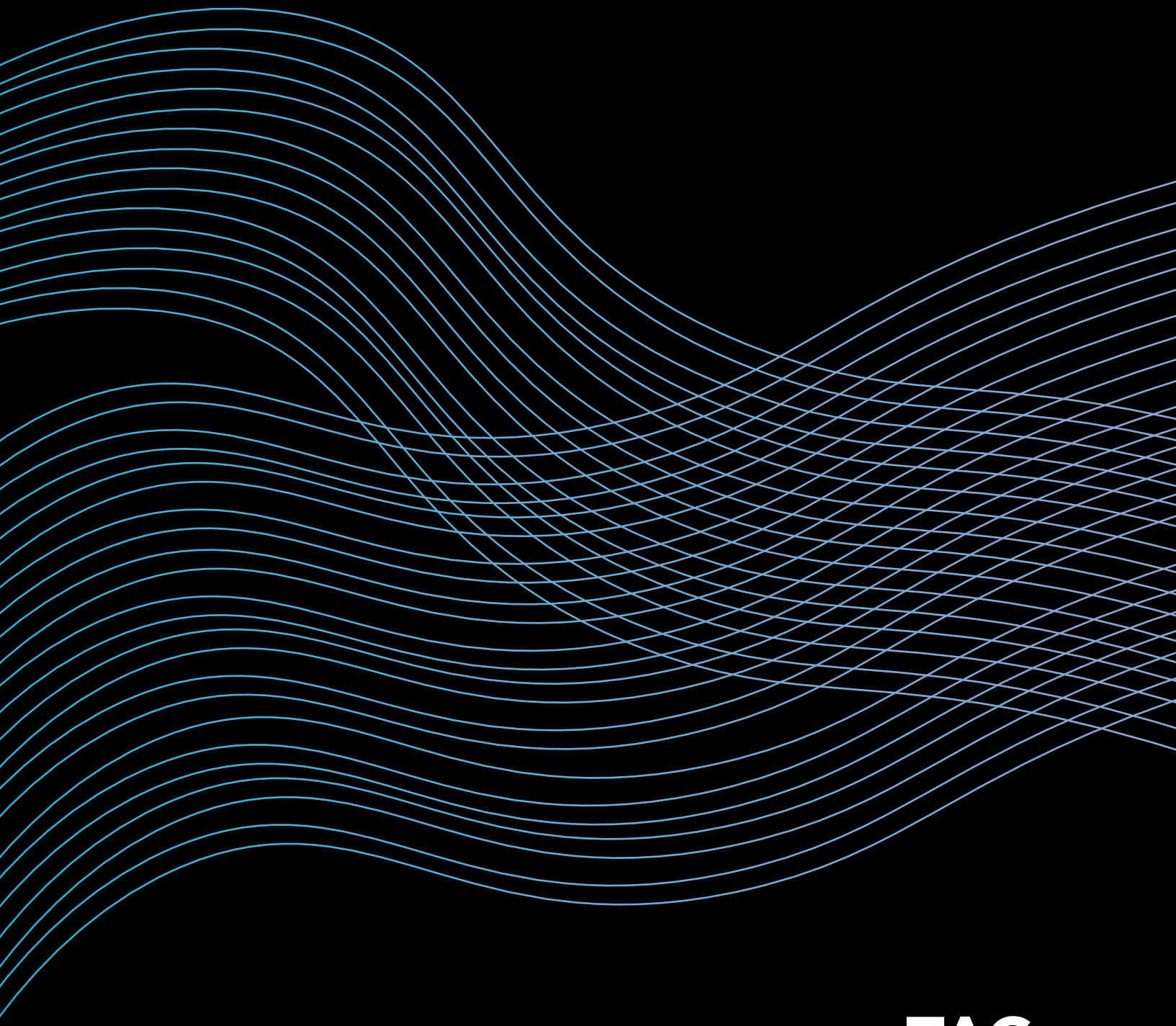
Pipeline Report » 2024

Research Toward a Cure and Immune-Based Therapies



TAG
Treatment Action Group

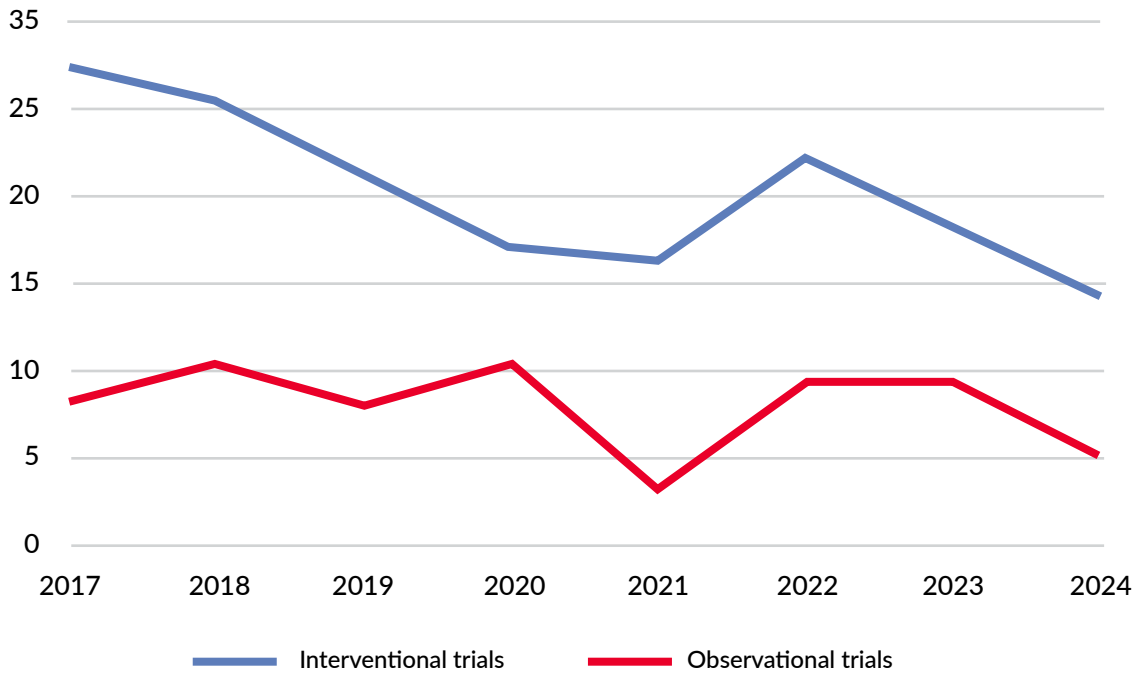
2024 Pipeline Report: Research Toward a Cure and Immune-Based Therapies

By Richard Jefferys

Introduction

Research toward a widely applicable cure for HIV continues to make incremental progress, but no major breakthroughs have been reported over the past year. The number of trials of candidate interventions added since the 2023 edition of this report has declined slightly compared to past years (see figure 1), but this is counterbalanced by a notable development: the initiation of phase II trials recruiting far larger numbers of participants than has previously been typical.

Figure 1: Numbers of New Interventional Trials and Observational Studies Added Each Year, 2017–2024



Prominent among these new protocols is AbbVie's phase II evaluation of two antibodies that block cell surface receptors: budigalimab, a PD-1 inhibitor, and ABBV-382, which targets the alpha4beta7 integrin. The new trial plans to recruit 140 participants and will involve an analytical treatment interruption (ATI), making it the largest HIV cure-related interventional trial with an ATI conducted to date. There are sites in multiple countries including Belgium, Canada, France, Germany, Italy, Japan, Poland, Puerto Rico, South Africa, Spain, and the United States. Encouraging preliminary results from phase I trials of budigalimab were presented in November 2022 — see the Combinations section for additional details.

Advancing Clinical Therapeutics Globally (ACTG; formerly known as the AIDS Clinical Trials Group) is launching a comparably sized 135-person phase II trial investigating a dual combination of long-acting

broadly neutralizing antibodies (bNAbs) given at the time participants are starting antiretroviral therapy (ART). The research aims to build on prior findings that bNAb administration at the time of ART initiation can accelerate the decay in levels of HIV-infected cells and promote enhanced control of viral load after a subsequent ATI.[1] The same dual bNAb combination is the focus of another ACTG study named PAUSE, which will recruit 48 participants already receiving ART.

The ACTG studies are both taking place in the African countries of Botswana, Malawi, South Africa, and Zimbabwe. The AbbVie trial includes at least one site in South Africa. While smaller in size, the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 095 study, another new addition in South Africa this year, is planning to evaluate dual bNAbs given either a week before or at the same time ART is initiated. These protocols represent an expansion of HIV cure-related research on the African continent compared to past years: 11 interventional studies with sites in Africa are listed in table 1, compared to 5 last year. Of the 14 new interventional trials added to the listing during the past year, 5 have African sites (compared to none of the 18 added in the 2023 edition of the report).

The geographic broadening of HIV cure-related clinical research is a welcome development — it's essential for understanding how candidate therapies work in all populations that stand to benefit. But there are implications for community engagement because trials with ATIs are relatively new on the African continent and in other resource-limited settings, and may be perceived as conflicting with educational messaging emphasizing the importance of adherence to ART and the benefits of maintaining viral load suppression (including undetectable=untransmittable or U=U).

In January 2024, in response to the increasing global reach of HIV cure-related research, social scientists Karine Dubé and Amaya Perez-Brumer published a call for justice-informed ATI trial designs that incorporate communityinformed knowledge to mitigate potential harms in the local context where the research is taking place (see figure 2 for their list of key questions that should be addressed).[2]

Figure 2: Key Questions to Mitigate Potential Harms Related to HIV Cure-Related Research with Analytical Treatment Interruptions

Participants	▪ **How are the physical, psychosocial, and emotional harms of participation assessed? How are harms discussed with potential participants?** ▪ **What are the contextual sociostructural processes that shape harms?**
Partners of participants	▪ **What are the physical, psychosocial and emotional harms for partners? How are these potential harms acknowledged and mitigated?** ▪ **Should partners be counselled on risk of HIV acquisition (partners without HIV) or risk of HIV superinfection (partners with HIV)?**
Affected communities	▪ **How are affected communities included in designing strategies to mitigate potential analytical treatment interruptions-related harms** ▪ **How is local knowledge assessed and integrated in research design and implementation?** ▪ **How do institutional systems and sociopolitical environments shape potential harms?**
Global HIV science	▪ **What are the processes of accountability to ensure the harms are mitigated for participants and affected communities immediately and in the long-term?** ▪ **How do multiple intersecting systems of oppression influence potential for undue harms?**

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The Sub-Saharan African Network for TB/HIV Research Excellence (SANTHE) and U.S. Military HIV Research Program (MHRP) also sponsored a workshop in May 2024 to generate new recommendations for designing trials with ATIs, with a particular focus on resource-limited locations. A report from the workshop is due to be published before the end of the year.

The interventions being investigated in the larger phase II trials now getting underway have been associated with isolated cases of extended posttreatment control of HIV viral load in prior smaller studies.[1,18,19,29] Results from greater numbers of participants will shed important light on the proportion of recipients who experience potentially beneficial viral load reductions during ATI.

In tandem with their new protocols, the ACTG has opened an observational posttreatment controller (PTC) cohort study "for any participants in these or other network (or related) trials who experience sustained (at least 24 weeks) low viral load levels." Hopefully this can help inform efforts to develop a cure by providing a more comprehensive picture of the factors that contribute to cases of PTC.

The number of established cases of apparent cures of HIV remains at seven: five individuals who received stem cell transplants (SCT) from donors with the CCR5Δ32 mutation to treat life-threatening cancers and two elite controllers whose immune systems appear to have cleared all intact, viable HIV from their bodies (see review by Raphael J. Landovitz and colleagues[3]).

One possible addition was reported by Asier Sáez-Cirión at the 2023 International AIDS Society conference: an individual who received SCT to treat cancer from a donor lacking the CCR5Δ32 mutation but nonetheless showed undetectable levels of HIV after ART withdrawal for 20 months at the time of the presentation.[4] Referred to as the "Geneva Patient," he has since disclosed his name is Romuald, and he currently remains off ART, with a manuscript describing the case pending publication.[5]

Previous cases of SCT from donors lacking the CCR5Δ32 mutation have only led to temporary delays in HIV viral load rebound, so this individual is being carefully monitored. At the current time, there remains some uncertainty whether one of the drugs administered to prevent graft-versus-host disease, ruxolitinib, is contributing to the absence of HIV rebound or if all viable viruses have been cleared. Ruxolitinib has been reported to have anti-reservoir activity.[6,7]

The IciStem consortium in Europe is following many of the potential HIV cure cases involving SCT for cancer. The consortium recently published an analysis of 30 recipients of SCT indicating that reductions in the size of the HIV reservoir were primarily caused by donor immune cells clearing virus-infected host cells,[8] echoing findings from the simian immunodeficiency virus (SIV)/macaque model.[9]

This year's table of HIV cure-related clinical research contains 75 interventional trials and 42 observational studies. Not all the interventional research involves evaluation of therapeutic candidates:

- Two imaging studies seek to map the locations of the HIV reservoir and immune activation in the body.
- Two protocols are conducting long-term safety follow up of recipients of experimental gene therapies, as required by the U.S. Food and Drug Administration (FDA).
- Two trials are part of a new effort to inform the design of preventive HIV vaccines that aim to induce bNAbs (as noted with italics in the Therapeutic Vaccines section of the table). The idea is

to test how candidate vaccine constructs work in the setting of pre-existing immune responses to the virus in people with HIV. The research may generate information that assists cure development, but it's not the primary goal. One of the studies includes an optional ATI.

Outside the cure realm, there remains a need for immune-based therapies capable of promoting immune reconstitution in people who experience suboptimal CD4+ T cell recovery on ART despite viral load suppression. The risks faced by this population have been emphasized by reports of associations between CD4+ T cell count and severity of disease from the emerging pathogens SARS-CoV-2[10,11] and mpox.[12,13] CD4+ T cell counts below 200 have also been correlated with a significantly reduced chance of curing hepatitis C with direct-acting antivirals.[14] But there are very few studies of potential immune-based interventions, and only one new protocol was identified during the past year: a study of an artemisinin derivative used in Chinese medicine that may have effects on the thymus (the gland in which new T cells mature prior to entering circulation; see table 2).

Table 1. Research Toward a Cure 2024: 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					
Assessment of HIV remission in early treated individuals with the MHC B35/53Bw4TTC2 genotype	**ATI**	NCT05482854	French National Agency for Research on AIDS and Viral Hepatitis (ANRS)	France	N/A
SCOPE-ATI	**ATI**	NCT04359186	The University of California, San Francisco (UCSF)	United States	N/A
Imaging and biopsy of individuals undergoing ATI	**ATI**	NCT05419024	National Cancer Institute (NCI)	United States	Phase II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
ANTI-α4β7 INTEGRIN ANTIBODIES					
Vedolizumab	Anti-α4β7 integrin antibody, **ATI**	NCT03147859	Ottawa Hospital Research Institute	Canada	Phase II
ANTI-INFLAMMATORY					
Fecal Microbiota Transplantation (FMT)		NCT06022406 (not yet open for enrollment)	Jean-Pierre Routy, McGill University Health Centre	Canada	Phase II
BCL-2 ANTAGONISTS					
Venetoclax	BCL-2 antagonist	NCT05668026	University of Aarhus	Australia, Denmark	Phase I/ IIb
BISPECIFIC T-CELL ENGAGERS					
GS-8588		No clinicaltrials.gov entry, listed on UPenn website	Gilead Sciences	United States	Phase I
BROADLY NEUTRALIZING ANTIBODIES					
VRC01	Analytical treatment interruption in HVTN 703/HPTN 081 Antibody-Mediated Prevention (AMP) trial participants, **ATI**	NCT04860323	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
10-1074-LS + 3BNC117-LS (RIO)	Long-acting bNAbs in primary infection, **ATI**	NCT04319367	Imperial College London	United Kingdom	Phase II
3BNC117-LS + 10-1074-LS (ACACIA: Antiretrovirals Combined With Antibodies for HIV-1 Cure In Africa)	Long-acting bNAbs at ART initiation, **ATI**	NCT06205602 (not yet open for enrollment)	ACTG	Botswana, Malawi, South Africa, Zimbabwe	Phase II
3BNC117-LS + 10-1074-LS	Long-acting bNAbs in primary infection, **ATI**	NCT05300035	ANRS	France	Phase II
VRC07-523LS + PGT121.414.LS	Long-acting bNAbs, **ATI**	NCT05719441 (not yet open for enrollment)	NIAID	Brazil, Peru, United States	Phase II
3BNC117-LS-J + 10-1074-LS-J (PAUSE: Pausing Antiretroviral Treatment Under Structured Evaluation)	Long-acting bNAbs, **ATI**	NCT06031272	ACTG	Botswana, Malawi, South Africa	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
3BNC117-LS + 10-1074-LS	Long-acting bNAbs	NCT05612178	NIAID	United States	Phase I
AAV8-VRC07	bNAb delivered by adeno-associated virus (AAV) vector	NCT03374202 (closed to enrollment)	NIAID	United States	Phase I
CAP256V2LS + VRC07-523LS	Long-acting bNAbs, **ATI**	PACTR202309578224660 (not yet open for enrollment)	CAPRISA	South Africa	Phase I
CD4 ATTACHMENT INHIBITORS					
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
COMBINATIONS					
VRC07-523LS, CAP256V2LS, vesatolimod	Long-acting bNAbs + TLR7 agonist, **ATI**	NCT05281510 (closed to enrollment)	Gilead Sciences	South Africa	Phase IIa
Budigalimab +/- ABBV-382	Anti-PD-1 antibody + anti-$\alpha_4\beta_7$ integrin antibody, **ATI**	NCT06032546	AbbVie	Belgium, Canada, France, Germany, Italy, Japan, Poland, Puerto Rico, South Africa, Spain, United States	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
Ad26.Mos4.HIV, MVA-BN-HIV, PGT121, PGDM1400, VRC07-523LS	Therapeutic vaccines, bNAbs, **ATI**	NCT04983030	Boris Juelg, MD, PhD	United States	Phase I/ IIa
ChAdOx1.tHIVconsv1, ChAdOx1.HIVconsv62, MVA. tHIVconsv3, MVA.tHIVconsv4, 3BNC117-LS, 10-1074-LS, vesatolimod	Therapeutic vaccines, bNAbs, TLR7 agonist, **ATI**	NCT06071767	NIAID	Brazil, United States	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	The International Maternal, Pediatric, Adolescent AIDS Clinical Trials Network (IMPAACT)/ NIAID/The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	Argentina, Brazil, Haiti, Kenya, Malawi, Puerto Rico, South Africa, Tanzania, Thailand, Uganda, United States, Zambia, Zimbabwe	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, bNAbs, **ATI**	NCT04357821 (closed to enrollment)	UCSF	United States	Phase I/II
HVRRICANE: HIVIS DNA + MVA-CMDR vaccines ± Cervarix (TLR4 agonist)	Therapeutic vaccines + TLR4 agonist	NCT04301154 (closed to enrollment)	PENTA Foundation	Italy, South Africa, Thailand	Phase I
N-803 ± VRC07-523LS + 10-1074	Recombinant human super agonist IL-15 complex, bNAbs, **ATI**	NCT04340596	NIAID	United States	Phase I
N-803, 3BNC117-LS, 10-1074-LS	Recombinant human super agonist IL-15 complex, long-acting bNAbs, **ATI**	NCT05245292	Rockefeller University	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
GENE THERAPIES					
EBT-101	AAV9 vector delivering CRISPR/ Cas9 gene-editing tool targeting HIV provirus, **ATI**	NCT05144386 (closed to enrollment)	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
An ATI study to evaluate the impact of AGT103-T to suppress HIV replication in the absence of ART	Gene-modified HIV-specific CD4+ T cells, **ATI**	NCT05540964 (enrolling by invitation)	American Gene Technologies International Inc.	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
CMV-specific HIV-CAR T Cells	Autologous CMV-specific T cells gene-modified to express a CAR targeting HIV	NCT06252402	City of Hope Medical Center	United States	Phase I
EBT-101 (long-term follow-up study)	AAV9 vector delivering CRISPR/Cas9 gene-editing tool targeting HIV provirus	NCT05143307 (enrolling by invitation)	Excision BioTherapeutics	United States	Phase I
Long-term follow-up of study participants treated with AGT103-T	Gene-modified HIV-specific CD4+ T cells	NCT05529342 (enrolling by invitation)	American Gene Technologies International Inc.	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
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS					
Gene therapy in treating patients with HIV-related lymphoma receiving stem cell transplant	Stem cells gene-modified with CCR5 shRNA/TRIM5α/TAR decoy	NCT02797470 (closed to enrollment)	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
IMAGING STUDIES					
Imaging immune activation in HIV by PET-MR	Intravenous [18F]F-AraG + whole-body positron emission tomography-magnetic resonance (PET-MR) imaging	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	University of Melbourne	Australia	Phase I/II
Nivolumab + ipilimumab	Anti–PD-1 antibody + anti–CTLA-4 antibody in people with advanced HIV-associated solid tumors	NCT02408861	NCI	Australia, United States	Phase I
Pembrolizumab	Anti–PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms	NCT02595866 (closed to enrollment)	NCI	United States	Phase I
IMMUNOMODULATORS					
Lenalidomide, adenosylmethionine	Immunomodulatory agents	NCT05598580	First Affiliated Hospital of Zhejiang University	China	Phase IV
JANUS KINASE INHIBITORS					
Baricitinib	Janus kinase inhibitor	NCT05452564	Emory University	United States	Phase II
LATENCY-REVERSING AGENTS					
Lauric acid	Saturated fatty acid	NCT05687565	Hospital Universitari Vall d'Hebron Research Institute	Spain	N/A
Panobinostat, lenalidomide + pyrimethamine	HDAC inhibitor, immunomodulator + dihydrofolate reductase inhibitor	NCT06240520 (not yet open for enrollment)	Erasmus Medical Center	Netherlands	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
Topiramate	Antiepileptic, candidate GRIK5 inhibitor	NCT06282783 (not yet open for enrollment)	Erasmus Medical Center	Netherlands	Phase I/II
Arsenic trioxide	Chemotherapy	NCT03980665	Guangzhou 8th People's Hospital	China	Phase I
Decitabine, romidepsin	Chemotherapy, HDAC inhibitor	NCT05230368	ANRS	France	Phase I
OBSERVATIONAL STUDIES					
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)	Mayo Clinic	United States	N/A
ANRS CO24 OncoVIHAC: Immune checkpoint inhibitors in HIV+ individuals with cancers		NCT03354936	Inserm-ANRS	France	N/A
APRIL: Analysis of the persistence, reservoir, and HIV latency		NCT05752318 (not yet open for enrollment)	University Hospital, Strasbourg, France	France	N/A
ARCH: Analysis of the reservoir in individuals controlling HIV infection		NCT06016114 (not yet open for enrollment)	Sponsor University Hospital, Ghent	Belgium	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
Characterization of acute and recent HIV-1 infections in Zurich: a long-term observational study		NCT00537966	University of Zurich	Switzerland	N/A
CHRONO: Prospective cohort for ex vivo cure studies with chronic HIV+ patients in the Netherlands		NCT04888754	Erasmus Medical Center	Netherlands	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
CODEX (the 'Extreme' cohort)	Long-term non-progressors and HIV controllers	NCT01520844	Inserm-ANRS	France	N/A
Comparing immune activation and HIV reservoir size between PWHIV on tenofovir-containing versus NRTI-free ART		NCT05584397 (enrolling by invitation)	University of Washington	United States	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 (suspended)	Barbara Ensoli, MD, PhD, Istituto Superiore di Sanità	Italy	N/A
Extended follow-up of the ISS T-003 trial volunteers (ISS T-003 EF-UP2020)		NCT05680948	Istituto Superiore di Sanità	South Africa	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
HI-ART: Optimizing cohorts for HIV cure interventions		NCT05852301	Bayside Health	Australia	N/A
HIV-Mercuri: HIV study on measuring the reservoir on cellular level to cure infection		NCT04305665	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		hivcure.com.au (no registry 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**	IciStem website (no registry entry)	amfAR	International	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
Identification and quantification of HIV central nervous system latency biomarkers		NCT02989285	St Vincent's Hospital, Sydney	Australia	N/A
Immuno-virological evaluation of persons living with HIV (PLWH)		NCT05973825 (not yet open for enrollment)	University Hospital, Ghent	Belgium	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	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
NOVA: Netherlands cohort study on acute HIV infection		NCT05728996	Prof. Jan Prins	Netherlands	N/A
Observational post-intervention controller (PIC) destination cohort		NCT05985642	ACTG	United States	N/A
PediacamNEG: Negative serology in children with HIV treated early with ART		NCT06302933	Inserm-ANRS	Cameroon	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	Institut National de la Santé et de la Recherche Médicale, France	France	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
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
TatLat: Development of a new family of HIV latency regulators (LRAs) targeting the Tat viral protein		NCT06441123 (not yet open for enrollment)	University Hospital, Montpellier	France	N/A
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 six months life expectancy due to terminal illness)		UCSD study website (no registry entry)	University of California – San Diego (UCSD)	United States	N/A
The role of the gastrointestinal-associated lymphoid tissue in the cure of HIV infection		NCT05652088	Icahn School of Medicine at Mount Sinai	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		hivcure.com.au (no registry entry)	Kirby Institute	Australia	N/A
T-CELL RECEPTOR-BASED BISPECIFICS					
IMC-M113V in HLA-A*02:01-positive people		2021-002008-11	Immunocore	Belgium, Spain, United Kingdom	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
THERAPEUTIC VACCINES					
BELIEVE: BCG vaccination	BCG vaccination effect on latent reservoir size in treated HIV-1 infection	NCT05004038 (closed to enrollment)	University of Zurich	Switzerland	Phase IIa
HB-502/HB-501	Arenavírus vaccine vectors	NCT06430905 (not yet open for enrollment)	Hookipa Biotech GmbH	United States	Phase Ib
GS-1966/GS-1144 HIV vaccine regimens	Self-amplifying mRNA and adenoviral vector prime-boost platform	No registry entry, #7 on Midway Research Center list	Gilead Sciences	United States	Phase Ib
HIV Env mosaic immunogens MOS1SIP, MOS2SIP, M3SIP8 + MPLA-5 adjuvant *(*primarily focused on preventive HIV vaccine development but may also assist cure research)*	HIV envelope proteins + adjuvant	NCT06449196 (not yet open for enrollment)	IAVI	Uganda, Zambia	Phase I
426c.Mod.Core-C4b, 3M-052-AF + Alum *(*primarily focused on preventive HIV vaccine development but may also assist cure research)*	Germline targeting protein + adjuvant	NCT06006546	NIAID, HVTN	United States	Phase I
ChAdOx1.HIVconsv62-MVA.tHIVconsv4 (C62-M4), ChAdOx1.tHIVconsv1+C62-MVA.tHIVconsv3+M4 (C1C62-M3m4)	Viral vector vaccines	NCT05604209	University of North Carolina, Chapel Hill	United States	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
ICVAX	PD-1-enhanced HIV DNA vaccine	NCT06253533 (closed to enrollment)	Shenzhen Immuno Cure Biomedical Company Limited	China	Phase I
NETI: Trimer 4571 therapeutic vaccination	HIV envelope protein vaccine	NCT04985760	NIAID	United States	Phase I
Therapeutic vaccine based on aDC1 dendritic cells	Dendritic cell-based vaccine, **ATI**	NCT05786937 (not yet open for enrollment)	University of Sao Paulo General Hospital	Brazil	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Location(s)	Phase
TREATMENT INTENSIFICATION/EARLY TREATMENT					
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
TYROSINE KINASE INHIBITORS					
Dasatinib		NCT05527418	Eva Bonfill, Institut d'Investigacions Biomèdiques August Pi i Sunyer	Spain	Phase II
Dasatinib		NCT05780073	Fundació Institut Germans Trias i Pujol	Spain	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 2023 Pipeline Report.

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

Anti-Inflammatory

Jean-Pierre Routy at the Research Institute of the McGill University Health Centre in Canada is planning to launch a trial that will investigate the safety and effects of fecal microbiota transplantation (FMT) on gut integrity, inflammatory biomarkers, and HIV reservoir measures in people on ART. As outlined in a recent meta-analysis of 10 prior studies,[15] FMT has shown some potential efficacy in restoring healthy gut bacteria and reducing the rate of gastrointestinal infections in people with HIV, with a safety profile similar to that observed in HIV-negative people. Routy's study will enroll 20 participants, with half randomized to receive FMT capsules and half receiving a placebo equivalent. The researchers are limiting the study to people with a CD4:CD8 ratio of <1 to focus on a population most at risk for persistent inflammation.

Bispecific T-Cell Engagers

Gilead Sciences is one of the few large pharmaceutical companies pursuing an HIV cure research program. As part of this effort, a phase I trial has been initiated of GS-8588, an immune-based therapeutic candidate described as a bispecific T cell engager.

The approach derives at least in part from research conducted with public funding at the National Cancer Institute by Dimiter Dimitrov and Weizao Chen.[16] The scientists developed and patented a protein with two components (bispecific): mD1.22, an element from the human CD4 protein, and m36.4, from a human antibody, each specific for a different vulnerable target on HIV's outer gp120 envelope protein. The approach was subject to a licensing offering by the National Institutes of Health (NIH), which Gilead acquired. The Gilead construct includes a CD3 molecule to engage T cells to kill cells expressing the HIV gp120 protein, but the complete ingredients have yet to be publicly presented.

Gilead hasn't entered the GS-8588 trial into the clinicaltrials.gov registry, taking advantage of the lack of a requirement to register phase I trials. This has been a consistent problem with Gilead's HIV cure research program, and it runs counter to their public commitments to community engagement in HIV research — it's not possible for people to engage with a clinical trial if they're not aware of it. Limited information is available online from individual study sites, such as the entry in the UPenn Medicine website. Gilead also states on their website pipeline page that GS-8588 is in a phase I trial, but no additional detail is provided.

Broadly Neutralizing Antibodies (bNAbs)

As noted in the introduction, three new bNAb trials are ongoing or imminent on the African continent.

The ACTG's Antiretrovirals Combined With Antibodies for HIV-1 Cure In Africa (ACACIA) study will evaluate a combination of two long-acting bNAbs, 3BNC117-LS and 10-1074-LS, with infusions given at the time ART is initiated. After 24 weeks, eligible participants will have the option to undergo an ATI to assess capacity to control HIV viral load in the absence of ART.

According to the registry listing, the study is pending and not yet open for enrollment. No location information is provided yet, but in a presentation at the 2024 Pre-CROI Community HIV Cure Research Workshop Dr. Katherine Bar — co-chair of the ACTG's HIV cure research committee — indicated sites will include Botswana, Malawi, South Africa, and Zimbabwe. The aim is to enroll 135 participants, and the estimated completion date is February 2029.

The second ACTG bNAb trial is called PAUSE and is testing the long-acting bNAbs 3BNC117-LS-J and 10-1074-LS-J (the additional "-J" in the name reflects slight modifications made to ease manufacturing). In this protocol, the bNAbs are given to participants who've been on ART with suppressed viral loads for at least 96 weeks. An ATI will be started the day after the bNAbs are infused. The HIV Vaccine Trials Network (HVTN) and the HIV Prevention Trials Network (HPTN) are cosponsors because, while the primary focus is HIV cure research, there's potential to generate information on bNAbs that will be relevant to the HIV prevention field. The opening of enrollment was announced via press release on June 13, 2024.[17] The dual bNAb combination of 3BNC117 and 10-1074 has been tested in multiple prior studies and found to be safe and, in a few cases, associated with prolonged control of viral load after ATI.[18,19,20]

The third study is sponsored by CAPRISA. Named NeutArt or CAPRISA 095, the aim is to assess two bNAbs:

- CAP256V2LS, which was discovered by CAPRISA researchers in samples from a person living with locally prevalent clade C variants of HIV.[21]
- VRC07-523LS, an enhanced version of the bNAb VRC01, which was isolated in 2008 from an untreated slow progressor living with clade B HIV infection by scientists at the NIH in the United States.[22]

Both bNAbs are already being investigated as potential preventive options in HIV-negative women South Africa and have been found to be safe.[23] The new study isn't yet open for enrollment but plans to recruit 30 participants and investigate whether the bNAb combination can enhance the immune system's ability to control HIV viral load after an ATI.

Combinations

Potentially important results from several trials of combination strategies have emerged during the past 12 months.

The IMPAACT P1115 study is a complex multinational research protocol based on the widely publicized case of the Mississippi Baby, an infant who experienced an extended period of remission from detectable HIV after an unplanned ART interruption.[24,25] Newborns diagnosed with HIV are immediately started on ART and then later evaluated for various markers of HIV persistence to assess whether an ATI should be undertaken. The original plan was for evaluations to occur after two years of follow up on ART, but the COVID pandemic delayed this milestone for the initial enrollees into the trial.

Initial findings from the pre-ATI portion of the study were published in December 2023, showing that the probability of maintaining an undetectable viral load ranged from 33–57 percent.[26] A small subset of children also displayed undetectable levels of HIV DNA and negative HIV antibody tests. At the 2024 Conference on Retroviruses and Opportunistic Infections (CROI), principal investigator Deborah Persaud presented the first results obtained in six children who qualified for a carefully monitored ATI.[27]

Two of the children experienced a rebound in HIV viral load after three and eight weeks, respectively. In another case, there was a reemergence of viral load but after an extended delay of around one and a half years. At the time of the presentation, the remaining three children were still without viral load rebound after 48, 52, and 64 weeks, respectively (and counting).

The findings confirm that extended periods of ART-free remission are possible in children treated very rapidly after birth. Persaud noted that improved biomarkers are needed to predict which children are most likely to control viral load after ATI because, despite meeting the study criteria for ART interruption, two participants rebounded rapidly. Viral load rebound was also associated with symptoms of acute infection in two cases. A revised version of the IMPAACT P1115 protocol remains ongoing, including integrase inhibitors that are now available as treatment options for children and the bNAb VRC01.

Results from a completed combination study of the histone deacetylase (HDAC) inhibitor panobinostat plus the cytokine pegylated interferon-α2a were published by Marie Armani-Tourret and colleagues in the journal *Cell* in February 2024.[28] There was no significant overall effect on the size of the HIV reservoir, but the researchers used new investigative tools (described in last year's edition of this Pipeline Report) to show that the proportion of cells containing HIV that may be most capable of driving viral load rebound were slightly diminished.

The findings offer evidence that interventions can accelerate immune clearance of the HIV-infected cells that occasionally produce viral components and display them on the cell surface where they can be recognized. As a loose analogy, it's similar to weeding a garden — the weeds only become visible for removal when they appear above the surface of the soil. This type of low level production of HIV proteins by infected cells can occur naturally and, in this study, there were indications that it was also triggered by the latency-reversing effects of panobinostat.

The large AbbVie phase II trial mentioned in the introduction is predicated on results obtained with their PD-1 inhibitor candidate budigalimab that were presented first by Jean-Pierre Routy at the 19th European AIDS Conference in October 2023.[29] PD-1 inhibitors are part of a family of molecules called immune checkpoint inhibitors, several of which are approved for the treatment of cancers. The mechanism of action involves blocking receptors on the surface of cells that act as brakes on the immune response, which has the potential to enhance activity against cancers or pathogens like HIV while also carrying a risk of autoimmunity (activating unwanted immune responses against body tissues).

Routy focused on 11 participants who received the highest tested budigalimab dose of 10 mg, given four times biweekly, and underwent an ATI after the first infusion. Nine of the 11 experienced viral load rebound but with an average delay of 29 days (compared to 21 for placebo recipients), and four maintained levels below 1,000 copies/ml and didn't meet the ART restart criteria. Two participants restarted ART by request without meeting the formal criteria of a viral load of 1,000 copies/ml for four weeks.

Two participants were able to control viral load to less than 200 copies/ml for an extended period after early blips slightly above that level and remained off ART at the time of the presentation for 18 and 19 months, respectively.

The dose of budigalimab was considerably lower than PD-1 inhibitor doses used for cancer therapy, and the safety profile was reported to be favorable. There were three cases of mild and reversible autoimmune side effects, two thyroiditis, and one skin reaction (all less than grade two in severity). These findings compare favorably to two previous non-cancer studies of PD-1 inhibitors in people with HIV, both of which were stopped early because of adverse events.[30,31,32]

AbbVie's 140-person international phase II trial of budigalimab is now enrolling and will investigate effects either alone or in combination with ABBV-382, an antibody that targets the alpha4beta7 integrin. Results from phase I studies of ABBV-382 haven't been publicly disclosed yet, but a presentation at CROI 2024 described the capacity of the antibody to promote presentation of HIV antigens to T cells, suggesting it could work in concert with budigalimab, which aims to boost T cell function.[33]

The other new combination trial in table 1 is sponsored by the ACTG and investigating a combination of three different types of immune-based candidates: therapeutic vaccines, long-acting bNAbs, and a toll-like receptor 7 agonist (vesatolimod). The vaccines are based on chimpanzee adenovirus (ChAd) and modified vaccinia Ankara stain (MVA) viral vectors containing selected HIV components that are highly conserved among different variants. The bNAbs are the now common partners 3BNC117-LS and 10-1074-LS, while vesatolimod is manufactured by Gilead Sciences and has shown immune-modulating activity in previous human studies.[34]

Lastly, two planned trials of combinations described in last year's report were unable to get off the ground: the natural killer cell product FT538 became unavailable to researchers at the Masonic Cancer Center, University of Minnesota, and they're now looking at potential alternatives. The MHRP study of the bNAbs VRC07-523LS and PGDM1400LS together with the cytokine N-803 was withdrawn, with the registry record stating "protocol was changed during development."

Gene Therapies

Preliminary results from the first clinical trial of a gene editing approach targeting the HIV reservoir were presented at the American Society of Gene & Cell Therapy annual meeting in May 2024. The candidate, EBT-101, was developed by Excision Biotherapeutics and uses CRISPR gene editing technology to try to cut out or disable the HIV genetic code present in virus-infected cells. The CRISPR gene editing tool is delivered into the body via an adeno-associated virus (AAV) vector.

In the study, five male participants with HIV received EBT-101 without any serious adverse events. Three recipients underwent an ATI, but only one experienced a delay in HIV viral load rebound lasting 16 weeks. This individual was also the only participant who showed a slight decline in the size of the intact HIV reservoir after EBT-101 administration. The results may hint at the challenges associated with trying to use CRISPR against a highly mutable virus: the gene editing tool needs to recognize conserved genetic sequences in order to work, and some study participant samples displayed evidence of variation at the HIV sites targeted by EBT-101. Additional details are due to be presented by principal investigator Rachel Presti at the AIDS 2024 conference in July 2024.

American Gene Technologies published preliminary information from an ATI trial for recipients of AGT103-T, a gene therapy candidate that modifies HIV-specific CD4+ T cells to render them resistant to infection by the virus.[35] The rationale for the approach is that HIV-specific CD4 T cells should be responsible for coordinating an effective immune response against the virus but instead become preferential targets for infection and dysregulation.[36,37]

The results offer some evidence of diminished viral load rebound, particularly after a second ATI, although the limited number of participants and open label study design make it difficult to evaluate the contribution of the gene-modified HIV-specific CD4 T cells. The authors also emphasize the expansion of CD8 T cells

that occurred after ATI, which is atypical and may suggest that the modified HIV-specific CD4 T cells were able to better support proliferation of HIV-specific CD8 T cells in response to viral load rebound. American Gene Technologies have spun off a new company named Addimmune, which is now trying to raise funds to support a larger trial of the approach.

A new gene therapy trial is now open and recruiting at the City of Hope Medical Center in Los Angeles. The novel approach will focus on sampling T cells from study participants that specifically target cytomegalovirus (CMV), a very common virus that most people carry for life. These CMV-specific T cells will then be genetically modified to equip them with an additional receptor that recognizes part of the outer HIV envelope. The rationale is that the low levels of CMV present in a person's body will help stimulate and maintain the modified CMV-specific chimeric antigen receptor (CAR) T cells, allowing them to persistently target HIV-infected cells via the secondary receptor.

Latency-Reversing Agents

Two new studies of candidate HIV latency-reversing agents are pending at Erasmus Medical Center in the Netherlands.

The first is a phase I/II trial at multiple sites that aims to build on evidence from a prior study that the antiparasitic drug pyrimethamine has HIV latency-reversing activity.[38] A total of 49 participants will be recruited and given single doses of pyrimethamine, the HDAC inhibitor panobinostat, and the immunomodulator lenalidomide either alone or in the following dual combinations: panobinostat + lenalidomide, panobinostat + pyrimethamine, or lenalidomide + pyrimethamine. The investigators will assess levels of HIV RNA production by latently infected cells after dosing and any change in the size of the HIV reservoir between the baseline visit and the end of study follow-up (120 days later).

The second is investigating the anti-epileptic drug topiramate. The rationale derives from laboratory studies showing that a particular cellular gene — glutamate ionotropic receptor kainate type subunit 5 (GRIK5) — is involved in the maintenance of HIV latency. Topiramate is an inhibitor of GRIK5 and was found to reverse HIV latency in cell line models and in CD4 T cells isolated from people on ART, without inducing immune activation or causing significant toxicity.[39] The clinical trial will administer a single topiramate dose of 400 mg to assess HIV latency-reversing activity, toxicity, and any differences in response related to sex assigned at birth.

Therapeutic Vaccines

This category of trial has the most additions in 2024, with four in total. However, as noted in the introduction (and flagged in table 1), there's a significant caveat: two of the protocols are primarily focused on generating information that can inform the design of *preventive* HIV vaccines capable of inducing bNAbs. While it's possible that results may be of some help for HIV cure research involving therapeutic vaccines, the studies don't involve candidates that are envisioned as therapeutics. Recruitment will depend on the altruism of people with HIV who want to contribute to preventive vaccine development.

The first of the more specifically therapeutic studies involves a novel DNA construct called ICVAX developed by the biotech company Immuno Cure. The vaccine encodes a mosaic form of the HIV Gag protein fused to a soluble human PD-1 protein. Mosaic means that the Gag protein consists of elements

from multiple different HIV variants, with the aim of inducing T cell responses capable of responding to diverse viruses (in this case the focus is on variants circulating primarily — but not only — in China). The reason for the inclusion of the PD-1 protein is to target the HIV Gag protein to dendritic cells, which are responsible for initiating immune responses. Dendritic cells express molecules called ligands that interact with PD-1, and delivering antigens such as the HIV Gag protein via this pathway is associated with superior induction of CD8 T cell responses. Promising results have been reported in both macaque and mouse models.[40]

In a presentation at the recent IAS HIV Cure & Immunotherapy Forum in Brisbane, Zhiwei Chen from the University of Hong Kong described the vaccine approach and disclosed that the first doses were administered to study participants in March 2023. The study design involves a stepwise assessment of escalating doses, and Chen explained that the lowest dose cohort has been completed with no safety issues identified. The researchers have now initiated a medium dose cohort. An ATI will be considered in the future if all goes according to plan.

The second trial is sponsored by the German company Hookipa Pharma and will test two therapeutic HIV vaccine candidates based on an arenavirus vector platform in people with HIV on ART. The majority of vaccine vectors are altered to prevent replication, but Hookipa's arenaviruses can replicate while also being modified and attenuated for safety. The two arenavirus vectors under investigation are derived from Pichindé virus (PICHV) and lymphocytic choriomeningitis virus (LCMV).

The vaccines have induced immune responses associated with a significant lowering of SIV viral load in macaque experiments, which were published in the journal *npj Vaccines* in November 2023.[41] Shortly after publication, Hookipa announced that the FDA had given the green light to launch a clinical trial.[42] The registry record currently only lists one site, Beth Israel Deaconness Medical Center in Boston, and enrollment has not yet begun. The research is part of a collaborative agreement with Gilead Sciences aiming to develop curative interventions for HIV and hepatitis B.[43]

Table 2. Immune-Based Therapy Pipeline 2024

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Status
Fostemsavir	Attachment inhibitor	NCT05220358	Orlando Immunology Center	Phase IV
Mismatched allogeneic adoptive immune therapy (AAIT)	Allogeneic adoptive immunotherapy	NCT04098770	Beijing 302 Hospital	Phase II
Mesenchymal stem cells	Human umbilical cord mesenchymal stem cells	NCT05872659	Shandong Qilu Cell Therapy Engineering Technology Co., Ltd.	Phase I
Pembrolizumab	Anti-PD1 antibody, immune checkpoint inhibitor	NCT03367754	National Institutes of Health Clinical Center	Phase I
Bifidobacteria and *Lactobacilli* triple viable capsules	Probiotics	NCT04297488	Peking Union Medical College Hospital	Not specified
Haoqin Qingdan Granules	Artemisinin derivative	ITMCTR2023000019 (not yet open for enrollment)	China Academy of Chinese Medical Sciences	Not specified

The lone newly identified study for people with suboptimal immune recovery is entered into the International Traditional Medicine Clinical Trial Registry. The intervention, Haoqin Qingdan granules, is a herbal compound from traditional Chinese medicine that may have effects on the thymus, the conduit for newly-produced T cells, which appears potentially compromised in people with poor CD4 T cell restoration on ART.[44] According to the registry entry, the trial is not yet open for enrollment at the China Academy of Chinese Medical Sciences.

Advocates continue to promote the importance of expanding therapeutic research in this area, including contacting companies with candidates believed to have potential and engaging in dialogues with regulators about appropriate study designs. But progress remains limited. Results are pending from the ongoing RECOVER trial of the approved HIV attachment inhibitor fostemsavir (trade name Rukobia); the estimated completion date is August 31, 2024. Prior studies have hinted that the drug may have an ability to enhance CD4+ T cell recovery that isn't seen with other antiretrovirals.[45]

Conclusion

Over recent years there may be a slight trend toward fewer new cure-related trials being initiated on an annual basis, but this could represent variation and recovery from the COVID pandemic period. An important development in 2024 is the launching of larger phase II protocols and an increase in studies with sites on the African continent.

HIV cure research continues to be a key priority for the National Institute of Allergy and Infectious Diseases (NIAID), now under the new leadership of Dr. Jeanne Marrazzo. As documented by AVAC and the International AIDS Society, the NIH — under which NIAID falls — is the most significant funder in this area, contributing approximately 80 percent of the $439.8 million total in 2021.[46]

NIAID has recently approved plans for another round of support for the Martin Delaney Collaboratories (MDCs), which represent the core of their cure program. There are currently ten MDCs, and the new round of support available in 2026 will fund six to eight adult MDCs and one focused on pediatric research.

The prominence of NIH investment does raise concern for the future given the current political situation in the United States. Republicans in Congress are already proposing a massive overhaul of NIH based heavily on misrepresentations and unfounded conspiracy theories regarding the scientific response to the COVID-19 pandemic.[47] These proposals are currently being shoehorned into appropriations bills, and while the prospects for enactment look slim, these efforts will certainly continue. A second Trump presidency promises to be even more deranged and viciously authoritarian and might well change the equation with little regard for the importance of HIV research.

The lack of therapeutic development for people experiencing suboptimal immune recovery on ART is a profoundly disappointing and long-standing concern. Advocates including Nelson Vergel from the Program for Wellness Restoration and TAG haven't given up on efforts to push this area higher up the HIV research agenda. Current United States guidelines for the use of antiretrovirals in adults and adolescents offer advice for managing poor CD4+ cell recovery despite viral suppression, but there are no specific therapeutic options and additional clinical studies are urgently needed.

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