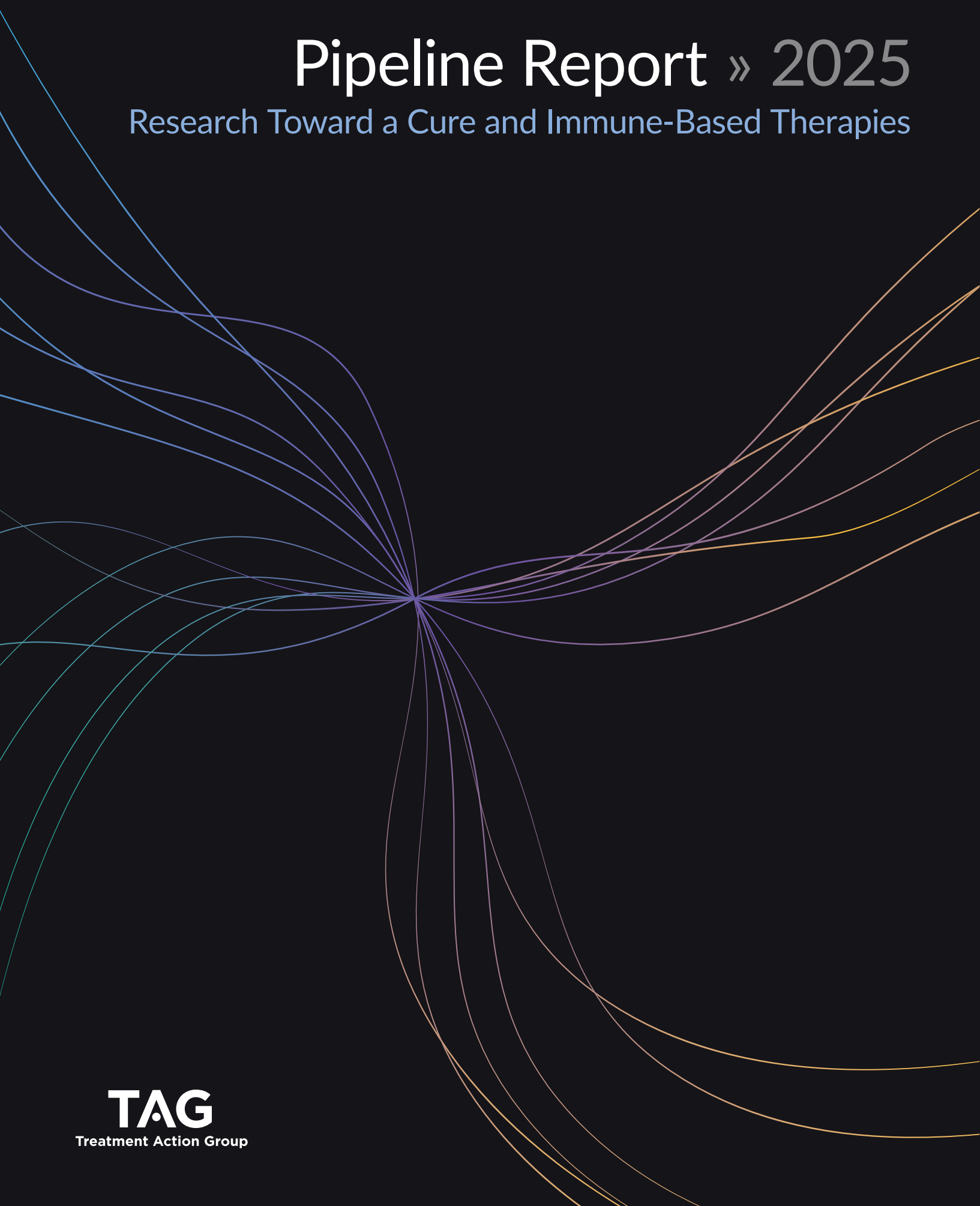
Pipeline Report » 2025

Research Toward a Cure and Immune-Based Therapies



TAG
Treatment Action Group

2025 Pipeline Report: Research Toward a Cure and Immune-Based Therapies

By Richard Jefferys

Introduction

Notable developments in HIV cure research over the past year include the presentation of evidence that broadly neutralizing antibodies (bNAbs) can promote control of HIV viral load after an antiretroviral therapy (ART) interruption in a substantial proportion of recipients. There's also been a report indicating a novel immune-based intervention can reduce the HIV reservoir in people on ART, albeit slightly. Additionally, four new cases of possible HIV cures in people who needed stem cell transplants to treat cancers have been described, bringing the total number to ten since Timothy Ray Brown paved the way in 2008.

The number of newly registered HIV cure-related interventional trials added this year is 21, plus two new observational studies (see table 1). This represents a slight increase compared to last year, when there 14 and five additions, respectively.

Update on Dual bNAbs

Significant results from two studies of dual bNAbs were disclosed at the 2025 Conference on Retroviruses and Opportunistic Infections in March.

Sarah Fidler debuted results from the RIO trial, the largest evaluation of the approach.[1] A total of 68 cisgender men who began ART during acute HIV infection were evenly randomized to receive infusions of the long-acting bNAbs 3BNC117-LS and 10-1074-LS or placebo, followed by an analytical treatment interruption (ATI).

Receipt of the bNAbs was associated with a significantly greater likelihood of maintaining viral load suppression during ATI at multiple timepoints. After 20 weeks, 75% of bNAb recipients were controlling viral load compared to 8.8% of those in the placebo arm, consistent with prior studies demonstrating prolonged activity after a single infusion of long-acting bNAbs.

Participants with suppressed viral load at week 20 were eligible for a second infusion of bNAbs or placebo, and this was associated with high rates of continued control of viral load: 57% at 48 weeks and 39% after 72 weeks. Demonstrating the importance of control arms, there were also two cases of post-treatment control to beyond 72 weeks in the placebo arm (5%).

Fidler pointed out that there were three observed patterns of viral load rebound during ATI: rapid (8/34 participants), delayed (14/29) and post-treatment control (7/29 for >72 weeks). There no safety concerns related to the bNAbs, but several participants experienced high viral load rebounds during ATI to greater than a million copies/ml — the ART restart criteria was a confirmed measurement >100K copies/ml, but in these cases levels continued to ascend while confirmation was pending.

Thumbi Ndung'u from the Africa Health Research Institute presented broadly consistent findings from a study in the FRESH cohort of young women in South Africa sponsored by Gilead Sciences.[2] The protocol was a single arm, open label design administering a combination of two long-acting bNAbs (VRC07-523LS and CAP256V2LS) and the toll-like receptor 7 agonist vesatolimod. The 20 participants had received ART

for an average of seven years, after starting a median of just one day after the detection of acute HIV infection. Sensitivity of HIV samples to at least one of the two bNAbs was a requirement for study entry.

Vesatolimod was dosed every other week for ten weeks, the bNAbs were given via infusion on day seven. An ATI was initiated after four weeks. The researchers also observed three patterns of viral load rebound: seven early cases while bNAbs were still likely present; another seven during the period bNAb levels were waning, and six participants who restarted ART late or displayed post-treatment control of viral load and remained off ART through 48 weeks.

Unusually, four participants (20%) continued to experience post-treatment control until week 55 and are still off ART post-trial, now for an average of 1.5 years. Krista Dong also discussed the study during the Pre-CROI Community HIV Cure Research Workshop, highlighting that in one case control of viral load has now persisted for more than two years.[3]

Ndung'u noted that only one of the bNAbs (CAP256V2LS) was specific to the prevalent local HIV clade C, leaving open the possibility that better results might be attainable if both components of dual bNAb regimens are targeted to geographically relevant variants.

Additional information was presented from RIO in the form of several CROI 2025 posters. John Frater and colleagues described a participant with extended post-treatment control for two years (and counting), associated with enhanced HIV-specific T cell immune responses and a reduction in the size of the intact HIV reservoir.[4] An analysis led by Mohammed Altaf indicated that the bNAbs had a "vaccinal effect" by promoting HIV Gag-specific T cell responses that were associated with control of viral load.[5] A third poster from Marcilio Jorge Fumagalli and colleagues reported that the decay of the intact HIV reservoir in among RIO participants was approximately 7-8 fold faster than prior reports.[6]

Taken together, the FRESH cohort and RIO studies offer encouraging evidence that the proportion of participants who experience post-treatment control can be increased beyond the rare cases reported previously. For both protocols, the rates of post-treatment control were around 20%.

Dr. Ole Søgaard gave an excellent plenary talk on HIV cure research at CROI 2025 delineating factors that likely contribute to control of viral load off ART.[7] These include increased numbers and functionality of HIV-specific T cells, natural killer cells, and antibody responses. Søgaard highlighted the importance of gaining an increased understanding of how these components of the immune response can combine most effectively, in order to design interventions capable of promoting higher rates of post-treatment control of viral load after ATI.

Bispecific T cell Engager

As first covered in TAG's 2023 Pipeline Report, the biotech company ImmunoCore is developing a soluble bispecific T cell engager called ImmTAV for HIV. The molecule is designed to facilitate recognition and destruction of HIV-infected cells by CD8 T cells regardless of their original specificity (e.g. a CMV-specific CD8 T cell could potentially be brought into action against HIV by ImmTAV). The ImmTAV molecule acts as a sort of bridge between CD8 T cells that wouldn't normally recognize HIV and reservoir cells that are displaying HIV fragments to alert the immune system that elimination is needed.

The first iteration of ImmTAV being tested, IMC-M113V, is designed to recognize a part of the HIV Gag protein when presented on the outside of infected cells by an immune system molecule named HLA-A*02:01. HLA molecules act like an immunological alarm system, ferrying fragments of proteins made inside of cells to the surface so that they can be monitored for signs of foreign materials derived from pathogens like HIV.

T-cell recognition of an HLA molecule carrying a protein fragment from a pathogen occurs via the T-cell receptor (TCR), and typically triggers destruction of the infected cell. IMC-M113V serves as free-roaming TCR that can link any CD8 T cell to an HIV-infected cell displaying the specific Gag fragment via an HLA-A*02:01 molecule. An initial safety portion of a first-in-human trial was described at CROI 2023 with no concerns emerging, leading to further assessments for efficacy.[8]

At CROI 2025, Beatriz Mothe presented preliminary results from a small phase I trial involving dose escalation and an ATI.[9] Because IMC-M113V is based on recognizing a component of the HIV Gag protein presented by HLA-A*02:01, candidates for the study were screened to ensure they possessed this HLA type (HLA is the most diverse region of the human genome and there are many different variant molecules).

Enrolled participants on ART received 12 weekly infusions of IMC-M113V at various doses ranging from 60-300 micrograms (the first two infusions being lower doses to "step up" to these targets). There were no serious adverse events, with grade 1 cytokine release syndrome (transient fever) seen at the highest dose, indicative of T cell activation. Viral load blips occurred in half of the recipients, suggesting that this immune activation was associated with some stimulation of the latent HIV reservoir to produce viral RNA.

HIV reservoir measurements showed a significant reduction in the levels of cell-associated HIV RNA and a statistical trend toward lower levels of intact HIV DNA. Of 16 participants, 15 completed an ATI and three showed evidence of at least transient post-treatment control of viral load to less than 200 copies/ml. A cohort receiving a higher dose is now under evaluation.

New Stem Cell Transplantation HIV Cure Cases

Four new cases of potential HIV cures resulting from stem cell transplants required to treat life-threatening cancers have been reported since the 2024 Pipeline Report.

At the AIDS 2024 conference in Munich, Christian Gaebler presented the case of a German man with HIV who received a stem cell transplant to treat acute myeloid leukemia (AML).[10] Both the individual and the donor were heterozygous for the CCR5Δ32 mutation, meaning it was only inherited from one parent. Heterozygosity is associated with lower levels of the HIV co-receptor CCR5 on cells, but not the complete absence seen in people homozygous for CCR5Δ32. Post-transplant evidence of ablation of the HIV reservoir led to ART interruption in September 2018, and the individual (born in 1964) has shown no evidence of viral load rebound for over five years.

A second instance of a cisgender woman possibly cured by stem cell transplantation was described by Olivia Zaegel-Faucher at the HIV Glasgow conference in November 2024.[11] The woman is in her mid-50s and had been living with HIV for over 20 years when she received a stem cell transplant to treat AML in July 2020, from a donor homozygous for the CCR5Δ32 mutation. ART was interrupted in October 2023 and no viral load rebound has occurred; monitoring is ongoing.

CROI 2025 included two presentations of likely cures achieved by stem cell transplants from donors homozygous for the CCR5Δ32 mutation.

Marius Trøseid and colleagues from Oslo University debuted information on the Oslo patient, a 58-year-old man who received a stem cell transplant from this brother to treat myelodysplastic syndrome.[12] ART was interrupted two years later, with no return of HIV over four years of subsequent follow up. Trøseid noted that ruxolitinib was administered to treat graft versus host disease (GvHD), which may have contributed to reservoir clearance. The drug has previously been speculated to have contributed to the only reported HIV cure case in a recipient of a stem cell transplant from a donor lacking the CCR5Δ32 mutation.[13]

Two years ago at CROI, Paul Rubinstein from the University of Illinois reported on a 67-year-old man with HIV who'd received a stem cell transplant from donor homozygous for the CCR5Δ32 mutation to treat AML.[14] ART was eventually interrupted post-transplant but low-level viral load rebound occurred, leading to the reinitiation of treatment. HIV viral load rebound in a recipient of cells lacking CCR5 hadn't been documented previously, and the virus appeared to derive from lingering host cells expressing the co-receptor (while the donor cells remained uninfected). At CROI 2025, Rubinstein revealed that a second ATI was undertaken two years after ART re-initiation, and after ten months of ongoing follow up there has been no recrudescence of HIV viral load.[15]

Immune-Based Therapies to Promote Immune Reconstitution

Sadly there's a dwindling amount of research into immune-based therapies that might have the capacity to improve CD4+ T cell recovery in people with suboptimal immune reconstitution despite ART-mediated viral load suppression. Two new clinical trials were identified in registries during the past year, both involving micronutrient supplementation with either nicotinamide mononucleotide (NMN) or zinc (see table 2).

Table 1. Research Toward a Cure 2025: 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 (closed to enrollment)	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 (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
ANTI-α4β7 INTEGRIN ANTIBODIES					
Vedolizumab	Anti-α4β7 integrin antibody, **ATI**	NCT03147859	Ottawa Hospital Research Institute	Canada	Phase II
ANTI-CMV THERAPY					
letermovir (Prevymis)	Antiviral	NCT06626555 (not yet open for enrollment)	University College, London	United Kingdom	Phase II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Location(s)	Phase
ANTI-INFLAMMATORY					
Fecal Microbiota Transplantation (FMT)		NCT06022406	Jean-Pierre Routy, McGill University Health Centre	Canada	Phase II
ANTIRETROVIRAL THERAPY					
Administration of high doses of antiretrovirals		NCT06640192	Fundacion para la Investigacion Biomedica del Hospital Universitario Ramon y Cajal	Spain	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					
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 (enrollment paused)	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 (enrollment paused)	NIAID	Brazil, Peru, United States	Phase II
Tatelo Plus: PGDM1400LS, VRC07-523LS, PGT121.414.LS	Long-acting bNAbs, **ATI** in early-treated children	NCT06508749	NIAID	Botswana	Phase I/II
3BNC117-LS-J + 10-1074-LS-J (PAUSE: Pausing Antiretroviral Treatment Under Structured Evaluation)	Long-acting bNAbs, **ATI**	NCT06031272 (enrollment paused)	ACTG	Botswana, Malawi, South Africa	Phase I
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	CAPRISA	South Africa	Phase I
VH4527079 bispecific antibody	Bispecific bNAb	NCT06652958	ViiV Healthcare	United States	Phase I
VRC07-523LS + PGT121.414.LS	Long-acting bNAbs, **ATI**	NCT06987318 (not yet open for enrollment)	NIAID	Brazil, Peru, United States	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Location(s)	Phase
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					
Sindilizumab + chidamide	PD-1 inhibitor + HDAC inhibitor, **ATI**	NCT06902038 (not yet open for enrollment)	Jun Chen, MD	China	N/A
maraviroc, dolutegravir, dendritic cell vaccine, auranofin, nicotinamide	CCR5 inhibitor, therapeutic vaccine, anti-rheumatic, HDAC inhibitor	NCT06805656 (not yet open for enrollment)	Federal University of São Paulo	Brazil	N/A
AbVax: ChAdOx1.tHIVconsv1 + HIVconsv62, MVA.tHIVconsv4, teropavimab, zinlirvimab	Therapeutic vaccines + bNAbs, **ATI**	NCT07054931 (not yet open for enrollment)	University of Oxford	United Kingdom	Phase II
Budigalimab +/- ABBV-382	Anti-PD-1 antibody + anti-$\alpha_4\beta_7$ integrin antibody, **ATI**	NCT06032546 (closed to enrollment)	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
N6-LS (VH3810109) +/- fostemsavir	Broadly neutralizing antibody, CD4 attachment inhibitor	NCT07053384 (not yet open for enrollment)	ViiV Healthcare	United States, Europe	Phase Ib
Ad26.Mos4.HIV, MVA-BN-HIV, PGT121, PGDM1400, VRC07-523LS	Therapeutic vaccines, bNAbs, **ATI**	NCT04983030 (closed to enrollment)	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 (enrollment paused)	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 (closed to enrollment)	NIAID	United States	Phase I
N-803, 3BNC117-LS, 10-1074-LS	Recombinant human super agonist IL-15 complex, long-acting bNAbs, **ATI**	NCT05245292 (closed to enrollment)	Rockefeller University	United States	Phase I
VRC07-523LS, PGDM1400LS, ChAdOx1.tHIVconsv1, ChAdOx1.HIVconsv62, MVA.tHIVconsv4, A244d11 gp120/ALFQ	bNAbs + therapeutic vaccines	NCT06484335 (not yet open for enrollment)	Henry M. Jackson Foundation for the Advancement of Military Medicine	Thailand	Phase I
CYTOKINES					
N-803	Recombinant human super agonist IL-15 complex in acute HIV infection	NCT04505501 (closed to enrollment)	Thai Red Cross AIDS Research Centre	Thailand	Phase II
GENE THERAPIES					
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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Location(s)	Phase
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
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
HIV-CAR-T: Efficacy and safety study of CAR-T Cells for functional cure		NCT06880380 (not yet open for enrollment)	Institute of Hematology & Blood Diseases Hospital	China	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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Location(s)	Phase
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
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					
NIVO-LD: Low dose nivolumab in adults living with HIV on antiretroviral therapy	Anti–PD-1 antibody, **ATI**	NCT05187429	University of Melbourne	Australia, Singapore	Phase I/II
IMMUNOMODULATORS					
Lenalidomide, adenosylmethionine	Immunomodulatory agents	NCT05598580	First Affiliated Hospital of Zhejiang University	China	Phase IV
PEACH: Pomalidomide as an immune-enhancing agent for the control of HIV		NCT06660498	University of Aarhus	Australia, Denmark	Phase I/IIb
JANUS KINASE INHIBITORS					
Baricitinib	Janus kinase inhibitor	NCT05452564	Emory University	United States	Phase II
Baricitinib	Janus kinase inhibitor	NCT07028385 (not yet open for enrollment)	Fundación FLS de Lucha Contra el Sida	Spain	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
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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Location(s)	Phase
OBSERVATIONAL STUDIES					
Accurate staging of immuno-virological dynamics during acute HIV infection (ACS)		NCT03449706	University Hospital, Ghent	Belgium	N/A
Analytical treatment interruption after combination bNAb therapy	**ATI**	NCT06908083 (enrolling by invitation)	NIAID	United States	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	University Hospital, Strasbourg, France	France	N/A
ARCH: Analysis of the reservoir in individuals controlling HIV infection		NCT06016114 (not yet open for enrollment)	University Hospital, Ghent	Belgium	N/A
ATGALIG-HIV: Study of auto-phagy 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 de-termine the cartography of virologic reservoir related to antiretroviral concentrations in HIV-1+ patients on first-line treatment containing bictegravir, emtricitabine, and tenofovir alafenamide		NCT05222945	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 (closed to enrollment)	Erasmus Medical Center	Netherlands	N/A
CODEX (the 'Extreme' cohort)	Long-term non-progres-sors and HIV controllers	NCT01520844	Inserm-ANRS	France	N/A
Comparing immune activation and HIV reservoir size between PWHIV on tenofovir-contain-ing 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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Location(s)	Phase
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
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)	Aidsfonds	International	N/A
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 (closed to enrollment)	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

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
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
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	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 gastrointesti-nal-associated lymphoid tissue in the cure of HIV infection		NCT05652088 (enrolling by invitation)	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 Neuro-logical 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
ViPer: Role of viral reservoir, immune activation and depletion in persistent viremia		NCT07015164 (not yet open for enrollment)	Assistance Publique - Hôpitaux de Paris	France	N/A
STEM CELL TRANSPLANTATION					
Analytical treatment interrup-tion in PWHIV post-allogeneic stem cell transplantation from a CCR5 delta32 homozygous donor	**ATI**	NCT06582797 (not yet open for enrollment)	University of Kansas Medical Center	United States	N/A
TARGETED ACTIVATOR OF CELL KILL (TACK) MOLECULES					
Efavirenz T cell activator of cell killing study		NCT06823596	University of Toronto	Canada	N/A
MK-4646		NCT07042945	Merck Sharp & Dohme LLC	Moldova	Phase I
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
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
HB-502/HB-501	Arenavírus vaccine vectors	NCT06430905 (closed to enrollment)	Hookipa Biotech GmbH	United States	Phase Ib
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, **ATI**	NCT06006546	NIAID, HVTN	United States	Phase I
CH505 TF chTrimer vaccine		NCT06680479	NIAID	United States	Phase I
GRAdHIVNE1	Gorilla adenovírus vaccine vector	NCT06617091 (not yet open for enrollment)	IAVI	South Africa, Zimbabwe	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
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
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
Codivir in addition to standard antiretroviral treatment		NCT06676410	Code Pharma	Brazil	Phase II
EARLIER: early ART to limit infection and establishment of reservoir	Combination ART	NCT02859558 (closed to enrollment)	ACTG	Brazil, Malawi, Peru, South Africa, Thailand, United States, Zimbabwe	Phase II
Gammora plus antiretroviral treatment		NCT06799650	Federal University of São Paulo	Brazil	Phase II
Lenacapavir intensification to disrupt HIV reservoirs		NCT06819176 (not yet open for enrollment)	NIAID	United States	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Location(s)	Phase
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 2024 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-CMV Therapy

Researchers in the UK are planning to initiate a study of the anti-CMV drug letermovir primarily to assess effects on T cell activation in people with HIV on ART. Markers of HIV persistence will also be measured as secondary endpoints. The trial appears similar to a previous pilot protocol conducted by Peter Hunt and colleagues, which reported evidence of modulation of inflammatory pathways[16] and potentially beneficial effects on aging parameters,[17] but didn't document changes of sufficient magnitude to meet pre-specified criteria for expanding the number of participants.

Antiretroviral Therapy

A clinical trial in Madrid, Spain is investigating the effects on the tissue HIV reservoir of higher than usual doses of the antiretroviral drugs dolutegravir, maraviroc, and lamivudine. While most studies have concluded that current ART regimens completely suppress HIV replication,[18,19] the registry entry for this new trial states that there's some evidence of reduced drug concentrations in lymphoid tissue that may be linked to higher levels of HIV RNA.[20] The goal of the protocol is to assess whether ART that can be safely administered at slightly higher doses affects measures of HIV persistence. The trial aims to enroll 24 participants.

Broadly Neutralizing Antibodies (bNAbs)

The NIH-supported Advancing Clinical Therapeutics Globally (ACTG) network has registered a new trial of dual broadly neutralizing antibodies (bNAbs), VRC07-523LS and PGT121.414.LS, in people who initiated antiretroviral therapy (ART) during acute HIV infection. The protocol includes an ATI to assess whether receipt of the bNAbs is associated with continued suppression of viral load after ART withdrawal. The registry entry lists sites in Brazil and Peru, so plans for the study could also be affected by the current "pause" on provision of NIH grant subawards that fund international clinical trial units[21] (see the conclusion section of this report for discussion of the current political attacks on scientific research in the United States).

ViiV Healthcare is recruiting for a new first-in-human clinical trial of a bispecific bNAb currently codenamed VH4527079. Bispecific means that the antibody has been engineered to block two different parts of HIV that are involved in the process of infecting vulnerable cells (a regular bNAb only has one target). The study will administer VH4527079 to people with HIV on ART and a cohort of participants without HIV.

Tatelo Plus is a newly launched study that aims to follow up on a prior smaller evaluation of dual bNAbs in children with HIV in Botswana (the Tatelo study[22]). The research project is primarily testing bNAbs as an alternative to ART for maintaining HIV viral load suppression, but straddles the boundary with cure research by including detailed investigations of effects on the HIV reservoir (and using reservoir measurements as part of the criteria for deciding whether to interrupt ART).

In the original Tatelo study, 11 of 25 infants (44%) who received the bNAbs 10–1074 and VRC01-LS maintained undetectable viral loads during a 24 week ART interruption. The new trial, which is under the aegis of the IMPAACT network, will administer three long-acting bNAbs: PGDM1400LS, VRC07-523LS, and PGT121.414.LS.

Based on information gleaned from Tatelo, the protocol includes additional criteria for determining whether a participant will be able to enter the ART interruption phase. These criteria include undetectable levels of HIV DNA using a qualitative test and, for the first time, results from sophisticated analyses of where HIV has integrated its genetic code into the genome of infected cells. Specifically, the protocol requires that >80% of intact HIV proviruses detected with these assays are located in inhospitable regions of the cell's genome that are less likely to allow the virus to reactivate and replicate.

As a metaphor for this biological phenomenon, if you think of a cell's genome as a factory for producing all the proteins the cell needs to go about its daily business, HIV DNA tends to integrate in machinery that gets switched on regularly. This gives the virus opportunities to hijack that machinery to make more HIV proteins (and potentially more copies of infectious HIV). But HIV DNA can also land in the genomic equivalent of a disused and shuttered factory storage room (sometimes referred to as a "gene desert") — in that case, the virus can become locked in, and unable to reactivate.

Analyses of the Tatelo study presented at CROI 2023 suggest that HIV viral load rebound during ART interruption was associated with an HIV reservoir primarily located in regions of the genome that allow for virus reemergence.[23] These findings led to the new eligibility criteria for undergoing ART interruption in Tatelo Plus, with the goal of trying to select participants with the best chance of maintaining HIV viral load suppression.

An observational protocol sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) is inviting participants from a large trial of dual broadly neutralizing antibodies (bNAbs) to undergo an ATI. The parent study has been ongoing since 2023, involving the administration of the long-acting bNAbs 3BNC117-LS and 10-1074-LS to around 200 participants with HIV on antiretroviral therapy (ART). The invitational trial will assess whether receipt of the bNAbs promotes viral load suppression after ART interruption. The dual bNAb combination of 3BNC117 and 10-1074 was used in the RIO trial described in the introduction, and has been tested in multiple prior studies and found to be safe and associated with prolonged control of viral load after ATI in a subset of recipients.[24,25,26]

Combinations

Five new investigations of combination approaches have been added since the 2024 Pipeline Report, and this remains the most populated category of interventional studies with 14 in total.

Jun Chen, MD is leading a trial of a combination of the PD-1 inhibitor sindilizumab with chidamide, a candidate latency-reversing agent from the HDAC inhibitor class. The study plans to enroll 33 participants at the Shanghai Public Health Clinical Center in China and includes an ATI. Some evidence of PD-1 inhibitors enhancing control of HIV viral load after an ATI have emerged from early-phase studies conducted by the pharmaceutical company AbbVie.[27]

A research group led by Dr. Ricardo Diaz at the Federal University of São Paulo in Brazil has registered a 70-person study investigating a combination regimen that previously showed some promise in enhancing post-treatment control in a smaller study that first reported results at CROI in 2019,[28] but to our knowledge hasn't yet had full findings shared in a journal article. The components being added to standard ART include the CCR5 inhibitor maraviroc, the integrase inhibitor dolutegravir, a dendritic cell-based therapeutic vaccine,[29] auranofin,[30] and nicotinamide (a form of vitamin B3). Participants will undergo an ATI to evaluate any effects on HIV viral load rebound.

The US Military HIV Research Program (MHRP) is planning to launch a revised version of a previously withdrawn protocol that will assess a combination of broadly neutralizing antibodies and therapeutic vaccines in people with HIV in Bangkok, Thailand. The long-acting broadly neutralizing antibodies are VRC07-523LS and PGDM1400LS, while the therapeutic vaccine regimen involves two viral vectors — chimpanzee adenovirus (ChAd) and modified vaccinia Ankara strain (MVA) —and an HIV envelope protein with adjuvant. The previous version of the protocol also included the IL-15 superagonist N-803, now removed from the regimen.

The trial plans to enroll people with HIV between 18 and 60 years old who were diagnosed during acute infection (soon after HIV acquisition) and have taken ART for at least 48 weeks or are willing to initiate ART as part of the protocol. After receipt of the interventions, participants will undergo an ATI to evaluate any effects on the timing and magnitude of HIV viral load rebound.

Oxford University in the UK is sponsoring a phase II investigation of dual bNAbs combined with therapeutic vaccines in the "AbVax" study. Similar to the MHRP trial, the vaccines are ChAd and MVA vectors, but the bNAbs are long-acting versions of 3BNC117 and 10-1074 (listed under their Gilead Sciences names, teropavimab and zinlirvimab). The aim is to enroll 48 participants on ART and assess whether receipt of the interventions can promote containment of viral load after an ATI.

ViiV Healthcare is launching a novel phase Ib combination protocol that will evaluate the long-acting bNAb N6-LS combined with their licensed CD4 attachment inhibitor fostemsavir. Approximately 100 participants will be enrolled, either already receiving a standard of care ART regimen with an integrase inhibitor or naïve to ART and initiating such a regimen on entry. Controls will receive ART alone, while two other groups will be administered N6-LS or N6-LS and fostemsavir. The primary endpoints involve the size and activity of the HIV reservoir measured by cell-associated HIV RNA and assessments of intact and defective HIV DNA.

Gene Therapies

Only one new gene therapy study is added this year. Researchers in China plan to evaluate chimeric antigen receptor (CAR) T cells, a gene therapy approach that involves equipping T cells with receptors designed to recognize a specific target (in this case, HIV). The registry entry doesn't offer any details regarding the specific makeup of the CAR T cells. The study is taking place at Tsinghua University in Beijing.

Immunomodulators

A collaborative study led by researchers in Denmark and Australia will assess the effects of an immunomodulatory anti-cancer drug, pomalidomide (a safer analog of thalidomide), in people with HIV on ART. The protocol includes an ATI to evaluate whether pomalidomide alters HIV viral load rebound. Pomalidomide has previously shown evidence of efficacy and immune modulation in people with HIV and Kaposi's sarcoma.[31]

JAK Inhibitors

Preclinical research has produced evidence that the Janus kinase (JAK) inhibitor baricitinib can suppress reactivation of the HIV reservoir[32] and potentially have beneficial effects on neurocognition via suppression of viral transcription.[33] An ongoing study at Emory University is particularly focused on the impact of baricitinib on the central nervous system in people with HIV on ART.

A second trial is now planned in Spain, which will gauge pharmacokinetics, safety, tolerability, and effects on the HIV reservoir and T cells. The site is in Barcelona and the enrollment target is 30 people on long-term suppressive ART.

Stem Cell Transplantation

Dr. Wissam El Atrouni at the University of Kansas Medical Center has registered a protocol for conducting ATIs in people with HIV who've received successful stem transplants to treat cancers. The criteria require that the stem cell transplants were sourced from donors homozygous for the CCR5Δ32 mutation. The study hasn't yet opened for enrollment but the protocol has been designed for a specific local candidate; the researchers are open to additional recruitment if other potential participants are identified.

Targeted Activator Of Cell Kill (TACK) Molecules

TACK molecules are potentially exciting variants of the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of ART drugs, optimized to trigger an innate mechanism that leads to the death of HIV-infected cells.

The mechanism involves the drugs causing the HIV protease enzyme to be produced prematurely during the viral life cycle, which leads to recognition by an innate sensor called CARD8 and triggers an antiviral signaling cascade leading to the death of the infected cell.[34,35]

For the first time in HIV cure research, two clinical trials are investigating the TACK approach.

In Toronto, a trial led by Dr. Mario Ostrowski aims to discern whether the licensed NNRTI efavirenz may be able to exert this cell-killing activity. The scientific literature offers disparate viewpoints, with at least one paper reporting that efavirenz may achieve concentrations capable of inducing TACK activity[36] while others suggest it's unlikely.[37]

Dr. Ostrowski has recruited people on antiretroviral therapy (ART) with a history of low-level detectable HIV viral load (between 20-400 copies/ml). Participants will add a daily dose of 600mg of efavirenz to their regular ART regimen for two months, with various measures of HIV persistence compared before and after the intervention. The hope is that efavirenz might have sufficient TACK activity to deplete the HIV-infected reservoir cells suspected of generating low-level viral load that can't be suppressed by ART (sometimes referred to as "non-suppressible viremia").[38]

Merck researchers are among those skeptical about the capacity of licensed NNRTIs to mediate TACK activity, and are pursuing optimized compounds. Promising laboratory results were published in 2023,[37] with supportive findings from humanized mice presented at CROI 2024.[39]

The first clinical candidate, designated MK-4646, was tested in a first-in-human safety trial in Belgium during 2024 but to our knowledge results haven't yet been publicly presented. A second study has now been initiated in people with HIV who are naïve to ART in Bucharest, Romania, suggesting safety parameters were favorable.

Therapeutic Vaccines

The ACTG has started a trial at multiple US sites to investigate the capacity of a therapeutic vaccine to promote neutralizing antibody responses against HIV. The vaccine contains a stabilized part of the outer HIV envelope designed to mimic the natural three-pronged conformation of the protein, delivered with an Alum adjuvant. The construct, called a stabilized CH505 TF chTrimer, has previously been reported to show promise as a preventive vaccine in the SHIV/macaque model.[40]

The non-profit vaccine development organization IAVI has registered a new trial that plans to investigate an HIV vaccine candidate based on an adenovirus variant derived from gorillas. The study will recruit people with HIV on ART and a cohort of HIV-negative participants. The modified gorilla adenovirus serves as a vector for delivering selected HIV components known to induce CD8 T cell responses. The main outcome measures will be safety and levels of vaccine-induced HIV-specific T cells. For the cohort of people with HIV, individuals with past CD4 nadirs (lowest ever values) less than 200 are excluded, presumably based on concerns that immune responses to the vaccine might be diminished.

Treatment Intensification/Early Treatment

A new study involving an FDA-approved antiretroviral plans to intensify ART by adding the capsid inhibitor lenacapavir. The protocol will evaluate whether the approach can promote greater reductions in the size of the HIV reservoir. A recently published paper has reported that lenacapavir may enhance natural antiviral mechanisms in HIV-infected cells by disrupting the capsid protein, which typically shields viral DNA from recognition by innate immune sensors.[41] The trial is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and scheduled to take place at the NIH Clinical Center in Bethesda.

The two other additions to this category involve a compound that is steeped in controversy. Several years ago a company named Zion Medical made a variety of implausible claims about the potential efficacy of an HIV drug candidate they named Gammora, supposedly based on protein fragments derived from HIV integrase.[42] A small clinical trial was said to have taken place in Uganda, but — if it did occur — wasn't approved by appropriate regulatory authorities, as the company eventually admitted in response to an investigation by Bekhisisa.[43]

Even more concerningly, substances called Gammora started to be sold as a purported HIV cure, both online and locally.[44] A release was issued (since deleted but archived) stating they'd entered into an agreement with a Swiss "seller of unlicensed medicines"[45] but the extent of their role in sales is unclear. Representatives from Zion Medical published an abstract rehashing claims about the Uganda trial in 2021, not mentioning that they'd already admitted it was improperly conducted.[46]

Some of the same protagonists now appear to have returned with a different company, Code Pharma, and seemingly a different name for the same compound: Codivir. They're collaborating with researchers in Brazil to conduct a study in which Codivir is administered alone and then in combination with standard ART.

The group has also registered another trial in Brazil, for which the intervention is still called Gammora and is added to a boosted darunavir ART regimen. Preliminary results appear to have been presented at the HIV Glasgow conference in November 2024.[47] The abstract claims very rapid declines in HIV DNA levels, but the past actions of the manufacturer leave some uncertainty regarding the extent to which the data can be trusted (at least from TAG's perspective).

We'll continue to monitor for the presentation of results from these trials, with the caveat that we're extremely skeptical regarding the integrity of this company. At the time of the HIV Glasgow conference, sales of the compound still appeared to be a major focus, with the company website stating: "Code Pharma has already received emergency approvals from several countries and is preparing for mass production of Gammora in different production sites worldwide based on the received orders."[48] TAG emailed the company to ask which countries have granted emergency approvals, but they refused to answer and the webpage has since been edited to remove the claim.[49]

Table 2. Immune-Based Therapy Pipeline 2025

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Status
Nicotinamide mononucleotide (NMN)	Micronutrient, nicotinamide adenine dinucleotide (NAD) precursor	NCT06889142 (not yet open for enrollment)	TriHealth Inc.	N/A
Zinc supplementation	Micronutrient	NCT06612554 (not yet open for enrollment)	Parc de Salut Mar	N/A
Fostemsavir	Attachment inhibitor	NCT05220358	Orlando Immunology Center	Phase IV
Mesenchymal stem cells	Human umbilical cord mesenchymal stem cells	NCT05872659	Shandong Qilu Cell Therapy Engineering Technology Co., Ltd.	Phase I
Haoqin Qingdan Granules	Artemisinin derivative	ITMCTR2023000019 (not yet open for enrollment)	China Academy of Chinese Medical Sciences	Not specified

Despite substantial evidence that limited CD4 recovery after HIV viral load suppression by ART is associated with elevated risk of morbidity and mortality,[50,51] there remains a paucity of research into interventions to enhance immune reconstitution. Only two new trials were identified in registries over the past year, and in both cases enrollment is listed as pending.

A study sponsored by TriHealth Inc. in Cincinnati intends to evaluate the micronutrient nicotinamide mononucleotide (NMN), a precursor of nicotinamide adenine dinucleotide (NAD) which plays a key role in cell metabolism. The hypothesis behind the research is that NMN supplementation can improve CD4 function and restoration by increasing intracellular NAD levels.

At the Parc de Salut Mar Hospital in Barcelona, Dr. Robert C Güerri-Fernández and colleagues plan to investigate whether zinc supplementation can improve CD4 recovery, with a randomized open label design involving approximately 120 participants

Conclusion

The past year has seen incremental but encouraging progress in HIV cure research, but there's now an ominous and toxic cloud engulfing science broadly. The administration that took power in the US on January 20, 2025 has launched an egregious, politically motivated, and unprecedented assault on scientific research, profoundly threatening the role of NIH and other US institutions as drivers of science globally.[52,53]

The scale of the assault makes it impossible to fully describe here. Thousands of grants have been terminated,[54] and scientists deemed insufficiently aligned with the extreme right wing anti-science views of the current US President and his fellow travelers ousted from their positions — including Dr. Jeanne Marrazzo, the highly qualified and only recently appointed head of NIAID.[55]

Massive cuts are being proposed to the NIH budget. Funding for research in South Africa was banned[56] (before some signs of slight reversals[57]), and needless obstacles placed in the way of obtaining funds already approved and committed for international partners on NIH grants.[58] These partners include critical study sites for the HIV research networks, including the ACTG, which has had to place holds on enrollment on multiple trials including HIV cure-related protocols. Appalling, bigoted, and flatly false claims about transgender people and the biology of sex are now posted on official US government websites.

The current Secretary of the Department of Health and Human Services (HHS), Robert F. Kennedy Jr., proudly disclosed his belief in the lies of AIDS denialism to a journalist just two years ago, stating: "There are much better candidates than HIV for what causes AIDS."[59] The statement indicates his embrace of conspiracy theories and complete lack of any familiarity with more than four decades of scientific research on HIV and AIDS.

As documented in the last available report by AVAC and the International AIDS Society, the NIH is the most significant funder of HIV cure research contributing approximately 80 percent of the $439.8 million total in 2021.[60] This proportion isn't likely to have changed significantly in recent years.

It's too early to predict exactly how these ugly and often opaque machinations may affect the future of the HIV cure and immune-based therapy pipelines, but there will undoubtedly be damage. Advocates are doing all they can to push back via Congressional representatives and other avenues. We encourage all people in the US who care about science and medical research do whatever they can to alert Congressional representatives, media, and their communities to the unfolding crisis.

Adapted in part from posts to the TAG HIV Basic Science, Vaccines, and Cure Project Blog *covering the monthly updates to TAG's* listing of HIV cure-related clinical research.

Endnotes

1. Fidler S, Lee MJ, Collins S, et al. RIO: A Randomised Placebo-Controlled Study of 2 LS-bNAbs in People Treated in Early HIV (Abstract 107). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
2. Dong K, Asari V, Govender V, et al. Evaluation of 2 bNAbs Plus Vesatolimod in Early-Treated South African Women With HIV-1 During ATI (Abstract 105). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
3. Dong K. HIV Cure Research in the FRESH Cohort in South Africa. 2025 Pre-CROI Community HIV Cure Research Workshop. 2025 March 8.
4. Frater J, Fox J, Lee MJ, et al. Sustained Post-Rebound HIV Remission With Enhanced T-Cell Immunity After LS-bNAbs: A Case Report (Abstract 505). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
5. Altaf M, Tipoe T, Nel C, et al. Sustained T Cell-Mediated Immunity After LS-bNAbs in the RIO Trial: A Vaccinal Effect (Abstract 506). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
6. Fumagalli MJ, Kaczynska A, Allombert M, et al. HIV-1 Reservoir Decay During Broadly Neutralizing Antibody Therapy in the RIO Trial (Abstract 513). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
7. Søgaard O. HIV Cure: A Translational Research Perspective (Abstract 16). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
8. Vandekerckhove L, Fox J, Mora-Peris B, et al. HIV Gag x CD3 Soluble TCR Bispecific: Safety and Activity in a First in Human Trial (Abstract 436). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19-22; Seattle, WA.
9. Dorrell L, Boffito M, Moreno S, et al. HIV GAG x CD3 Soluble TCR Bispecific Reduces the Active HIV Reservoir in a Phase I/II Trial (Abstract 104). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
10. Gaebler C, Kor S, Allers K, et al. The next Berlin patient: sustained HIV remission surpassing five years without antiretroviral therapy after heterozygous CCR5 WT/Δ32 allogeneic hematopoietic stem cell transplantation (Abstract SS0402LB). Paper presented at: AIDS 2024; 2024 July 22-26; Munich, Germany.
11. Zaegel-Faucher O, Boschi C, Benkouiten S, et al. Absence of viral rebound without antiretrovirals after CCR5Δ32/Δ32 allogeneic hematopoietic stem cell transplantation: a new case of a potential cure of HIV? (Abstract P206). Paper presented at: HIV Glasgow; 2024 November 10–13; Glasgow, UK.
12. Trøseid M, Myhre AE, Gullaksen HH, et al. HIV Remission After Allogeneic Hematopoietic Stem Cell Transplant From CCR5Δ32/Δ32 Sibling Donor (Abstract 532). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
13. Sáez-Cirión A, Mamez AC, Avettand-Fenoel V, et al. Sustained HIV remission after allogeneic hematopoietic stem cell transplantation with wild-type CCR5 donor cells. Nat Med. 2024 Dec;30(12):3544-3554.
14. Rubinstein P, Perez L, Rondelli D, et al. HIV-1 viral reservoir reactivation after CCR5 DELTA 32/32 stem cell transplantation (Abstract 434). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.
15. Rubinstein P, Pérez L, Rondelli D, et al. Sustained HIV Remission Despite Transient Rebound Viremia After a CCR5Δ32/Δ32 Stem Cell Transplant (Abstract 531). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
16. Gianella S, Kitch DW, Beck-Engeser GB, et al. Suppressing Asymptomatic CMV With Letermovir Reshapes Cardiometabolic Proteome in Treated HIV (Abstract 354). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2024); 2024 March 3–6; Denver, CO.
17. Gianella S, Erlandson KM, Kitch DW, et al. Letermovir for CMV Suppression Improves Immunologic and Functional Aging Outcomes in Treated HIV (Abstract 182). Paper presented at: Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2025); 2025 March 9–12; San Francisco, CA.
18. Bozzi G, Simonetti FR, Watters SA, et al. No evidence of ongoing HIV replication or compartmentalization in tissues during combination antiretroviral therapy: Implications for HIV eradication. Sci Adv. 2019 Sep 25;5(9):eaav2045.
19. Van Zyl GU, Katusiime MG, Wiegand A, et al. No evidence of HIV replication in children on antiretroviral therapy. J Clin Invest. 2017 Oct 2;127(10):3827-3834.
20. Rosen EP, Deleage C, White N, et al. Antiretroviral drug exposure in lymph nodes is heterogeneous and drug dependent. J Int AIDS Soc. 2022 Apr;25(4):e25895.
21. Reardon S. NIH funding policy deals new blow to HIV trial networks. Science. 2025 Jun 5;388(6751):1012-1013.

22. Shapiro RL, Ajibola G, Maswabi K, et al. Broadly neutralizing antibody treatment maintained HIV suppression in children with favorable reservoir characteristics in Botswana. Sci Transl Med. 2023 Jul 5;15(703):eadh0004.
23. Niesar A, Lian X, Hua R, et al. Viral Reservoir Landscape of Children with HIV in Botswana Treated with Dual bNAbs (Abstract 141). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.
24. Mendoza P, Gruell H, Nogueira L, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. Nature. 2018 Sep;561(7724):479–84.
25. Gaebler C, Nogueira L, Stoffel E, et al. Prolonged viral suppression with anti-HIV-1 antibody therapy. Nature. 2022 Jun;606(7913):368–74.
26. Sneller MC, Blazkova J, Justement JS, et al. Combination anti-HIV antibodies provide sustained virological suppression. Nature. 2022 Jun;606(7913):375–81.
27. Highleyman L. PD-1 inhibitor budigalimab may delay viral rebound. Aidsmap. 2023 October 26.
28. Diaz RS, Giron LB, Hunter J, et al. Randomized Trial of Impact of Multiple Interventions on HIV Reservoir: SPARC-7 Trial (Abstract 399). Paper presented at: Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2019); 2019 March 4-7; Seattle, WA.
29. de Almeida Baptista MV, da Silva LT, Samer S, et al. Immunogenicity of personalized dendritic-cell therapy in HIV-1 infected individuals under suppressive antiretroviral treatment: interim analysis from a phase II clinical trial. AIDS Res Ther. 2022 Jan 12;19(1):2.
30. Diaz RS, Shytaj IL, Giron LB, et al. Potential impact of the antirheumatic agent auranofin on proviral HIV-1 DNA in individuals under intensified antiretroviral therapy: Results from a randomised clinical trial. Int J Antimicrob Agents. 2019 Nov;54(5):592-600.
31. Ramaswami R, Polizzotto MN, Lurain K, et al. Safety, Activity, and Long-term Outcomes of Pomalidomide in the Treatment of Kaposi Sarcoma among Individuals with or without HIV Infection. Clin Cancer Res. 2022 Mar 1;28(5):840-850.
32. de Armas LR, Gavegnano C, Pallikkuth S, et al. The Effect of JAK1/2 Inhibitors on HIV Reservoir Using Primary Lymphoid Cell Model of HIV Latency. Front Immunol. 2021 Aug 31;12:720697.
33. Gavegnano C, Haile WB, Hurwitz S, et al. Baricitinib reverses HIV-associated neurocognitive disorders in a SCID mouse model and reservoir seeding in vitro. J Neuroinflammation. 2019 Sep 27;16(1):182.
34. Kim JG, Shan L. Beyond Inhibition: A Novel Strategy of Targeting HIV-1 Protease to Eliminate Viral Reservoirs. Viruses. 2022 May 28;14(6):1179.
35. Jefferys R. TACK Molecules: Sabotaging HIV to Trigger the Death of Virus-Infected Cells. TAG HIV Basic Science, Vaccines, and Cure Project Blog. 2023 June 22.
36. Trinité B, Zhang H, Levy DN. NNRTI-induced HIV-1 protease-mediated cytotoxicity induces rapid death of CD4 T cells during productive infection and latency reversal. Retrovirology. 2019 Jun 26;16(1):17.
37. Balibar CJ, Klein DJ, Zamlynny B, et al. Potent targeted activator of cell kill molecules eliminate cells expressing HIV-1. Sci Transl Med. 2023 Feb 22;15(684):eabn2038.
38. Mohammadi A, Etemad B, Zhang X, et al. Viral and host mediators of non-suppressible HIV-1 viremia. Nat Med. 2023 Dec;29(12):3212-3223.
39. Diamond TL. From Mechanisms to Therapeutics: TACK Molecules Kill HIV-Infected Cells Through Inflammasome Activation (Abstract 42). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2024); 2024 March 3–6; Denver, CO.
40. Saunders KO, Edwards RJ, Tilahun K, et al. Stabilized HIV-1 envelope immunization induces neutralizing antibodies to the CD4bs and protects macaques against mucosal infection. Sci Transl Med. 2022 Sep 7;14(661):eabo5598.
41. Scott TM, Arnold LM, Powers JA, et al. Cell-free assays reveal that the HIV-1 capsid protects reverse transcripts from cGAS immune sensing. PLoS Pathog. 2025 Jan 28;21(1):e1012206.
42. Treatment Action Group HIV Cure Research Media Monitor. Story: Claims that "Gammora" Represents a Potential HIV Cure. 2018 October - November; updated 2024 September.
43. Ngcobo S, López González L. Company with false HIV 'cure' admits trial was not registered with regulatory body. Bekhisisa; 2018 November 9.
44. Khourie T. No, Gammora HIV 'cure kits' not medically proven – stick to approved treatment. Africa Check. 2023 February 28.
45. FarmaMondo (Press Release). Zion Medical appoints the FarmaMondo Group to support global named patient access to its novel therapy Gammora™. 2020 June 5.
46. Naftali E, Finkelshtein E, Ayni Z. Gammora is designed to kill HIV-infected cells, without harming uninfected cells - Unlike current antiretroviral drugs which merely suppress the spreading of the virus. Virology Research Journal (2021) Volume 5, Issue 2.
47. Diaz RS, Schechter M, Elbirt D, et al. Peptide-induced apoptosis of latently infected cells and reduction of the HIV reservoir in people living with HIV: preliminary results of a clinical trial (Abstract P212). Paper presented at: HIV Glasgow; 2024 November 10–13; Glasgow, UK.

48. Code Pharma. Research and Development Pipeline. 2024 November 9 (archived).

49. Code Pharma. Research and Development Pipeline. 2025 July 17.

50. Engsig FN, Zangerle R, Katsarou O, et al. Long-term mortality in HIV-positive individuals virally suppressed for more than 3 years with incomplete CD4 recovery. Clin Infect Dis. 2014 May;58(9):1312-21. doi: 10.1093/cid/ciu038. Epub 2014 Jan 22.

51. Zoufaly A, Cozzi-Lepri A, Reekie J, et al. Immuno-virological discordance and the risk of non-AIDS and AIDS events in a large observational cohort of HIV-patients in Europe. PLoS One. 2014 Jan 31;9(1):e87160.

52. Nature Editorial. Trump 2.0: an assault on science anywhere is an assault on science everywhere. Nature. 2025 Mar;639(8053):7-8.

53. Waldman A, Fields A, Clarke A. Science Shattered. ProPublica; 2025 June 12.

54. Kozlov M, Ryan C. How Trump 2.0 is slashing NIH-backed research — in charts. Nature. 2025 Apr;640(8060):863-865.

55. Kaiser J. Trump administration purges U.S. health agency leaders. Science Insider. 2025 April 1.

56. TAG, Médecins Sans Frontières, and the South African Medical Research Council. South Africa's TB and HIV Research at Risk: A Call to Catalyze Urgent Action by Funders. 2025 May.

57. Kaiser J. NIH restores grants to South Africa scientists, adds funding option for other halted foreign projects. Science Insider. 2025 July 3.

58. Kozlov M. Exclusive: NIH to end billions of dollars in foreign research grants. Nature. 2025 Apr 30.

59. Traister R. Robert F. Kennedy Jr.'s Inside Job. New York Magazine. 2023 Jun 30.

60. International AIDS Society Towards an HIV Cure Initiative, AVAC, Resource Tracking for HIV Prevention Research and Development Working Group. Global investment in HIV CURE research and development in 2021: a decade of progress. 2023 July.