately half with recent HIV infection (less than 6 months), and randomly assigned them to one of four groups:

- ART alone
- ART plus 3BNC117 at days 7 and 21 after ART initiation
- ART plus romidepsin at days 10, 17, and 24
- ART plus 3BNC117 and romidepsin

Participants were followed for a year and then given the option of undergoing a 12-week ATI at day 400 of follow-up. Most participants were white men; a total of five women were enrolled, but none were randomized to the arms that included 3BNC117.

The results showed that receipt of 3BNC117 was associated with greater declines in levels of cells expressing HIV RNA and the HIV p24 protein, as well as increases in HIV-specific CD8+ T-cell responses. The reduction in the intact HIV reservoir after one year of follow-up also appeared to be greater among recipients of 3BNC117 compared with those on ART alone.

Four out of the five participants whose pre-ART HIV samples were fully sensitive to 3BNC117 maintained HIV viral load below 5,000 copies/ml throughout the 12-week ATI, compared with three of 15 participants who had pre-ART evidence of HIV resistance to 3BNC117 or did not receive the antibody. These effects appeared independent of receipt of romidepsin.

One participant from the 3BNC117 and romidepsin group remains off ART and has maintained undetectable HIV viral load for 3.7 years and counting. Søgaard noted that the HIV reservoir in this individual (as measured by an intact proviral DNA assay) is continuing to shrink in size over time.

Søgaard's colleague Míriam Rosás-Umbert also presented evidence that 3BNC117 had a vaccinal effect.[46] Among participants with HIV that was sensitive to 3BNC117, Rosás-Umbert found that CD8+ T-cell responses targeting HIV Gag and Pol proteins were of significantly higher magnitude at months three and 12 of follow-up compared with other participants. The ability of T cells to produce the cytokine interferon gamma in response to HIV Gag was also significantly greater in participants with HIV that was sensitive to 3BNC117, and this capacity was associated with maintenance of viral load below 5,000 copies/ml during the ATI.

New combination trials that are getting underway include one of the first to be conducted on the African continent. The study will explore a combination of two long-acting bNAbs, VRC07-523LS and CAP256V2LS, plus the Toll-like receptor 7 (TLR7) agonist vesatolimod in women with clade C HIV who started ART early in infection. The participants are being recruited from the Females Rising through Education, Support, and Health (FRESH) cohort in the Umlazi township in KwaZulu-Natal, South Africa.[47] Vesatolimod has shown potential immune-enhancing activity in prior studies.[48,49]

Boris Juelg has instituted a study that will combine therapeutic vaccination with bNAbs, followed by an ATI. The plan is to enroll 36 participants who'll be randomized to receive the therapeutic vaccines Ad26.Mos4.HIV and MVA-BN-HIV (based on adenovirus and modified vaccinia Ankara strain vectors, respectively) and/or the bNAbs PGT121, PGDM1400, and VRC07-523LS.

In Taiwan, the company United Biopharma is testing whether its antibody inhibitor of HIV attachment to CD4, UB-421, can mediate improved control of HIV during an ATI when combined with the candidate latency-reversing agent chidamide (a histone deacetylase inhibitor licensed for use in the region).[50] Chidamide is also being combined with an immune checkpoint inhibitor, ASC22 (which blocks PD-L1), in a study sponsored by the Shanghai Public Health Clinical Center in China.[51]

The European HIV Vaccine Alliance (EHVA) has announced the launch a randomized, placebo-controlled trial marrying the therapeutic vaccine MVA HIV-B with vedolizumab, an immunotherapeutic antibody that blocks the α4β7 integrin receptor on immune cells.[52] The goal is to evaluate whether the combination can work synergistically to enhance control of HIV viral load during an ATI in people who started ART in either primary or chronic infection. The European AIDS Treatment Group (EATG) is collaborating as a community engagement partner.

Lastly, Rockefeller University is on the verge of opening a trial investigating the bNAbs 10-1074-LS and 3BNC-117-LS combined with N-803, a modified version of the cytokine interleukin-15 (IL-15) designed to have enhanced and extended biological activity. Studies in both animals and humans have indicated that N-803 is reasonably well tolerated and has immune-modulating activity, with evidence of post-ART viral load control observed in a study of SIV-infected macaques that also involved dual bNAb administration. 53,54 The AIDS Clinical Trials Group (ACTG) is now recruiting for a slightly larger trial that will also assess N-803 together with the bNAbs VRC07-523LS and 10-1074.

Dual-Affinity Re-Targeting (DART) Molecules

Researchers affiliated with the Martin Delaney CARE Collaboratory are investigating the effects of DART molecules produced by the company MacroGenics. Two different bispecific DART molecules will be assessed:

- MGD020, which binds the CD3 receptor on T cells and the gp41 subunit of the HIV envelope protein.
- MGD014, which binds the CD3 receptor on T cells and the gp120 subunit of the HIV envelope protein.

The aim of these dual-binding DART molecules is to redirect CD3-expressing T cells to kill HIV-infected CD4+ T cells. A prior study of MGD014 alone has been completed with results pending.

Gene Therapies

CROI 2022 featured an interactive session on CAR T cells, during which Jim Riley from the University of Pennsylvania revealed preliminary results from an ongoing clinical trial in people with HIV. The CAR approach involves genetic modification of T cells to equip them with receptors that enable better recognition and killing of specific targets. CAR T-cell candidates designed to recognize and kill cancerous cells have shown efficacy in clinical trials, and several are now licensed as cancer treatments.

The study administered CAR T cells designed to target HIV-infected cells, in combination with infusions of CD4+ T cells that were sampled from participants and then genetically modified to block expression of the CCR5 receptor (the latter approach was developed by Sangamo Therapeutics but is no longer being pursued commercially by the company).

Riley shared data from eight participants. Four started an ATI the day after receiving the cell infusions, and four waited eight weeks after the infusion before undergoing ATI. All participants in the first group experienced viral load rebounds over 100,000 copies/ml, which necessitated restarting ART before the end of the planned 16-week ATI. In contrast, the second group was able to complete the ATI with viral loads mostly in the low thousands.

One participant maintained a very low viral load and didn't restart ART after 16 weeks. This individual has now been followed for around 16 months off ART, and the most recent viral load was 37 copies/ml. Riley noted that this person had participated in previous Sangamo trials and had received two infusions of CD4+ T cells genetically modified to block expression of the CCR5 receptor. While this single case of extended viral load control off ART is an outlier in the context of the trial, the outcome suggests that strategies aiming to bolster the number of gene-modified cells are worth pursuing.

Riley's research group already has a potentially enhanced CAR T-cell design that they intend to move into trials. This newer CAR T cell includes the co-stimulatory molecules 4-1BB and CD28 and, in animal models, showed increased proliferative potential and activity.[55]

The company Excision Biotherapeutics achieved a significant milestone with the launch of the first clinical trial testing CRISPR/Cas9 gene-editing technology delivered into the body of people with HIV.[56] An adeno-associated virus type 9 (AAV9) vector is being used to convey the gene-editing tool, which is designed to remove or disable HIV genetic code in cells into which the virus has integrated. The approach has shown promise for reducing the HIV reservoir in mouse and macaque studies.[57,58,59]

The clinical trial will be small (nine participants) and is only enrolling men because the Food and Drug Administration (FDA) wants to see more data regarding potential reproductive toxicities before broadening eligibility. An ATI may be conducted if there is evidence of significant diminution of the HIV reservoir. There will be careful monitoring for off-target gene-editing effects of CRISPR/Cas9, which is the major safety concern. There have been reports of toxicity issues with AAV vectors in other non-HIV gene therapy research,[60] and this will also be a focus for investigators. All participants will subsequently be enrolled into a separate long-term follow safety study to monitor their health for 15 years.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are antibodies that are designed to block certain receptors on immune cells, with the aim of reinvigorating T-cell responses that have become exhausted and dysfunctional. Several are now licensed for the treatment of cancers but are attended by significant safety issues because they can inadvertently stimulate T cells that had been switched off because they targeted body tissues, leading to autoimmune disease.

There are two new trials getting underway in people with HIV. The research group of Sharon Lewin in Melbourne, Australia, plans to evaluate low-dose administration of the PD-1 inhibitor nivolumab. The study will involve two phases: the first testing escalating doses and the second incorporating an ATI.

In Beijing, China, the company Ascletis Pharma is sponsoring an assessment of a PD-L1 inhibitor, ASC22, in 30 participants with HIV. The primary goals are to assess safety, tolerance, and effects on immune parameters and HIV reservoir measures.

The pharmaceutical company AbbVie is also pursuing a PD-1 inhibitor, budigalimab, as part of an HIV cure research program. They are sponsoring two ongoing trials in HIV, with a plan to potentially combine budigalimab with another antibody that targets the α4β7 integrin receptor on immune cells (currently known as ABBV-382 and under investigation in a separate study). The combination antibody is codenamed ABBV-1882 but is yet to enter clinical testing.[61]

The rationale for this work has been bolstered by the publication of results from a study of the PD-1 inhibitor pembrolizumab in people with HIV and cancer diagnoses.[62] The researchers found evidence that pembrolizumab reversed HIV latency to a significant degree, potentially facilitating targeting of the viral reservoir by the immune system.

Therapeutic Vaccines

Joining the roster of therapeutic vaccine research over the past year are three trials. The IrsiCaixa AIDS Research Institute in Barcelona, Spain, will test two viral vector-based vaccines that have previously shown some promise, ChAdOx1.HTI and MVA.HTI,[63] with an HIV envelope protein boost that forms a trimer structure to mimic the natural virus conformation (ConM SOSIP.v7 gp140[64]).

Researchers at NIAID are also exploring the therapeutic potential of HIV envelope protein vaccination in people with HIV on ART. Led by Madhu Choudhary, the trial will administer Trimer 4571 in alum adjuvant, a vaccine construct that has been found safe in HIV-negative volunteers.[65]

The University of Zurich is sponsoring a novel study of the bacillus Calmette-Guérin (BCG) tuberculosis (TB) vaccine to assess whether it has any impact on the HIV reservoir in people with suppressed viral load on ART. While BCG is only partially effective against TB, it has been reported to have immune-modulating activity in multiple other settings.[66]

Table 2. Immune-Based Therapy Pipeline 2022

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Status
Fostemsavir	Attachment inhibitor	NCT05220358	Orlando Immunology Center	Phase IV
Zadaxin	Thymosin α-1	NCT04963712	Shanghai Public Health Clinical Center	Phase III
Canakinumab	IL-1β inhibitor	NCT02272946 (closed to enrollment)	University of California, San Francisco	Phase II
Letermovir (Prevymis)	Anti-cytomegalovirus drug	NCT04840199	NIAID	Phase II
Mismatched allogeneic adoptive immune therapy (AAIT)	Allogeneic adoptive immunotherapy	NCT04098770	Beijing 302 Hospital	Phase II
Pyridostigmine	Acetylcholinesterase inhibitor	NCT03312244 (suspended due to COVID-19: effective March 19, 2020, recruitment halted until further notice)	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán	Phase II
Allogeneic adoptive immune therapy	Granulocyte colony-stimulating factor–mobilized donor peripheral blood mononuclear cells	NCT02648516	Beijing 302 Hospital	Phase I/II
Brentuximab vedotin	Antibody-drug conjugate including a chimeric anti-CD30 monoclonal antibody and the microtubule inhibitor monomethyl auristatin E (MMAE)	NCT05244473	Seagen	Phase I
Camu camu	Brazilian fruit extract	NCT04058392	McGill University Health Centre/Research Institute of the McGill University Health Centre	Phase I
Pembrolizumab	Anti-PD1 antibody, immune checkpoint inhibitor	NCT03367754	National Institutes of Health Clinical Center	Phase I
Yuyang capsule	Traditional Chinese medicine	ChiCTR1900023860	Sichuan Academy of Traditional Chinese Medicine	Phase 0
Bifidobacteria and *Lactobacilli* triple viable capsules	Probiotics	NCT04297488	Peking Union Medical College Hospital	Not specified

Data from studies of COVID-19 vaccination in people with HIV has shown that there is still a rationale for trying to enhance immune reconstitution in cases where CD4+ T-cell counts remain low despite suppression of viral load. A relatively consistent finding to emerge from this research is that low CD4+ T-cell counts (for example, below 200 or below 350) are associated with reduced responses to vaccination and a greater risk of breakthrough COVID-19 infection and serious illness.[67,68,69]

Four new trials of possible adjunctive therapies have been registered over the past year, up from just one during the previous year. Fostemsavir (trade name Rukobia) is an antiretroviral drug that inhibits HIV attachment to the CD4 receptor. The FDA approved fostemsavir for the treatment of people with multidrug resistant HIV and limited options on July 2, 2020.[70]

An interesting and unexpected finding from studies was that receipt of fostemsavir appeared to be associated with CD4+ T-cell count gains of greater magnitude than might have been anticipated based on just direct suppression of HIV replication.[71] The effect was particularly prominent among participants with the lowest baseline CD4+ T-cell counts: after 96 weeks of follow-up, an average increase of 240 cells was demonstrated for those who started with less than 20 cells. Of the participants who began with less than 50 cells, 56% experienced immunologic recovery to greater than 200 cells.

The Orlando Immunology Center is now collaborating with manufacturer ViiV Healthcare on a study to investigate the phenomenon in greater detail. Given that fostemsavir is already approved, this could represent a very encouraging development for people with suboptimal CD4+ T-cell recovery on ART, after many years with no sign of progress.

Additionally, researchers at the Shanghai Public Health Clinical Center are looking at Zadaxin, also known as thymosin alpha 1 or thymalfasin, which is a peptide approved to treat hepatitis B in the region. The trial is open to people with CD4+ T-cell counts between 100 and 350 cells.

The company Seagen is sponsoring a study of the anticancer drug brentuximab vedotin for individuals with CD4+ T-cell counts between 51 and 200 cells despite suppression of viral load to undetectable levels for at least two years on ART. The main goal is to evaluate safety, but CD4+ T-cell increases will be measured as a secondary endpoint.

The Research Institute of the McGill University Health Centre has opened a trial of a Brazilian fruit extract, camu camu, with the primary aim of measuring changes in translocation of bacteria from the gut and inflammatory markers. The study seeks to enroll participants with CD4+ T-cell counts over 200 but a CD4:CD8 ratio less than one.

One of very few industry-sponsored studies included in last year's Pipeline Report, which was assessing an immune-modulating compound CD24Fc, has unfortunately now been terminated "for business reasons" according to the trial registry entry. No further details are provided.

The ability of probiotics to promote immune reconstitution has been tested in multiple trials, but only one such study remains ongoing in China. Two randomized controlled trials of the probiotic formulation Visbiome were published recently, with neither finding evidence of benefit.[72,73] In one case, the intervention appeared to increase CD4+ T-cell activation, which is not a desirable outcome. These findings likely spell the end of the road for probiotics as adjunctive immune modulators in HIV.

Conclusion

The expansion of the Martin Delaney Collaboratories and the renewed IAS Towards an HIV Cure Global Scientific Strategy have provided a welcome fillip for the HIV cure research field, as has news of a potential additional HIV cure case in New York City.

But against this backdrop, progress toward effective curative interventions is still painstaking and challenging. The finding of a preferential decline in levels of intact HIV in people on ART is encouraging, as are hints that this process might be accelerated by bNAbs.

The annual analysis from the International AIDS Society Towards an HIV Cure Initiative, AVAC, and the Resource Tracking for HIV Prevention Research and Development Working Group reports that, in 2020, HIV cure research was essentially flat funded compared with 2019.[74] The Working Group estimated that in 2020, US$337.4 million was invested globally, compared with US$334.5 million in 2019. The U.S. National Institutes of Health continues to contribute the bulk of all HIV cure research funding.

After a long, forlorn period without progress, the effort to establish whether fostemsavir can address the problem suboptimal immune recovery—at least to some extent—offers a welcome sliver of hope. But this area of research is still undersupported, and the possibility of new pandemics beyond COVID-19 only emphasizes the need to ensure that the immune systems of people with HIV are as robust as possible.

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