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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 past year has made for a difficult balancing act for scientists working to develop an HIV cure. The global COVID-19 pandemic limited activities in both laboratories and clinics, and challenging territory had to be navigated in order to safely initiate planned clinical trials. Many HIV researchers have also been drawn into the battle against COVID-19 due to their expertise in infectious disease. Nevertheless, the research has continued, albeit at a slightly slower pace. Since the 2020 Pipeline Report, 19 new HIV cure-related clinical trials or observational studies have opened, compared with 27 during the previous year (see Table 1).

Very unwelcome news for the cure field was the loss of Timothy Ray Brown, the generous and humble trailblazer whose case has done so much to spur the research effort over the last two decades. Brown died on September 29, 2020, from a recurrence of leukemia.[1] His HIV infection remained absent, a result of the cure achieved in 2007 by stem cell transplants from a donor lacking the CCR5 co-receptor used by most virus variants to gain entry into cells (the stem cell transplants were needed to treat the initial occurrence of the leukemia, which thereafter went into long-term remission).[2]

A part of Brown's extraordinary legacy as a cure research advocate are projects—particularly the amfAR-supported IciStem consortium—that seek to identify CCR5-negative donors for people with HIV who require stem cell transplants to treat life-threatening cancers. This work has led to a second HIV cure for 'the London patient', Adam Castillejo,[3] and possibly a third for an individual in Düsseldorf.[4] While stem cell transplants carry a high risk of mortality and are only appropriate for people with serious cancer diagnoses, these examples have provided essential evidence that a cure for HIV is achievable—the challenge is to achieve similar outcomes with practical therapeutic approaches.

Additional examples of possible cures have emerged from studies of elite controllers, rare HIV-positive people whose immune systems are able to suppress viral load for a long period—in some cases perhaps for life—without the need for antiretroviral therapy (ART). Over the past few years, the researcher Xu Yu from Harvard University has identified two elite controllers who appear to have possibly cleared from their bodies all the HIV that was capable of replicating.

The first case to be reported was Loreen Willenberg, a longtime advocate for elite controller research based in San Diego.[5,6] More recently, at the 2021 Conference on Retroviruses and Opportunistic Infections (CROI), Xu Yu described a second similar finding in an unnamed female elite controller (referred to as 'the Esperanza Patient').[7] Analyses of billions of peripheral blood cells from the individual were unable to detect HIV. These findings offer hope that efforts to enhance the immune response to HIV in people who aren't elite controllers may eventually pay off, although success to date remains limited.

To help support the continuation of HIV cure-related clinical trials during the COVID-19 crisis, community advocates have collaborated with scientists to publish several papers providing recommendations on best practices. The publications include guidance on the conduct of research involving analytical treatment interruptions (ATIs) [8,9,10] and providing COVID-19 vaccines to study participants.[11] The International AIDS Society has also issued guidance that addresses HIV research more broadly.[12]

There are no signs of progress when it comes to the development of immune-based therapies that might enhance immunological recovery in people with poor CD4+ T cell gains despite successful ART-mediated viral load suppression. A small number of possible interventions continue to be assessed by academic researchers (see Table 2), but industry investment remains almost entirely absent. Results are pending from the large REPRIEVE trial, which will assess whether the anti-inflammatory activity of a statin drug is linked to health benefits in people on ART.

Table 1. Research Toward a Cure 2021: Current Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
ADOPTIVE IMMUNOTHERAPY					
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	USA	Phase I
HIV-1 specific T cells for HIV+ individuals	HIV-specific T cells with non-escaped epitope targeting (HST-NEETs)	NCT03485963	Children's Research Institute	USA	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
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, USA	N/A
GSK3810109A	Long-acting broadly neutralizing antibody formerly named N6-LS	NCT04871113 (not yet open for enrollment)	ViiV Healthcare	Europe, USA	Phase IIa
10-1074-LS + 3BNC117-LS	Long-acting broadly neutralizing antibodies in primary infection, **ATI**	NCT04319367	Imperial College London	UK	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
UB-421	Antibody inhibitor of HIV binding to CD4 receptors	NCT03743376 (closed to enrollment)	United BioPharma	Taiwan	Phase II
Vedolizumab	Anti-α4β7 integrin antibody, **ATI**	NCT03147859	Ottawa Hospital Research Institute	Canada	Phase II
PGT121 + VRC07-523LS ± PGDM1400	Broadly neutralizing antibody + long-acting broadly neutralizing antibody	NCT03721510	International AIDS Vaccine Initiative (IAVI)	USA	Phase I/IIa
VRC01	Broadly neutralizing antibody in infants	NCT03208231 (closed to enrollment)	National Institute of Allergy and Infectious Diseases (NIAID)	Botswana, Brazil, Malawi, Zimbabwe	Phase I/II
VRC01LS + 10-1074	Long-acting broadly neutralizing antibody + broadly neutralizing antibody in early-treated children, **ATI**	NCT03707977 (closed to enrollment)	NIAID	Botswana	Phase I/II
ABBV-382	Antibody with undisclosed mechanism of action	NCT04554966	AbbVie	USA	Phase Ib

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
10-1074-LS ± 3BNC117-LS	Long-acting broadly neutralizing antibodies	NCT03554408 (closed to enrollment)	Rockefeller University	USA	Phase I
3BNC117 + 10-1074	Broadly neutralizing antibodies, **ATI**	NCT03526848 (closed to enrollment)	Rockefeller University	USA	Phase I
3BNC117-LS + 10-1074-LS	Long-acting broadly neutralizing antibodies in viremic individuals	NCT04250636	Rockefeller University	USA	Phase I
AAV8-VRC07	Broadly neutralizing antibody delivered by adeno-associated virus (AAV) vector	NCT03374202	NIAID	USA	Phase I
SAR441236	Tri-specific broadly neutralizing antibody	NCT03705169	NIAID	USA	Phase I
VRC01	Broadly neutralizing antibody in acute HIV infection	NCT02591420	NIAID	Kenya, Tanzania, Thailand, Uganda	Phase I
ANTI-CMV THERAPY					
Letermovir (Prevymis)	Anti-cytomegalovirus drug	NCT04840199 (not yet open for enrollment)	NIAID	USA	Phase II
ANTI-INFLAMMATORY					
Canakinumab	IL-1β inhibitor	NCT02272946 (closed to enrollment)	University of California, San Francisco (UCSF)	USA	Phase II
CD24Fc	Human CD24 extracellular domain and human IgG1 Fc fusion protein	NCT03960541 (closed to enrollment)	OncoImmune	USA	Phase II
ANTIRETROVIRAL THERAPY					
Doravirine concentrations and antiviral activity in cerebrospinal fluid	Non-nucleoside reverse transcriptase inhibitor	NCT04079452 (not yet open for enrollment)	Fundació Lluita Contra la SIDA	Spain	Phase III
IDOLTIB: Impact of dolutegravir + lamivudine simplification on HIV-1 reservoirs	Integrase inhibitor + nucleoside reverse transcriptase inhibitor	NCT04034862 (not yet open for enrollment)	University of Liège	Belgium	Phase III
CANNABINOIDS					
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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
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)	USA	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, USA	Phase IIa
Albuvirtide + 3BNC117	Fusion inhibitor + broadly neutralizing antibody, ATI	NCT04819347 (not yet open for enrollment)	Frontier Biotechnologies Inc.	China	Phase II
eCLEAR: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody	NCT03041012 (closed to enrollment)	Aarhus University Hospital	Denmark, UK	Phase II
MVA HIV-B ± vedolizumab	Viral vector vaccine ± anti-$\alpha_4\beta_7$ integrin antibody, **ATI**	NCT04120415 (not yet open for enrollment)	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	France, Germany, Italy, Netherlands, Spain, Switzerland, UK	Phase II
Research in viral eradication of HIV reservoirs (RIVER): ART, ChAdV63. HIVconsv, and MVA. HIVconsv vaccines, vorinostat	Therapeutic vaccines + HDAC inhibitor	NCT02336074 UK CPMS18010 (closed to enrollment)	Imperial College London	UK	Phase II
Vorinostat ± tamoxifen in postmenopausal women	HDAC inhibitor + estrogen receptor modulator	NCT03382834 (closed to enrollment)	NIAID	USA	Phase II
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, USA, Zambia, Zimbabwe	Phase I/II
Panobinostat + pegylated interferon-α2a	HDAC inhibitor + cytokine	NCT02471430	Massachusetts General Hospital	USA	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
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	USA	Phase I/II
Elipovimab (formerly GS-9722) ± vesatolimod	Broadly neutralizing antibody + TLR7 agonist	GS-US-420-3902 (no clinicaltrials.gov entry)	Gilead Sciences	USA	Phase Ib
CD4ζ ± interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	USA	Phase I
Chidamide + CAR T or TCR T cell therapy	HDAC inhibitor + chimeric antigen or T-cell receptor T-cell therapy	NCT03980691	Guangzhou 8th People's Hospital	China	Phase I
HVRRICANE: HIVIS DNA + MVA-CMDR vaccines ± Cervarix (TLR4 agonist)	Therapeutic vaccines + TLR4 agonist	NCT04301154 (not yet open for enrollment)	PENTA Foundation	Italy, South Africa, Thailand	Phase I
N-803 ± VRC07-523LS + 10-1074	Recombinant human super agonist interleukin-15 complex, broadly neutralizing antibodies, **ATI**	NCT04340596	NIAID	USA	Phase I
Peginterferon α-2b + 3BNC117 + 10-1074	Cytokine, broadly neutralizing antibodies, **ATI**	NCT03588715	Wistar Institute	USA	Phase I
VRC07-523LS + vorinostat	Broadly neutralizing antibody, HDAC inhibitor	NCT03803605	University of North Carolina, Chapel Hill	USA	Phase I
Vorinostat + HXTC: HIV-1 antigen expanded specific T-cell therapy	HDAC inhibitor + adoptive immunotherapy	NCT03212989	University of North Carolina, Chapel Hill	USA	Phase I
CYTOKINES					
N-803	Recombinant human super agonist interleukin-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 interleukin-15 complex on B-cell follicles	NCT04808908	University of Minnesota	USA	Phase I
DUAL-AFFINITY RE-TARGETING (DART) MOLECULES					
MGD014	Bispecific DART molecule targeting the HIV Env protein and CD3-expressing T cells	NCT03570918	MacroGenics	USA	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
GENE THERAPIES					
LVgp120duoCAR-T cells	Autologous T cells gene-modified to express chimeric antigen receptors (CARs) targeting HIV	NCT04648046	Steven Deeks, UCSF	USA	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	USA	Phase I/II
SB-728-T	Autologous CD4+ T cells modified to inhibit CCR5 expression	NCT03666871	Case Western Reserve University	USA	Phase I/II
AGT103-T	Gene-modified HIV-specific CD4+ T cells	NCT04561258	American Gene Technologies International Inc.	USA	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	University of Pennsylvania	USA	Phase I
CAR T-cell therapy	Autologous T cells gene-modified to express a CAR targeting HIV	NCT03240328	Guangzhou 8th People's Hospital	China	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	USA	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	USA	Phase I
shRNA-modified CD34+ cells	Infusion of autologous CD34+ cells transduced with short hairpin RNAs targeting CCR5 and the HIV genome	NCT03517631	Shanghai Public Health Clinical Center	China	Phase I
Third-generation CAR T-cell therapy	Autologous T cells gene-modified to express chimeric antigen receptors targeting HIV	NCT04863066 (not yet open for enrollment)	Beijing 302 Hospital	China	Phase I
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS					
Safety of transplantation of CRISPR CCR5 modified CD34+ cells in HIV-infected subjects with hematological malignances	Stem cells gene-modified to abrogate CCR5 expression using CRISPR technology, ATI	NCT03164135	307 Hospital of PLA (Affiliated Hospital of Academy to Military Medical Sciences)	China	Not listed
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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
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	USA	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	USA	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	USA	Phase I
GONADOTROPIN-RELEASING HORMONE (GnRH) AGONISTS					
Triptorelin acetate depot		NCT03536234	Immune System Regulation AB	Sweden	Phase II
HORMONES					
Somatotropin	Human growth hormone	NCT03091374	McGill University Health Center	Canada	Phase II
IMAGING STUDIES					
Imaging immune activation in HIV by PET-MR		NCT03684655	UCSF	USA	Phase I
Radiolabeled VRC01	Radiolabeled broadly neutralizing antibody	NCT03729752	UCSF	USA	Phase I
IMMUNE CHECKPOINT INHIBITORS					
Durvalumab in solid tumors	Anti–PD-L1 antibody	NCT03094286 (closed to enrollment)	Spanish Lung Cancer Group	Spain	Phase II
Budigalimab	Anti–PD-1 antibody, ATI	NCT04223804	AbbVie	Australia, Canada, France, USA	Phase Ib
Budigalimab	Anti–PD-1 antibody	NCT04799353	AbbVie	Puerto Rico, USA	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, USA	Phase I
Pembrolizumab	Anti–PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms	NCT02595866	National Cancer Institute	USA	Phase I
Pembrolizumab	Anti–PD-1 antibody, single dose	NCT03239899	National Institute of Neurological Disorders and Stroke	USA	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
LATENCY-REVERSING AGENTS					
Arsenic trioxide	Chemotherapy	NCT03980665	Guangzhou 8th People's Hospital	China	Phase I
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	USA	Phase I
mTOR INHIBITORS					
Metformin		NCT04500678	University of Hawaii	USA	Phase II/III
OBSERVATIONAL STUDIES					
2000 HIV Human Functional Genomics Partnership Program (2000HIV)		NCT03994835	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	USA	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
CHRONO: A 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	USA	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
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
FXReservoir: study of the effects of farnesoid X receptor (FXR) ligands on the reactivation of latent provirus		NCT03618862	Hospices Civils de Lyon	France	N/A
HEATHER: HIV reservoir targeting with early antiretroviral therapy		UK CPMS17589	University of Oxford/Medical Research Council/British HIV Association	UK	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
Host and viral factors associated with HIV elite control		UK CPMS16146	University College London Hospitals NHS Foundation Trust	UK	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
HSCT-HIV: Allogeneic hematopoietic stem cell transplantation in HIV+ patients		NCT02732457	Kirby Institute	Australia	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
Identification and quantification of HIV CNS latency biomarkers		NCT02989285	St Vincent's Hospital, Sydney	Australia	N/A
Impact of ART adherence on HIV persistence and inflammation		NCT02797093 (closed to enrollment)	University of Colorado, Denver	USA	N/A
Long-term effects of ART in acute HIV infection		ChiCTR1800015006	Key Laboratory of AIDS Immunology of National Health and Family Planning Commission, Department of Laboratory Medicine, The First Affiliated Hospital, China Medical University	China	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
PITCH: prospective interruption of therapy towards a cure for HIV pilot study	**ATI**	No clinicaltrials.gov entry	University of Oxford	UK	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
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
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans		NCT02154035 (closed to enrollment)	NIAID	Uganda	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
SCOPE-ATI: SCOPE analytic treatment interruption protocol	**ATI**	NCT04359186 (enrolling by invitation)	UCSF	USA	N/A
TESOVIR	Tracking and exploring the source of viral rebound after **ATI**	NCT03117985	Centre Hospitalier Régional d'Orléans	France	N/A
The Gemini Study: Safety and survival of genetically modified white blood cells in HIV+ twins		NCT04799483 (closed to enrollment)	NIAID	USA	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	USA	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
The use of leukapheresis to support HIV pathogenesis studies		NCT01161199	UCSF	USA	N/A
Thinking and memory problems in people with HIV		NCT01875588	National Institute of Neurological Disorders and Stroke	USA	N/A
TRESAX: T follicular helper reservoir in axillary lymph nodes study		No clinicaltrials.gov entry	Kirby Institute	Australia	N/A
PROTEASOME INHIBITORS					
Ixazomib		NCT02946047 (closed to enrollment)	Mayo Clinic	USA	Phase I
STEM CELL TRANSPLANTATION					
HIVECT: HIV eradication through cord-blood transplantation	ATI	NCT02923076	Puerta de Hierro University Hospital	Spain	N/A
IMPAACT P1107	Cord blood transplantation using CCR5Δ32 donor cells for the treatment of HIV and underlying disease	NCT02140944	IMPAACT/ NIAID/Eunice Kennedy Shriver National Institute of Child Health and Human Development	USA	N/A
Cord blood transplant with OTS for the treatment of HIV+ hematologic cancers		NCT04083170	Fred Hutchinson Cancer Research Center	USA	Phase II
STIMULANTS					
EMRLHD: effect of methamphetamine on residual latent HIV disease study		NCT03825536	UCSF	USA	Phase IV
THERAPEUTIC VACCINES					
Ad26.Mos4.HIV + MVA-Mosaic or clade C gp140 + mosaic gp140	Adenovirus and modified Vaccinia Ankara strain vectors encoding mosaic HIV antigens + Env protein boosts	NCT03307915 (closed to enrollment)	Janssen Vaccines & Prevention B.V.	USA	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
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	USA	Phase I
DNA.HTI + MVA.HTI + ChAdOx1.HTI	DNA + viral vector vaccines, **ATI** extension	NCT04385875 (closed to enrollment)	Fundació Lluita Contra la SIDA	Spain	Phase I
MVA.tHIVconsv3 ± MVA.tHIVconsv4	Viral vector vaccines	NCT03844386	University of North Carolina, Chapel Hill	USA	Phase I
TREATMENT INTENSIFICATION/EARLY TREATMENT					
P25-INACTION: implication for strategies of long-term control of viral replication in patients with primary HIV infection	Combination ART	NCT04225325	Adriano Lazzarin, MD	Italy	Phase IV
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	USA	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, USA, Zimbabwe	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 2020 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.

Broadly Neutralizing Antibodies

Broadly neutralizing antibodies (bNAbs) continue to be a major focus of HIV cure research. Advances in technology have allowed for the identification, isolation, and manufacture of an increasing number of these rare antibodies with strong anti-HIV activity against a broad range of virus variants.

The interest in cure research is driven by evidence that some bNAbs have the potential to enhance immune control of HIV replication by flagging virus-infected cells for destruction.[13] The primary mechanism is called antibody-dependent cellular cytotoxicity (ADCC), which involves bNAbs binding to HIV fragments on the surface of infected cells and marking them for destruction by other immune cells, particularly natural killer (NK) cells. There is also evidence that bNAbs can beneficially modulate the activity of CD8+ T cells, another key immune cell with the capacity to recognize and eliminate virus-infected cells.

Pharmaceutical companies have taken notice of the possible promise of bNAbs, with Gilead licensing at least three from academic researchers: PGT121 (now modified and known as elipovimab) and 10-1074 and 3BNC-117 (long-acting versions have been renamed as GS-5423 and GS-2872 for future Gilead-sponsored trials). ViiV has licensed N6 and will soon open a trial of long-acting version christened GSK3810109A (see Table 1). AbbVie has also initiated a trial of an anti-HIV antibody, but the mechanism has not yet been publicly disclosed; it might be a bNAb but alternatively could target a host protein used by HIV, such as CCR5.

Hopes that bNAbs may enhance immune control of HIV have been bolstered by a few examples of individuals maintaining low viral loads for extended periods after administration in trials. In a study published by researchers at Rockefeller University, short-term dosing of 10-1074 and 3BNC-117 led to prolonged (>30 weeks) control of HIV viral load in two recipients after an ATI.[14] Analyses indicated that these participants had shown a notable early increase in CD4+ and CD8+ T cell responses targeting HIV compared with counterparts whose viral load rebounded sooner.[15] A small trial of a single infusion of the bNAb PGT121 administered to HIV-positive people who were not on ART identified two participants with low viral loads at baseline who displayed sustained suppression for over five months.[16]

One of the first bNAbs to be discovered, VRC01, was recently assessed for preventive efficacy in two large trials (the Antibody-Mediated Prevention, or AMP, studies) sponsored by the HVTN and the HIV Prevention Trials Network (HPTN). The results did not demonstrate success overall, but there was a significant reduction in HIV incidence among a subset of participants exposed to viruses that were not resistant to VRC01.[17] HVTN is now sponsoring two follow-up studies for participants who acquired HIV and initiated ART during the trials, to explore whether receipt of VRC01 can promote viral load control during a subsequent ART interruption (see Table 1). The results will hopefully assist efforts to understand the potential therapeutic benefits of bNAbs.

Combinations

The evaluation of combination strategies represents the most common type of cure-related clinical research, with a total of 20 trials currently ongoing. There are two new additions to the roster in 2021, both involving bNAbs:

- Frontier Biotechnologies in China plans to initiate a trial of its proprietary peptide-based HIV fusion inhibitor albuvirtide in combination with the bNAb 3BNC117. Participants will undergo an ATI to assess the potential for HIV reservoir reduction and viral load control off ART.

- Gilead Sciences is conducting a study combining the bNAb elipovimab (formerly known as GS-9722) with their Toll-like receptor 7 (TLR7) agonist vesatolimod. Both interventions have shown preliminary evidence of safety and favorable pharmacokinetics in previous clinical trials.[18,19,20] Details on the study design are lacking because the company has a frustrating reluctance to enter its early-phase trials into public registries such as clinicaltrials.gov.

An AIDS Clinical Trials Group (ACTG) trial opening at multiple sites in the United States is testing the effects of two bNAbs, VRC07-523LS and 10-1074, together with N-803, a modified version of the cytokine interleukin-15 (IL-15) designed to have enhanced and extended biological activity.

As noted in last year's Pipeline Report, preclinical studies of N-803 have indicated possible immune-enhancing and HIV latency-reversing activity.[21,22] A phase I trial at the University of Minnesota reported that administration was safe and led to activation of natural killer cells and T cells.[23] The combination of N-803 with two bNAbs has been explored in macaques infected with a hybrid simian-human immunodeficiency virus (SHIV), with the majority of recipients displaying sustained control of virus replication of an ART interruption.[24] The ACTG trial will similarly involve an ATI.

Results from the most complex combination study conducted to date caused a stir when they were presented at the virtual AIDS 2020 conference by lead investigator Ricardo Diaz.[25] The attention resulted from the disclosure that one of the participants had displayed an absence of HIV viral load rebound for over a year after an ATI.

The trial was launched in 2015 and involved a complex design in which 30 participants with HIV were divided into six groups of five people each. One group continued on a standard ART regimen and served as controls, while the other five groups received the following additional interventions:

- Group 2: Dolutegravir and the CCR5 inhibitor maraviroc (which has been reported to also exert HIV latency-reversing effects[26])
- Group 3: Dolutegravir, maraviroc, and nicotinamide (a water-soluble form of vitamin B3 that may have HIV latency-reversing activity[27])
- Group 4: Dolutegravir, maraviroc, and auranofin (an antiproliferative drug)
- Group 5: Dolutegravir and a dendritic-cell therapeutic vaccine
- Group 6: Dolutegravir, a dendritic-cell therapeutic vaccine, auranofin, and nicotinamide

The original study design did not include an ATI, but the protocol was later revised and 25 of the participants underwent an ATI approximately 2.5 years after the end of the 48-week period during which the interventions were administered.

A previous presentation at the 2019 HIV Persistence Workshop noted that two participants in group six and one in group three did not immediately experience viral load rebounds during the ATI. After around 16 weeks, viral load did reappear in the two people from group six, prompting reinitiation of ART.[28]

The focus of the AIDS 2020 report was the single individual in group three who did not experience viral load rebound. HIV DNA levels had declined to undetectable levels prior to the ATI, and antibody responses against HIV waned. Diaz suggested the case represented an example of long-term remission, drawing considerable news coverage.

To less fanfare, Diaz presented a short report at CROI 2021 noting that viral load rebound did eventually occur in this individual after around 20 months.[29] The researchers have conducted preliminary analyses that suggested the reappearing virus may have mutated to escape T cell immune responses, although they are also considering the possibility of reinfection.

The role of the study interventions in the potentially encouraging but lone example of prolonged HIV control is unclear. The person began ART relatively early after infection and did not have a very high viral load at the time (20,221 copies/mL). Notably, of the other 30 study participants, nine received nicotinamide and 14 received dolutegravir and maraviroc. No additional examples of similarly prolonged absence of viral load rebound were observed. The uncertainty about the role of the study drugs is important to stress, given that nicotinamide is available over the counter as a supplement. At the current time, there is no evidence to suggest that adding dolutegravir, maraviroc, and nicotinamide to ART regimens would lead to similar outcomes in other people with HIV.

According to reporting by the Associated Press,[30] Diaz will receive support to conduct a larger 60-person trial, which should help clarify whether these experimental regimens can play a role in promoting post-treatment control of HIV.

Cytokines

N-803 is also the subject of two new studies for people on ART. In Bangkok, Thailand, researchers affiliated with the Thai Red Cross AIDS Research Centre and the U.S. Military HIV Research Program (MHRP) will evaluate whether subcutaneous injections of N-803 reduce the viral reservoir in lymph nodes of ART-treated people with acute HIV infection.[31]

The University of Minnesota is conducting a small trial to investigate whether the addition of N-803 to ART can increase the ability of CD8+ T cells to access a particular area of lymph nodes called the B-cell follicle, typically a major site of HIV persistence. The rationale for the experiment derives from a preclinical study in macaques that demonstrated increased CD8+ T cell trafficking into B-cell follicles and decreased amounts of SIV RNA and DNA in these locations.[32]

Gene Therapies

Three new trials of gene therapies were initiated over the past year, highlighting that this remains an active area of HIV cure research. Some researchers believe that the vulnerability of CD4+ T cells to HIV infection makes it essential to pursue gene modification strategies to protect these key components of the immune system. The cases of Timothy Ray Brown and Adam Castillejo offer some support for this notion: the stem cell transplants they received equipped them with donor-derived CCR5-negative CD4+ T cells that are resistant to most HIV variants.

A countervailing view is that the potential obstacles to widespread implementation of gene therapies—including the expense and laboratory requirements for modifying cells outside of the body—are likely to make the approach impractical. But work is underway to address these issues and promote global access to existing gene therapies for cancer.

The nonprofit Caring Cross, led by researchers previously involved in the company Lentigen, is at the forefront of this effort. The Bill & Melinda Gates Foundation (BMGF) and the National Institutes of Health (NIH) are also collaborating to develop accessible gene therapy approaches for both HIV and sickle cell disease.[33] Boro Dropulić from Caring Cross and Mike McCune from the HIV Frontiers initiative at BMGF presented updates on this work at the 2021 virtual Pre-CROI Community HIV Cure Research Workshop (videos of these presentations are available online [34,35]).

Caring Cross is involved in one of the new gene therapy trials, an assessment of a chimeric antigen receptor (CAR) approach targeting HIV being conducted at the University of California, San Francisco (UCSF). T cells from study participants will be extracted and modified to express two CAR molecules that facilitate both recognition of HIV components and protection of the cell from infection (dubbed duoCARs). Gene-modified T cells are then reinfused, with some participants receiving a 'conditioning' dose of cyclophosphamide to deplete existing T cells, with the aim of creating room for the

transferred cells. An ATI will be conducted to assess whether the modified T cells can mediate control of viral load in the absence of ART. The duoCARs have demonstrated control of HIV replication in a humanized mouse model in preclinical studies.[36]

A Maryland-based company, American Gene Technologies, has opened the first trial of a novel gene therapy (AGT103-T) that aims to focus modification on HIV-specific CD4+ T cells (the subset of CD4+ T cells that recognize and respond to HIV antigens). Typically, virus-specific CD4+ T cells would be expected to lead the immune system's effort to contain a viral infection by sending important signals to immunological compatriots, including CD8+ T cells and B cells. But HIV has been shown to preferentially target HIV-specific CD4+ T cells for infection,[37] leaving the immune system leaderless in its battle to suppress viral replication.

The American Gene Technologies technique involves expanding and gene-modifying HIV-specific CD4+ T cells sampled from study participants in order to protect them from infection. Large numbers of these cells will then be infused to assess safety and effects on HIV persistence. The initial study does not involve an ATI, but they will be implemented in future studies if all goes well.

The company has made some bullish statements about the potential for AGT103-T to be curative, but it is important to temper expectations because many unknowns remain, including the possibility that other factors beyond direct infection disrupt the function of HIV-specific CD4+ T cells. The rationale for testing the idea is solid, however, with two recently published studies suggesting that the best responses to a previous generalized approach to gene-modifying CD4+ T cells (designed by the company Sangamo Therapeutics) were linked to enhanced HIV-specific immunity.[38,39] Additionally, a preclinical study in macaques reported that protection of SHIV-specific CD4+ T cells by gene modification was associated with reduced viral load, enhanced immune responses, and maintenance of unprotected CD4+ T cells after a SHIV challenge.[40]

The third trial is taking place in China, assessing a third-generation CAR T-cell therapy. In the study, T cells sampled from study participants will be modified to express a CAR based on a bNAb fragment that targets HIV. In preclinical laboratory experiments, the CAR T cells were effective in mediating killing of HIV-infected CD4+ T cells sampled from people on ART.[41]

Therapeutic Vaccines

At the 2021 CROI, Beatriz Mothe debuted data from a small trial of a therapeutic HIV vaccine strategy developed by the company AELIX Therapeutics.[42] The centerpiece is a proprietary HIVACAT T-cell immunogen (HTI) designed to focus T cell responses against certain conserved and vulnerable parts of HIV that have been identified in studies of people who naturally control viral load to low levels.[43]

In the AELIX-002 trial, 45 participants with HIV who had started ART within six months of diagnosis received the HTI immunogen delivered by a series of different vaccine vectors (DNA, modified vaccinia virus Ankara, and chimpanzee adenovirus) or placebo immunizations. The vaccines were successful in inducing T-cell responses to the HTI antigens. The second part of the study conducted an ATI in 41 participants to assess any impact of vaccination on ability to control viral load in the absence of ART.

All participants rebounded, but generally to levels lower than those documented prior to ART. Among people who lacked certain human leukocyte antigen (HLA) genes known to be associated with viral load control, vaccination was associated with an increased likelihood of remaining off ART for the 24-week treatment interruption, but the criteria for restarting ART were very lax (one viral load measurement over 100,000 copies or a viral load over 10,000 copies for more than eight weeks). Five vaccine recipients and one placebo recipient controlled viral load to less than 2,000 copies during the ATI.

The results offer some evidence of beneficial enhancement of HIV-specific immunity, but the degree of viral load containment achieved falls considerably short of the ideal goal. The researchers are now conducting a trial of the HTI vaccines in combination with Gilead's TLR7 agonist vesatolimod.

Anti-CMV Therapy

Letermovir (trade name Prevymis) is a new antiviral drug approved for the prevention of cytomegalovirus (CMV) disease in adults receiving bone marrow transplants. Researchers at UCSF are undertaking a trial to investigate whether the drug can indirectly reduce inflammation and/or affect the HIV reservoir in people on ART by inhibiting CMV, which is an extremely common co-infection in people with HIV. The primary endpoints of the trial relate to inflammatory biomarkers, so the results should shed light on whether the drug could have a role as an adjunct to ART, in addition to any evidence that might be uncovered related to effects on HIV persistence.

Table 2. Immune-Based Therapy Pipeline 2021

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Status
Isoprinosine		NCT03883334 (closed to enrollment)	Universidad San Francisco de Quito	Phase IV
Metformin		NCT03774108 (closed to enrollment)	Hospital Civil de Guadalajara	Phase IV
Canakinumab	IL-1β inhibitor	NCT02272946 (closed to enrollment)	University of California, San Francisco	Phase II
CD24Fc	Human CD24 extracellular domain and human IgG1 Fc fusion protein	NCT03960541 (closed to enrollment)	OncoImmune	Phase II
Letermovir (Prevymis)	Anti-cytomegalovirus drug	NCT04840199 (not yet open for enrollment)	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
Visbiome	Probiotic	NCT02441231	University Health Network, Toronto	Phase II
Allogeneic adoptive immune therapy	Granulocyte colony-stimulating factor–mobilized donor peripheral blood mononuclear cells	NCT02648516	Beijing 302 Hospital	Phase I/II
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 (not yet open for enrollment)	Peking Union Medical College Hospital	Not specified

The lone new study of adjunctive immune-based therapy that could be identified in clinical trial registries features an approach dubbed mismatched allogeneic adoptive immune therapy (AAIT). The protocol involves infusion of large numbers of white blood cells derived from donors familially related to the study participants. The goal is to promote immune reconstitution in people with advanced disease and CD4+ T cell counts below 200, building on results from a smaller pilot study that appeared promising in terms of safety, symptom reduction, and T-cell count increases.[44] The trial is sponsored by the Beijing 302 Hospital in China, with a recruitment target of 240 participants.

In recent times, the problem of poor CD4+ T cell recovery despite viral load suppression by ART appears to have received more attention in China than elsewhere. Results from a pilot study of mesenchymal stem cells that suggested immunological benefit[45] led to a larger, randomized trial, the results of which were published recently. Overall, there was little evidence of efficacy, but the researchers continue to refine the strategy and are considering launching a phase III trial.[46]

Also in China, an open-label pilot study of adoptive transfer of NK cells for people with suboptimal CD4 recovery despite ART documented preliminary evidence of promise. A paper describing the results was published in December 2020, reporting greater CD4+ T cell gains in recipients of the NK cells compared with those continuing ART alone. The intervention appeared safe, but the authors note that further studies are needed.[47]

Findings from two additional studies of interventions for suboptimal CD4 recovery have trickled out over the past year, one assessing niacin and the other an artesunate tablet, but no evidence of efficacy could be documented in either case.[48,49]

Conclusion

Despite the many hurdles created by the unprecedented global COVID-19 pandemic, HIV cure research has continued, facilitated by productive (albeit largely virtual) dialogues between scientists, community advocates, funders, and other stakeholders.

The latest report from the International AIDS Society Towards an HIV Cure Initiative, AVAC, and the Resource Tracking for HIV Prevention Research and Development Working Group shows that investments in the field continued to increase from 2018 to 2019, but only marginally compared with previous years (approximately one percent, from US$323.9 million in 2018 to US$328.2 million in 2019).[50]

The major source of support remains the NIH, but here also, proposed NIH funding increases are minor: the Office of AIDS Research Professional Judgment Budget recommended a 9.2 percent increase for fiscal year 2021,[51] but the enacted increase was around six percent. President Biden's fiscal year 2022 budget is offering a measly 0.8% boost (from US$220 million to US$211.7 million);[52] however, this is an improvement on the cuts sought by the previous occupier of the office.

The lack of major breakthroughs in the pursuit of a broadly applicable HIV cure may be provoking some caution on the behalf of funders, but there is a danger of creating a self-fulfilling prophecy if the work is undersupported, and activists and advocates must push for greater resources.

The inadequacy of efforts to develop adjunctive therapies to address suboptimal immune recovery is an ongoing problem. The COVID-19 pandemic has underscored that it is not a trivial issue, because—unsurprisingly—the greatest risk of poor outcomes after SARS-CoV-2 infection in people with HIV is among those with the lowest CD4 counts.[53,54] These concerning findings emphasize the importance of reinvigorating this moribund area of research.

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