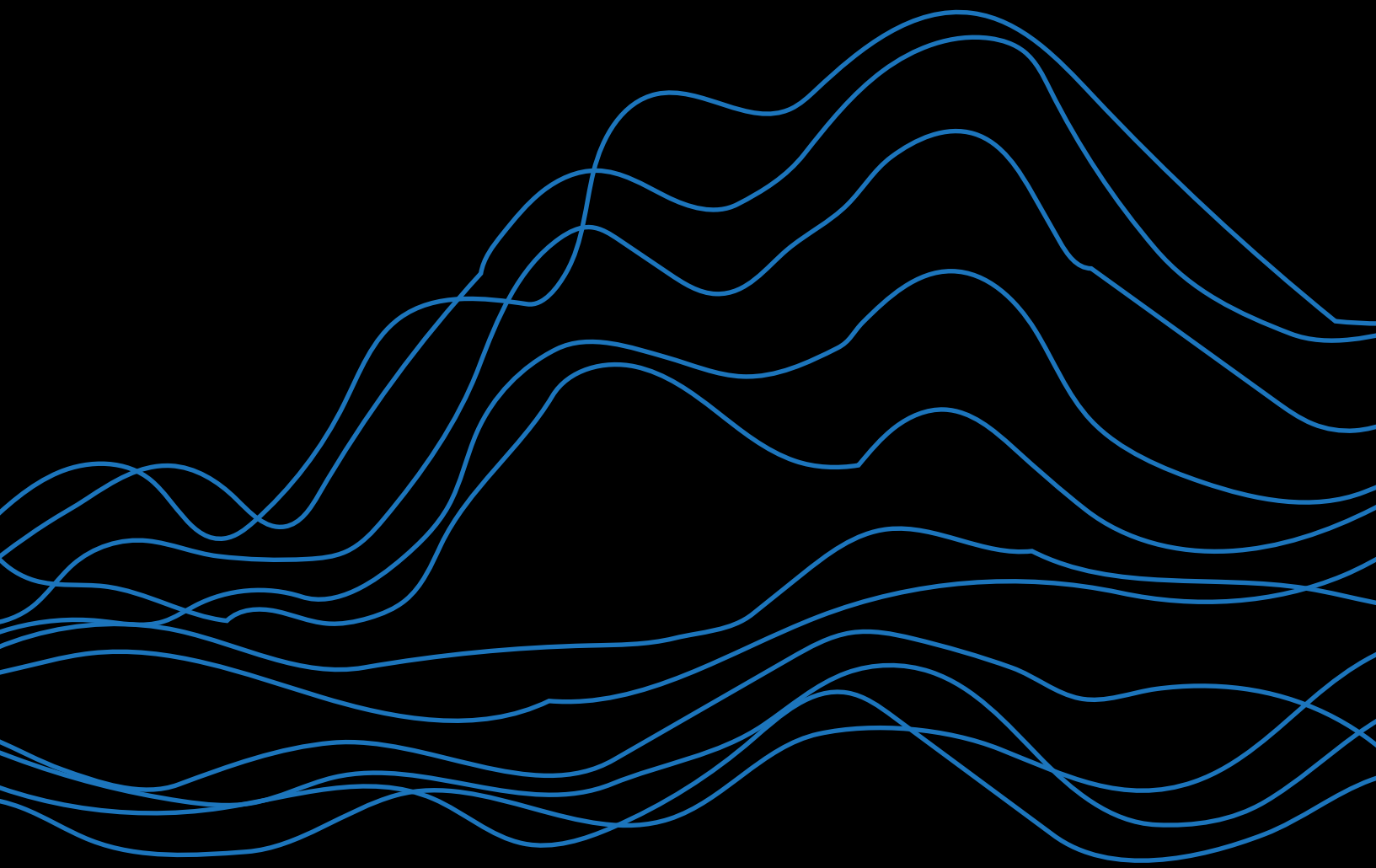
# Pipeline Report » 2023

## Research Toward a Cure and Immune-Based Therapies



TAG
Treatment Action Group

## Dedication

Dedicated to the memory of extraordinary activist and beloved colleague Giulio Maria Corbelli.

# Research Toward a Cure and Immune-Based Therapies

By Richard Jefferys

## Introduction

The HIV cure research field has seen significant developments over the past year. The number of apparent cures achieved in people with HIV who received stem cell transplants for cancers has expanded to five, with four having publicly identified themselves by name (see table 1).

## Table 1. Stem Cell Transplant HIV Cure Cases, July 2023

| Case | Outcome | Procedures |
|---|---|---|
| Timothy Ray Brown (The Berlin Patient) | Cured of HIV (>10 years), died due to a recurrence of cancer in 2020[1,2,3] | Two stem cell transplants to treat acute myelogenous leukemia (AML) from a donor homozygous for the CCR5Δ32 mutation, stopped ART in 2007 |
| Adam Castillejo (The London Patient) | Cured of HIV (>2 years), cancer in remission[4,5] | Stem cell transplant to treat Hodgkin's lymphoma from a donor homozygous for the CCR5Δ32 mutation, stopped ART in 2017 |
| Marc Franke (The Düsseldorf Patient) | Cured of HIV (>2 years), cancer in remission[6,7,8] | Stem cell transplant to treat AML from a donor homozygous for the CCR5Δ32 mutation, stopped ART in 2018 |
| The New York Patient | Possible cure of HIV (>18 months), cancer in remission[9,10,11] | Haplo-cord stem cell transplant to treat AML including cord blood stem cells from a donor homozygous for the CCR5Δ32 mutation, stopped ART in 2020 |
| Paul Edmonds (The City of Hope Patient) | Possible cure of HIV (>2 years), cancer in remission[12,13] | Stem cell transplant to treat AML from a donor homozygous for the CCR5Δ32 mutation, stopped ART in March 2021 |

Adapted from Landovitz RJ, Scott H, Deeks SG. Prevention, treatment and cure of HIV infection. Nat Rev Microbiol. 2023 Jun 21. doi: 10.1038/s41579-023-00914-1.

Additionally, there have been important advances in understanding the complexity of the reservoir of HIV that persists despite suppression of viral load by antiretroviral therapy (ART). New long-term study results have shown that — contrary to prior projections[14,15] — levels of persistent virus do not typically continue declining over decades on ART but stabilize and in some cases increase.[16,17]

While the finding may sound bleak, researchers have also uncovered evidence that the copies of intact HIV that linger after such long periods are more likely to be entrapped in the genetic code of the cells they have

infected and potentially unable to emerge from hiding and replicate.[18] The current theory is that the HIV-infected cells most capable of producing new viruses (or viral proteins) are more vulnerable to the immune system, because the generation of viral components acts as a flag for immune-mediated destruction.

In this scenario, the immune system slowly culls the HIV reservoir cells that persistently or intermittently produce viral components, and what gets left behind is the cells containing HIV that is less able to become active (in some cases, potentially completely inert and essentially locked inside the cell). Evidence supporting this idea comes from studies demonstrating that the number of reservoir cells containing intact, viable HIV typically declines on ART, whereas this is not the case for cells harboring defective HIV.[19,20,21,22]

The reason the size of the HIV reservoir can stabilize or increase over long periods on ART is because CD4+ T cells can proliferate (copy themselves), and, if they contain HIV integrated into their genetic code, the blueprint for making more virus gets copied along with the cell. Factors that can promote CD4 proliferation include non-specific balancing of immune cell numbers (called homeostatic proliferation) and specific responses to pathogens or other antigens that the CD4+ T cells recognize.[23,24]

Developments in HIV reservoir research were highlighted in an excellent plenary presentation by Janet Siliciano at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI 2023). Researcher Jared Stern also gave a clear, community-friendly explanation at the Pre-CROI Community HIV Cure Research Workshop.

The possibility that all intact, viable HIV might eventually be cleared in some people on long-term ART is controversial but under investigation. Siliciano is skeptical, and pointed to results presented at CROI 2023 by her colleague Natalie McMyn demonstrating that HIV capable of replicating could be grown from CD4+ T cells sampled from people who had been on ART for two decades or more, arguing against the likelihood of eventual elimination.[4] But the laboratory of Xu Yu at the Ragon Institute — who have been at the forefront of this area of research — reported evidence that HIV couldn't be grown from the CD4+ T cells of one individual who acquired HIV perinatally and had received ART for 15 years, perhaps offering a glimmer of encouragement that the reservoir could ultimately be extinguished in some cases.[25]

Furthermore, in a separate small study, Yu's lab found that achieving post-treatment control of viral load after an ART interruption was associated with an HIV reservoir that appeared to be preferentially located in areas of the cell's genetic code that are less amenable to virus reemergence.[26]

The ability of scientists to delve into the complexity of the HIV reservoir has been facilitated by new technologies that allow for:

- Better discernment of intact and defective viruses.
- The generation of information on where exactly HIV has integrated into the genetic code of an infected cell.

For studies of experimental interventions in HIV cure research, this means that researchers now have tools to assess whether candidates are capable of accelerating the preferential reduction of intact, viable HIV that occurs in people on ART.

This capacity to more directly assess anti-reservoir activity may allow for a reduced dependence on analytical treatment interruptions (ATIs). Up until now, ATIs have been considered the only method for assessing whether a meaningful decline in the size of the HIV reservoir has occurred during a study (by measuring whether HIV viral load rebound is delayed and/or control of viral load off ART has been enhanced).

A small number of clinical trials have already reported evidence of very slight reductions in the size of the intact HIV reservoir in people receiving cure-related interventions. Among them are a study of vesatolimod, a Toll-like receptor agonist, in people who were controlling HIV to low levels but nevertheless initiated ART,[27] an investigation into HIV-specific chimeric antigen receptor (CAR) T cells that took place in China,[28] and research involving two broadly neutralizing antibodies (bNAbs) that found a trend toward intact HIV reservoir decline in a subset of participants who had received ART for seven years or more.[29] In coming years it's likely that there will be increasing use of in-depth, sophisticated analyses of the HIV reservoir in cure-related studies.

In her CROI presentation, Siliciano expressed doubts about the potential to develop a widely applicable cure that entirely eliminates the viable HIV reservoir, but optimism regarding achieving post-treatment immune control of viral load. Her team has generated evidence supporting the latter possibility by demonstrating that antibody responses in people with HIV affect the ability of the virus to emerge from the reservoir. In laboratory studies involving CD4+ T cells sampled from people on ART, HIV that can be grown out from the reservoir shows resistance to circulating antibodies, whereas virus variants that are sensitive to the antibodies are blocked from reemergence.[30]

The research group of Jonathan Li has recently published evidence that antibody responses can similarly shape the variants of HIV that rebound when people interrupt treatment, with stronger antibody activity associated with a greater chance of post-treatment control of viral load.[31] These findings support ongoing efforts to enhance immune-mediated suppression of HIV with bNAbs and other candidate interventions such as therapeutic vaccines.

The new case of a potential HIV cure achieved by stem cell transplantation was reported at the 2022 International AIDS Conference by Jana Dickter and colleagues from the City of Hope in Los Angeles.[12] Similar to those reported previously, the individual was diagnosed with a life-threatening cancer requiring treatment with a stem cell transplant, which was sourced from a donor homozygous for the CCR5Δ32 mutation (which renders immune cells resistant to most HIV variants).

The person later publicly identified themselves as Paul Edmonds, a resident of Desert Hot Springs in California. At 67 years of age (63 at the time of the transplant), Edmonds is notably the oldest person to benefit from the procedure.

Details on the fourth case of a likely HIV cure in a New York City woman of mixed race — disclosed at CROI 2022 and described in last year's Pipeline Report — were published in the journal *Cell* in March of 2023.[11]

Additional developments in the arena of stem cell transplantation included the first reported instance of successful treatment of cancer with a transplant from a CCR5Δ32 homozygote donor that did not also lead to an HIV cure — at least not yet. The case was described in a poster presentation at CROI 2023 by Paul Rubinstein and colleagues.[32] Following a similar path to previous examples, the individual interrupted ART

after the transplant when there were indications that HIV was unlikely to rebound. However, a low level of HIV viral load was detected after eight weeks, and ART was restarted. The rebounding virus was of a type that uses the CCR5 receptor to infect cells, suggesting that residual pre-transplant cells were sustaining viral replication. HIV could not be found in donor cells. Follow-up is ongoing, and the lead author of the presentation has suggested that it is possible the remaining embers of HIV infection may eventually be extinguished.

A study in the macaque model of infection with SIV, HIV's simian counterpart, shed light on the mechanism by which stem cell transplantation can lead to a cure. Jonah Sacha and colleagues from Oregon Health Sciences University found that allogeneic immunity — an immune response generated from the donated stem cells — was responsible for progressively clearing virus reservoirs, first from the blood, then from peripheral lymph nodes, and lastly from mesenteric lymph nodes that drain the gastrointestinal tract.[33]

While research into stem cell transplant cure cases represents a critical source of clues for developing a more broadly applicable HIV cure, it's also important to appreciate that the option of receiving a stem cell transplant to treat serious cancers is still very limited globally. For example, there are reportedly only six African countries where the procedure is available (Algeria, Egypt, Morocco, Nigeria, South Africa, and Tunisia),[34] and a recent review of transplants performed in 2016 found that the majority took place in North America or Europe.[35] Identifying appropriate donors homozygous for the CCR5Δ32 mutation further restricts the number of people with HIV who might benefit if they develop cancer requiring stem cell transplantation.

Surveying all the HIV cure-related clinical research studies currently known to be ongoing (see table 3), 18 new trials involving interventions have been added since the time of the last Pipeline Report in July 2022. For observational studies, there are nine additions to the table, though not all are necessarily new in terms of when they started — for example, the study of people with acute HIV infection in Zurich has been ongoing for some time but just presented the first cure-related information on HIV reservoirs and post-treatment control.[36] In total, the table contains 78 interventional trials (two involving imaging techniques aiming to help map the HIV reservoir) and 43 observational trials.

An important consideration in HIV cure-related research is the diversity of study participation. TAG has started a project attempting to track the location and demographics of participants in cure-related trials, drawing the information from results that have been published or presented from the beginning of 2018 to date. As can be seen from the summary (table 2), diversity in these trials is far from optimal, with significant underrepresentation of cisgender women, transgender people, and non-White demographics. Geographic distribution of studies also remains heavily skewed toward the United States and Europe (see location column of table 3).

## Table 2. HIV Cure-Related Clinical Research Participant Demographics

Demographics of participation in HIV cure-related clinical studies with results presented or published from 2018 to date. Total of 134 clinical trials and observational studies (126 adult, eight pediatric/adolescent), with six providing no sex, gender, or race/ethnicity information and 40 providing no race/ethnicity information.

| **Total # of participants** | **6758** |
|---|---|
| | |
| **Total from studies reporting sex and gender** | **6646** |
| Female | 1211 (18.2%) |
| Male | 5357 (80.6%) |
| Transgender women | 30 (0.5%) |
| Transgender men | 3 (0.05%) |
| Transgender (not identified) | 3 (0.05%)* |
| Non-binary or gender non-conforming | 8 (0.1%) |
| Missing/not reported | 36 (0.5%) |
| | |
| **Total from studies reporting race/ethnicity** | **4733** |
| Asian | 299 (6.3%) |
| Black | 854 (18%) |
| Hispanic | 327 (6.9%)** |
| White | 2914 (61.5%) |
| Native American/Native Hawaiian, American Indian/Alaskan Native | 15 (0.3%) |
| Pacific Islander | 2 (0.04%) |
| Indigenous Australian | 1 (0.02%) |
| More than one race/ethnicity | 164 (3.5%) |
| Other/unknown/not reported | 308 (6.5%) |

*Includes two transgender participants reported additively to data presented on sex assigned at birth
**Includes 151 participants of Hispanic ethnicity reported additively to data on race

The development of candidate adjunctive immune-based therapies for people with suboptimal CD4+ T cell restoration on ART is still a relatively moribund area of research. TAG has been able to identify only one new registered trial for this population over the past year (see table 4).

## Table 3. Research Toward a Cure 2023: 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 (not yet open for enrollment) | 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 HIV+ individuals undergoing ATI | **ATI** | NCT05419024 | National Cancer Institute (NCI) | United States | Phase II |
| **ANTIBODIES** | | | | | |
| VRC01 | Analytical treatment interruption in HVTN 703/HPTN 081 Antibody-Mediated Prevention (AMP) trial participants, **ATI** | NCT04860323 | HIV Vaccine Trials Network (HVTN) | Botswana, Malawi, South Africa, Zimbabwe | N/A |
| VRC01 | Analytical treatment interruption in HVTN 704/HPTN 085 AMP trial participants, **ATI** | NCT04801758 (closed to enrollment) | HVTN | Brazil, Peru, United States | N/A |
| GSK3810109A | Long-acting broadly neutralizing antibody formerly named N6-LS | NCT04871113 (closed to enrollment) | ViiV Healthcare | Europe, United States | Phase IIa |
| 10-1074-LS + 3BNC117-LS | Long-acting broadly neutralizing antibodies in primary infection, **ATI** | NCT04319367 | Imperial College London | United Kingdom | Phase II |

| Trial | Additional Description | Trial Registry Identifier(s) | Manufacturer/ Sponsor(s) | Location(s) | Phase |
|---|---|---|---|---|---|
| 3BNC117-LS + 10-1074-LS | Long-acting broadly neutralizing antibodies in primary infection, **ATI** | NCT05300035 (not yet open for enrollment) | ANRS | France | Phase II |
| UB-421 | Antibody inhibitor of HIV binding to CD4 receptors | NCT04404049 (not yet open for enrollment) | UBP Greater China (Shanghai) Co., Ltd. | China | Phase II |
| Vedolizumab | Anti-α4β7 integrin antibody, **ATI** | NCT03147859 | Ottawa Hospital Research Institute | Canada | Phase II |
| VRC07-523LS + PGT121.414.LS | Long-acting broadly neutralizing antibodies, **ATI** | NCT05719441 (not yet open for enrollment) | National Institute of Allergy and Infectious Diseases (NIAID) | Brazil, Peru, United States | Phase II |
| ABBV-382 | Anti-α4β7 integrin antibody | NCT04554966 (closed to enrollment) | AbbVie | United States | Phase Ib |
| 3BNC117-LS + 10-1074-LS | Long-acting broadly neutralizing antibodies | NCT05612178 | NIAID | United States | Phase I |
| 3BNC117-LS + 10-1074-LS | Long-acting broadly neutralizing antibodies, **ATI** | NCT05079451 (suspended) | NIAID | United States | Phase I |
| AAV8-VRC07 | Broadly neutralizing antibody delivered by adeno-associated virus (AAV) vector | NCT03374202 (closed to enrollment) | NIAID | United States | Phase I |
| SAR441236 | Tri-specific broadly neutralizing antibody | NCT03705169 (closed to enrollment) | NIAID | United States | Phase I |
| **ANTI-CYTOMEGALOVIRUS THERAPY** | | | | | |
| Letermovir (Prevymis) | Anti-cytomegalovirus drug | NCT04840199 | NIAID | United States | Phase II |
| **ANTIRETROVIRAL THERAPY** | | | | | |
| IDOLTIB: Impact of dolutegravir + lamivudine simplification on HIV-1 reservoirs | Integrase inhibitor + nucleoside reverse transcriptase inhibitor | NCT04034862 (closed to enrollment) | University of Liège | Belgium | Phase III |
| **BCL-2 ANTAGONISTS** | | | | | |
| Venetoclax | BCL-2 antagonist | NCT05668026 (not yet open for enrollment) | University of Aarhus | Australia, Denmark | Phase I/IIb |
| **COMBINATIONS** | | | | | |
| VRC07-523LS, CAP256V2LS, vesatolimod | Long-acting broadly neutralizing antibodies + TLR7 agonist, ATI | NCT05281510 | Gilead Sciences | South Africa | Phase IIa |
| ASC22 + chidamide | Anti–PD-L1 antibody + HDAC inhibitor | NCT05129189 | Shanghai Public Health Clinical Center | China | 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 |

| Trial | Additional Description | Trial Registry Identifier(s) | Manufacturer/ Sponsor(s) | Location(s) | Phase |
|---|---|---|---|---|---|
| Vorinostat ± tamoxifen in postmenopausal women | HDAC inhibitor + estrogen receptor modulator | NCT03382834 (closed to enrollment) | NIAID | United States | Phase II |
| Ad26.Mos4.HIV, MVA-BN-HIV, PGT121, PGDM1400, VRC07-523LS | Therapeutic vaccines, broadly neutralizing antibodies, **ATI** | NCT04983030 | Boris Juelg, MD, PhD | United States | Phase I/IIa |
| 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, South Africa, Tanzania, Thailand, Uganda, United States, Zambia, Zimbabwe | Phase I/II |
| Panobinostat + pegylated interferon-α2a | HDAC inhibitor + cytokine | NCT02471430 (closed to enrollment) | Massachusetts General Hospital | United States | Phase I/II |
| IL-12 adjuvanted p24CE DNA vaccine, MVA/HIV62B vaccine, lefitolimod, VRC07-523LS, 10-1074 | Therapeutic conserved element DNA vaccine, MVA vaccine boost, TLR9 agonist, broadly neutralizing antibodies, **ATI** | NCT04357821 (closed to enrollment) | UCSF | United States | Phase I/II |
| FT538 ± vorinostat | Adoptive immunotherapy with natural killer cells generated from pluripotent stem cells ± HDAC inhibitor | NCT05700630 (not yet open for enrollment) | Masonic Cancer Center, University of Minnesota | United States | Phase I |
| HVRRICANE: HIVIS DNA + MVA-CMDR vaccines ± Cervarix (TLR4 agonist) | Therapeutic vaccines + TLR4 agonist | NCT04301154 | PENTA Foundation | Italy, South Africa, Thailand | Phase I |
| N-803 ± VRC07-523LS + 10-1074 | Recombinant human super agonist IL-15 complex, broadly neutralizing antibodies, **ATI** | NCT04340596 | NIAID | United States | Phase I |
| N-803, 3BNC117-LS, 10-1074-LS | Recombinant human super agonist IL-15 complex, long-acting broadly neutralizing antibodies, **ATI** | NCT05245292 | Rockefeller University | United States | Phase I |
| VRC07-523LS, PGDM1400LS, N-803, Ad26.Mos4.HIV, MVA-BN-HIV, A244d11gp120/ ALFQ | Long-acting broadly neutralizing antibodies, recombinant human super agonist IL-15 complex, therapeutic vaccines, **ATI** | NCT05769569 (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 | Thai Red Cross AIDS Research Centre | Thailand | Phase II |

| Trial | Additional Description | Trial Registry Identifier(s) | Manufacturer/ Sponsor(s) | Location(s) | Phase |
|---|---|---|---|---|---|
| **DUAL-AFFINITY RE-TARGETING (DART) MOLECULES** | | | | | |
| MGD020 ± MGD014 | Bispecific DART molecules targeting the HIV envelope gp41 and gp120 proteins and CD3-expressing T cells | NCT05261191 | MacroGenics | United States | Phase I |
| **GENE THERAPIES** | | | | | |
| EBT-101 | AAV9 vector delivering CRISPR/Cas9 gene-editing tool targeting HIV provirus, **ATI** | NCT05144386 | Excision BioTherapeutics | United States | Phase I/IIa |
| LVgp120duoCAR-T cells | Autologous T cells gene-modified to express chimeric antigen receptors (CARs) targeting HIV | NCT04648046 | Steven Deeks, UCSF | United States | Phase I/IIa |
| Cal-1: Dual anti-HIV gene transfer construct | Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 and a fusion inhibitor (C46) | NCT02390297 (long-term safety phase; closed to enrollment) | Calimmune | United States | Phase I/II |
| SB-728-T | Autologous CD4+ T cells modified to inhibit CCR5 expression | NCT03666871 (closed to enrollment) | Case Western Reserve University | United States | Phase I/II |
| 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 |
| 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 exposed to SB-728-T or SB-728mR-T | Autologous CD4+ T cells gene-modified to inhibit CCR5 expression | NCT04201782 (enrolling by invitation only) | Sangamo Therapeutics | United States | Phase I |
| 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 |

| Trial | Additional Description | Trial Registry Identifier(s) | Manufacturer/ Sponsor(s) | Location(s) | Phase |
|---|---|---|---|---|---|
| **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 |
| **IMAGING STUDIES** | | | | | |
| Imaging immune activation in HIV by PET-MR | | NCT03684655 | UCSF | United States | Phase I |
| Radiolabeled VRC01 | Radiolabeled broadly neutralizing antibody | NCT03729752 | UCSF | United States | Phase I |
| **IMMUNE CHECKPOINT INHIBITORS** | | | | | |
| ASC22 | Anti–PD-L1 antibody | NCT05330143 | Ascletis Pharmaceuticals Co., Ltd. | China | Phase II |
| NIVO-LD: Low dose nivolumab in adults living with HIV on antiretroviral therapy | Anti–PD-1 antibody, **ATI** | NCT05187429 | 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 | National Cancer Institute | Australia, United States | Phase I |
| Pembrolizumab | Anti–PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms | NCT02595866 (closed to enrollment) | National Cancer Institute | United States | Phase I |
| **IMMUNOMODULATORS** | | | | | |
| Lenalidomide, adenosylmethionine | Immunomodulatory agents | NCT05598580 (not yet open for enrollment) | First Affiliated Hospital of Zhejiang University | China | Phase IV |
| **JANUS KINASE INHIBITORS** | | | | | |
| Baricitinib | Janus kinase inhibitor | NCT05452564 | Emory University | United States | Phase II |

| Trial | Additional Description | Trial Registry Identifier(s) | Manufacturer/ Sponsor(s) | Location(s) | Phase |
|---|---|---|---|---|---|
| **LATENCY-REVERSING AGENTS** | | | | | |
| Lauric acid | Saturated fatty acid | NCT05687565 | Hospital Universitari Vall d'Hebron Research Institute | Spain | N/A |
| Arsenic trioxide | Chemotherapy | NCT03980665 | Guangzhou 8th People's Hospital | China | Phase I |
| Decitabine, romidepsin | Chemotherapy, HDAC inhibitor | NCT05230368 | ANRS | France | Phase I |
| **OBSERVATIONAL STUDIES** | | | | | |
| 2000 HIV Human Functional Genomics Partnership Program (2000HIV) | | NCT03994835 (closed to enrollment) | Radboud University | Netherlands | N/A |
| 2000HIVTrained | HIV trained innate immunity in HIV elite controllers | NCT04968717 (closed to enrollment) | Radboud University | Netherlands | N/A |
| Accurate staging of immuno-virological dynamics during acute HIV infection (ACS) | | NCT03449706 | University Hospital, Ghent | Belgium | N/A |
| Analytic treatment interruption to assess HIV cure | **ATI** | NCT02437526 (enrolling by invitation only) | Mayo Clinic | United States | N/A |
| ANRS CO24 OncoVIHAC: Immune checkpoint inhibitors in HIV+ individuals with cancers | | NCT03354936 | Inserm-ANRS | France | N/A |
| APRIL: Analysis of the persistence, reservoir, and HIV latency | | NCT05752318 (not yet open for enrollment) | University Hospital, Strasbourg, France | France | N/A |
| ATGALIG-HIV: Study of autophagy and the effects of GALIG gene products in HIV-1+ patients on ART since primary infection, chronic phase, or never treated | | NCT04160455 | Centre Hospitalier Régional d'Orléans | France | N/A |
| BICTEVOIR: Study to determine the cartography of virologic reservoir related to antiretroviral concentrations in HIV-1+ patients on first-line treatment containing bictegravir, emtricitabine, and tenofovir alafenamide | | NCT05222945 (not yet open for enrollment) | ANRS | France | N/A |
| Characterization of acute and recent HIV-1 infections in Zurich: a long-term observational study | | NCT00537966 | University of Zurich | Switzerland | N/A |

| Trial | Additional Description | Trial Registry Identifier(s) | Manufacturer/ Sponsor(s) | Location(s) | Phase |
|---|---|---|---|---|---|
| CHRONO: Prospective cohort for ex vivo cure studies with chronic HIV+ patients in the Netherlands | | NCT04888754 | Erasmus Medical Center | Netherlands | N/A |
| 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 |
| Developing a functional cure for HIV disease: clinical specimen collection from HIV+ individuals | Determination of levels of HIV-reactive CD4+ T cells, possible leukapheresis | NCT03215004 (closed to enrollment) | American Gene Technologies International | United States | N/A |
| DOLUVOIR: Cartography of virologic reservoir related to antiretroviral concentrations in people with HIV on first-line treatment containing dolutegravir and nucleoside/nucleotide reverse transcriptase inhibitors | | NCT04133012 | Inserm-ANRS | France | N/A |
| Early antiretroviral treatment in HIV+ children | | NCT05784584 (closed to enrollment) | PENTA Foundation | Mali, Mozambique, South Africa | 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 |

| Trial | Additional Description | Trial Registry Identifier(s) | Manufacturer/ Sponsor(s) | Location(s) | Phase |
|---|---|---|---|---|---|
| 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 |
| Identification and quantification of HIV central nervous system latency biomarkers | | NCT02989285 | St Vincent's Hospital, Sydney | Australia | N/A |
| Investigation of the impact of inducible, replication-competent latent HIV-1 as an impediment to HIV/AIDS cure in the context of sustained viral suppression | | NCT04938518 | Kenya Medical Research Institute | Kenya | N/A |
| LAMIVIH: Evolution of HIV reservoir, inflammation, and microbiota footprint of PLWH switching to long-acting injectable treatment | | NCT05303337 | 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 |
| MERCI: Measuring the HIV-1 reservoir during cure interventions studies | | NCT05783388 (not yet open for enrollment) | University Hospital, Ghent | Belgium | N/A |
| NOVA: Netherlands cohort study on acute HIV infection | | NCT05728996 | Prof. Jan Prins | Netherlands | 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 |
| Quantification of antisense HIV RNA | | NCT05381844 | Institut National de la Santé et de la Recherche Médicale, France | France | N/A |
| RESERVIH32: Bioclinical evaluation of two biomarkers of aviremic HIV-1 in CD4+ T cells of adults undergoing treatment | | NCT03940521 | Centre Hospitalier Universitaire de Nîmes | France | N/A |
| Role of the IL-33/ amphiregulin pathway as a potential therapeutic target in HIV infection | | NCT03622177 | Inserm-ANRS | France | N/A |
| Saturne-HIV: Sequential analysis before and after treatment initiation to unravel the role of naturally occurring extracellular vesicles in HIV infection | | NCT04653610 | University Hospital, Ghent | Belgium | N/A |
| The Gemini Study: Safety and survival of genetically modified white blood cells in HIV+ twins | | NCT04799483 (closed to enrollment) | NIAID | United States | N/A |
| The Last Gift Study (for people with HIV and less than 6 months life expectancy due to terminal illness) | | UCSD study website (no registry entry) | 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 |

| Trial | Additional Description | Trial Registry Identifier(s) | Manufacturer/ Sponsor(s) | Location(s) | Phase |
|---|---|---|---|---|---|
| TRESAX: T follicular helper reservoir in axillary lymph nodes study | | hivcure.com.au (no registry entry) | Kirby Institute | Australia | N/A |
| **STEM CELL TRANSPLANTATION** | | | | | |
| Cord blood transplant with OTS for the treatment of HIV+ hematologic cancers | | NCT04083170 | Fred Hutchinson Cancer Research Center | United States | Phase II |
| **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 |
| **THERAPEUTIC VACCINES** | | | | | |
| BELIEVE: BCG vaccination | BCG vaccination effect on latent reservoir size in treated HIV-1 infection | NCT05004038 | 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 |
| 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 |
| ChAdOx1.HTI, MVA.HTI, ConM SOSIP.v7 gp140 | Viral vector vaccines + HIV envelope protein, **ATI** | NCT05208125 (closed to enrollment) | IrsiCaixa | Spain | Phase I |
| DC-HIV04: a1DC + inactivated whole autologous HIV, a1DC + conserved HIV peptides | Autologous dendritic cell vaccine variants loaded with either autologous inactivated HIV or conserved HIV peptides | NCT03758625 | Sharon Riddler, University of Pittsburgh | United States | Phase I |
| 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 |
| **TOLL-LIKE RECEPTOR AGONISTS** | | | | | |
| Vesatolimod | TLR7 agonist drug interaction study | NCT05458102 (closed to enrollment) | Gilead Sciences | United States | 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 (not yet open for enrollment) | Eva Bonfill, Institut d'Investigacions Biomèdiques August Pi i Sunyer | Spain | Phase II |
| Dasatinib | | NCT05780073 (not yet open for enrollment) | 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 2022 Pipeline Report.

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

## Analytical Treatment Interruptions (ATIs)

A pending study in France will assess whether people with particular immune system genetics who start ART early after HIV acquisition are more likely to control viral load during an ATI. The specific genotype is human leukocyte antigen (HLA) B35/53Bw4TTC2.

HLA receptors are cell surface molecules that present fragments of pathogens to immune system cells to trigger an immune response, and they are generated by a highly variable family of inherited genes. In retrospective studies, the B35/53Bw4TTC2 genotype has been associated with post-treatment control of HIV viral load among people who started ART very early.[37,38] The mechanism is thought to involve the enhancement of natural killer cell immune responses against HIV.

The planned trial will prospectively evaluate the impact of B35/53Bw4TTC2 on control of viral load after ATI. Participants will be recruited from the large ongoing ANRS CO6 PRIMO cohort of people with HIV in France who were identified within three months of infection.

## Broadly Neutralizing Antibodies (bNAbs)

Two new trials of bNAbs have been registered over the past year, both sponsored by the National Institute of Allergy and Infectious Diseases (NIAID).

The first is a large phase I evaluation of two long-acting bNAbs — 3BNC117-LS and 10-1074-LS — looking at safety and effects on the HIV reservoir and HIV-specific immune responses in people on ART. The study is aiming to enroll 200 participants at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, and Rockefeller University in New York City.

The second is being undertaken by the AIDS Clinical Trials Group (ACTG) and aims to recruit 48 people with very recent HIV infection to study whether the addition of VRC07-523LS and PGT121.414.LS to ART leads to enhanced control of viral load after an ATI. Study sites are located in multiple U.S. states, Brazil, and Peru.

## BCL-2 Antagonists

Venetoclax is a drug approved for the treatment of blood cell cancers that antagonizes BCL-2, a protein involved in promoting the survival of white blood cells (including CD4+ T cells) by inhibiting apoptosis (a mechanism of cell death). A trial investigating venetoclax in people with HIV on ART is being initiated by Thomas Rasmussen from Aarhus University in Denmark in collaboration with Sharon Lewin from the Doherty Institute at the University of Melbourne in Australia.

The rationale for the research derives from evidence obtained in laboratory and animal studies indicating that CD4+ T cells containing integrated HIV — the cells that constitute the main HIV reservoir that persists despite ART — have high levels of the BCL-2 protein[39] and are resistant to apoptosis. In both the laboratory dish[40] and the humanized mouse model,[41] venetoclax has been shown to promote the death of HIV-infected CD4+ T cells when HIV is actively making viral proteins.

In the trial, venetoclax will be given daily in 14-day cycles of escalating doses (200 mg, 400 mg, 800 mg), with each dose increase only proceeding if safety is established at the lower dose. The primary goal is to evaluate the safety of venetoclax in people with HIV on ART, because the drug can cause a range of side effects. Secondary outcome measures include the size of the HIV reservoir and any effects of venetoclax on cell pathways involved in promoting apoptosis.

If the results support further research in people with HIV, the researchers will consider investigating venetoclax in combination with latency-reversing agents. Venetoclax's ability to promote the death of HIV-infected cells requires the virus to be actively making viral proteins, and, as outlined in the introduction, current information on the HIV reservoir in people on ART suggests that some cells actively make viral proteins (at least intermittently) whereas others contain HIV that is completely latent (inactive). The researchers believe that in this latter group of reservoir cells, HIV may need to be awakened by a latency-reversing agent to enable venetoclax to promote cell death.

## Combinations

Preliminary results from several studies of different combination approaches were presented at CROI 2023.

The TITAN trial investigated two bNAbs (3BNC117 and 10-1074) given with or without lefitolimod, an immune-stimulating agonist of Toll-like receptor 9 (TLR9).[42] Participants were screened and were eligible to enroll only if their HIV samples did not show evidence of resistance to the bNAbs. Lefitolimod was administered by weekly subcutaneous injection at weeks 1–8 of the study, while the bNAbs were delivered intravenously at weeks 3 and 6. Participants initiated an analytical ART interruption after three weeks and did not restart until week 26 unless viral load persistently rebounded to over 1,000 copies/mL.

A total of 46 participants were divided into four groups:

- Placebo (dummy) versions of lefitolimod and bNAbs (11 participants)
- Lefitolimod and placebo bNAbs (11 participants)
- bNAbs and placebo lefitolimod (12 participants)
- bNAbs and lefitolimod (12 participants)

Receipt of the bNAb combination was associated with a significant delay in time to HIV viral load rebound, with the first two groups meeting criteria for loss of control after around a month, whereas it took over three months on average in the latter two bNAb groups. Six participants (five of whom received bNAbs) did not meet ART restart criteria during the 24-week ATI. There was no evidence of any additive effect of lefitolimod. The interventions were generally safe and well tolerated, but there was one case of a severe infusion reaction linked to administration of 3BNC117.

Long-acting versions of these bNAbs are being evaluated in several ongoing studies, including the RIO trial in the United Kingdom and RHIVIERA-02 in France.

Researchers led by Beatriz Mothe Pujades at the IrsiCaixa Institute for AIDS Research in Spain described results from a study combining a therapeutic HIV vaccine regimen with the TLR7 agonist vesatolimod.[43] The vaccines are manufactured by AELIX Therapeutics and use viral vectors based on modified vaccinia Ankara strain (MVA) and chimpanzee adenovirus to deliver HIV protein fragments that have been shown to be targeted in rare individuals who display natural immune control of viral load.

Participants had started ART within six months of HIV acquisition and been on treatment for at least a year. A total of 47 enrollees underwent an ATI, 30 after receiving the vaccines plus vesatolimod and 17 in a comparison placebo group. The vaccines induced strong HIV-specific T-cell responses, and fewer participants in the active arm met ART restart criteria during the 24 weeks of the ATI (10 out of 30 versus 4 out of 17). However, ART restart criteria were not as strict as for TITAN, requiring viral load to rise above 10,000 copies/mL for eight weeks or a confirmed measurement of >100,000 copies/mL. Cresting the 100,000 copies/mL threshold accounted for most of the ART restarts (16 in the active arm and 8 in the placebo arm). The researchers found that higher magnitude and breadth of vaccine-induced immune responses were associated with longer time to viral rebound to >50 or >10,000 copies/mL and longer time off ART, suggesting that the vaccines may be able to contribute to beneficial outcomes as part of a combination strategy.

Luis Montaner and colleagues from the Martin Delaney BEAT-HIV Collaboratory shared results from the BEAT-2 trial, which evaluated a combination of the bNAbs 3BNC117 and 10-1074 with the cytokine alpha interferon.[44] Twelve participants received 29 weekly doses of alpha interferon and seven intravenous infusions of the bNAbs that commenced during ART and continued during a 26-week ATI. An additional two participants began the study but discontinued due to chills associated with bNAb administration.

The regimen was able to maintain HIV viral load suppression during the ATI in 10 of 12 participants (80%), and there was some evidence of lingering immune control after all interventions were stopped, with two participants maintaining viral loads below 50 copies/mL for more than 50 weeks. HIV samples were screened before entry to ensure sensitivity to the bNAbs, but the emergence of resistance during the study was common, being observed in 75% of participants. Additional poster presentations at CROI 2023 from the BEAT-2 trial reported evidence of an association between HIV-specific T-cell responses and the extended post-intervention viral load control experienced by several participants,[45] as well as described the experiences of participants, which were mostly positive but included feelings of frustration and disappointment related to the occurrence of viral load rebound.[46]

Another poster presentation at CROI 2023 by Michael Peluso and colleagues from the University of California, San Francisco, disclosed findings from a small 10-person trial administering a complex combination of different therapeutic candidates, including a prime-boost therapeutic HIV vaccine, two bNAbs (10-1074 and VRC07-523LS), and the TLR9 agonist lefitolimod.[47] The trial's kitchen sink approach was colloquially referred to as "JAWS," based on the famous line from the film, "we're going to need a bigger boat."

The report notes that 7 of 10 participants experienced "atypical" HIV rebound dynamics after an ATI, with five displaying set point viral loads below 1,000 copies/mL. In one participant, HIV viral load had not rebounded after 18 months off ART, with very low levels of viral DNA and RNA intermittently detectable in blood and only non-intact virus evident in gut tissue samples. As in the BEAT-2 trial, evidence of the development of HIV resistance to the bNAbs emerged over the course of the study. Work is ongoing to identify factors contributing to the apparent enhancement of post-treatment viral load control.

Two new trials of combination approaches have been registered over the past year, with both currently listed as not yet open for enrollment.

Researchers at the Masonic Cancer Center, University of Minnesota, are conducting a trial of a natural killer cell product, FT538, either alone or in combination with vorinostat, a histone deacetylase (HDAC) inhibitor and candidate HIV latency-reversing agent. Natural killer cells are immune cells that can potentially kill virus-infected targets, such as CD4+ T cells harboring HIV. FT538 is being developed by Fate Therapeutics using an approach that generates natural killer cells in the lab from specially engineered "mother" cells called induced pluripotent stem cells. There are several other ongoing trials in people with cancers. The HIV study will investigate the safety of intravenous dosing of FT538 and look for evidence of a reduction in the low amounts of HIV RNA that can be generated by the active HIV reservoir in people on ART. If FT538 proves safe, vorinostat will be administered to attempt to reactivate latent HIV and make additional HIV-containing cells vulnerable to destruction by the natural killer cells.

The U.S. HIV Military Research Program is sponsoring a study of multiple interventions, including the bNAbs VRC07-523LS and PGDM1400LS, N-803 (a modified version of the cytokine interleukin-15 designed to have enhanced and extended biological activity), and a therapeutic HIV vaccine regimen consisting of two viral vectors and an HIV envelope protein booster. People who started ART during acute HIV infection will be recruited at sites in Bangkok, Thailand, and the primary aim is to assess whether the interventions can delay time to a sustained rebound of HIV viral load to >1,000 copies/mL during an ATI.

In November of last year there was disappointing news about a planned protocol sponsored by the European HIV Vaccine Alliance (EHVA). The EHVA 02 trial intended to assess the combination of a therapeutic vaccine with vedolizumab, an antibody that blocks the $\alpha_4\beta_7$ integrin receptor on immune cells. Delays caused by the COVID-19 pandemic led to a late start, and researchers could not enroll participants quickly enough to administer the interventions before they reached expiration dates, leading to the cessation of the study.[48] An affiliated social science project investigating the perspectives of potential participants did generate information on the reasons why several individuals declined to enroll, with these results presented at the AIDS Impact conference in Stockholm in June 2023.[49]

## Dual-Affinity Re-Targeting (DART) Molecules

DART molecules are antibody-based therapeutic candidates that are bispecific, meaning that they simultaneously bind two targets, typically with the goal of killing a cancerous or pathogen-infected cell. The company Macrogenics is developing DART molecules designed to promote the killing of HIV-infected cells by redirecting T cells to recognize and destroy cellular targets that are displaying the viral envelope protein on their surface (indicating the presence of the virus). The molecules accomplish this task by binding the CD3 receptor, which is expressed on T cells, and a fragment (subunit) of the HIV envelope protein.

Results from a first-in-human study of MGD014 were presented at the 2022 International AIDS Conference by Jeffrey Nordstrom from Macrogenics.[50] MGD014 binds the CD3 receptor and the gp120 subunit of the HIV envelope protein. No dose-limiting toxicities or serious adverse events were documented among 24 recipients, and MGD014 achieved levels considerably above those required for activity.

An ongoing trial led by researchers from the Martin Delaney CARE Collaboratory is now evaluating two Macrogenics DART molecules either alone or in combination: MGD014 and MGD020, the latter of which binds CD3 and the gp41 subunit of the HIV envelope protein.

## Gene Therapies

The two new gene therapy studies added to the table both involve AGT103-T, a candidate developed by American Gene Technologies that focuses on modifying HIV-specific CD4+ T cells to render them resistant to infection by the virus. The process requires extracting CD4+ T cells, isolating and expanding those that specifically recognize HIV, then genetically modifying them to induce resistance and reinfusing them back into the study participant.

A trial has opened that is inviting participants from an initial AGT103-T single-dose safety evaluation to undergo an ATI. The company has noted that the results have been encouraging so far, but no details have yet been published or presented. Data from the safety study were published in the journal *Frontiers in Medicine* in November 2022, documenting no serious side effects and good uptake and persistence of the gene-modified CD4+ T cells.[51] American Gene Technologies has now spun off a new company, Addimmune, which will be responsible for initiating a phase II trial with 50–100 participants designed to optimize AGT103-T for an even larger efficacy study.[52]

As is typically required by the U.S. Food and Drug Administration (FDA) for new gene therapies, a second long-term follow-up study has begun for all recipients of AGT103-T. Participants will be monitored until 2038 to ensure there are no unexpected safety issues.

## Janus Kinase Inhibitors

Researchers from Emory University are recruiting for a study of the drug baricitinib, which belongs to a class called Janus kinase inhibitors and is FDA approved for the treatment of rheumatoid arthritis. Preparatory laboratory experiments in humanized mice demonstrated that baricitinib crossed the blood-brain barrier and reduced the persistence of HIV in the central nervous system.[53] The trial aims to investigate if similar effects can be obtained in people with HIV, using blood samples, neurocognitive testing, magnetic resonance imaging (MRIs), and lumbar punctures.

## Immunomodulators

A trial sponsored by First Affiliated Hospital of Zhejiang University in China is testing the effects of two immunomodulatory compounds, lenalidomide and adenosylmethionine, on the HIV reservoir. Lenalidomide (trade name Revlimid) is a derivative of thalidomide approved for the treatment of multiple myeloma. Adenosylmethionine is available as supplement in some countries but is sold as a prescription drug in China. The study is not yet listed as open for enrollment.

## Latency-Reversing Agents

Scientists in Spain have begun recruiting participants for a clinical assessment of the effects of lauric acid on the HIV reservoir. Lauric acid is a dietary fatty acid found in coconut milk, coconut oil, laurel oil, and palm kernel oil. In preclinical laboratory studies presented at a conference in Málaga in 2021, the researchers involved in the trial reported that lauric acid can reverse HIV latency without having any negative effects on CD8+ T cells[54] (a problem that has been reported with other candidate latency-reversing agents[55]).

## T-Cell Receptor–Based Bispecifics

T-cell receptor–based bispecifics represent an immune-based approach intended to promote the killing of HIV-infected cells by T cells that would normally recognize antigens other than HIV. In essence, the idea is to recruit T cells that would usually be doing other work to fight HIV, similar to the idea behind DART molecules (see above).

The intervention consists of bispecific soluble proteins made up of an enhanced T-cell receptor designed to recognize HIV components and a fusion protein that engages the CD3 molecule expressed on T cells. The research is being sponsored by a British company, Immunocore.

Results from a small phase I safety study were presented as a poster at CROI 2023.[56] Enrollment was limited to people possessing a specific immune response genotype, HLA-A*02:01. Twelve people with HIV were enrolled and sequentially received a single dose at one of three ascending dose levels. The researchers report that administration was safe and provide evidence of biological activity based on a transient increase in levels of the cytokine interleukin-6 after receipt of the highest dose. A larger trial investigating multiple ascending doses is now underway.

## Therapeutic Vaccines

The past year has seen three new therapeutic HIV vaccine trials added to TAG's cure-related research table.

Gilead Sciences has a checkered record when it comes to registering phase I trials in the ClinicalTrials.gov database, and the only evidence that they have launched a phase Ib study of a therapeutic HIV vaccine regimen comes from the website of the Midway Research Center in Florida. The vaccines under investigation are codenamed GS-1966 and GS-1144, likely reflecting candidates based on a self-amplifying mRNA and adenoviral vector prime-boost platform being developed collaboratively with Gritstone Oncology, Inc. (the collaboration was announced in 2021[57]).

Researchers affiliated with the Martin Delaney CARE Collaboratory at the University of North Carolina at Chapel Hill are testing whether therapeutic HIV vaccines based on viral vectors (MVA and chimpanzee adenovirus) can induce virus-specific T-cell responses against highly conserved viral components and potentially reduce residual low-level viral load that is present in some people on ART.

Lastly, investigators at the University of Sao Paulo General Hospital in Brazil are planning a study of a vaccine based on delivery of HIV antigens by dendritic cells (immune system cells responsible for triggering the development of immune responses). The approach has already been evaluated in a prior study in combination with multiple other interventions,[58] and the rationale for the new trial is to focus more specifically on the activity of the vaccine in the context of an ATI.

## Tyrosine Kinase Inhibitors

Dasatinib belongs to a class of drugs called tyrosine kinase inhibitors and is approved for certain types of cancer. Two trials are planned in Spain, based on previously published evidence that dasatinib therapy for cancer in people with HIV is associated with a smaller HIV reservoir and a reduced ability to reactivate viable HIV from latently infected cells.[59,60] One of the studies will enroll people who acquired HIV in the past 3–12 months and administer dasatinib for four weeks before the addition of ART. The other is targeted to people already on ART with suppressed HIV viral load.

## Table 4. Immune-Based Therapy Pipeline 2023

| Agent | Class/Type | Trial Registry Identifier(s) | Manufacturer/Sponsor(s) | Status |
|---|---|---|---|---|
| Fostemsavir | Attachment inhibitor | NCT05220358 | Orlando Immunology Center | Phase IV |
| Letermovir (Prevymis) | Anti-cytomegalovirus drug | NCT04840199 | NIAID | Phase II |
| Mismatched allogeneic adoptive immune therapy (AAIT) | Allogeneic adoptive immunotherapy | NCT04098770 | Beijing 302 Hospital | Phase II |
| Pyridostigmine | Acetylcholinesterase inhibitor | NCT03312244 (suspended due to COVID-19: effective March 19, 2020, recruitment halted until further notice) | Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán | Phase II |
| Allogeneic adoptive immune therapy | Granulocyte colony-stimulating factor–mobilized donor peripheral blood mononuclear cells | NCT02648516 | Beijing 302 Hospital | Phase I/II |
| 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 |

Just one new trial has been registered for people with suboptimal CD4+ T-cell recovery despite HIV suppression by ART. Sponsored by a Chinese company, Shandong Qilu Cell Therapy Engineering Technology, the protocol will assess the ability of human umbilical cord mesenchymal stem cells to enhance immune reconstitution in an estimated 20 participants. Prior research in China has suggested that mesenchymal stem cells may have promise, but the results have not been definitive.[61,62]

Recent evidence suggests that this type of study can sometimes be difficult to enroll — a planned investigation of the cancer drug brentuximab vedotin that was included in last year's table has been terminated because of difficulty recruiting participants.

As noted in 2022, the candidate therapy that currently appears to have the greatest potential to receive an indication for the treatment of people with suboptimal CD4 recovery is the drug fostemsavir (trade name Rukobia), an FDA-approved antiretroviral that inhibits HIV attachment to the CD4 receptor. An ongoing study led by the Orlando Immunology Center is attempting to verify evidence from previous research that fostemsavir may promote CD4+ T cell recovery to an extent beyond what would be expected based on anti-HIV activity alone.[63]

A potential new candidate is a revised version of SB-728-T, a gene therapy originally created by Sangamo Therapeutics. Researchers led by Rafick-Pierre Sekaly at the Case Western Reserve University have entered into a collaboration with the biotechnology company RORA Biologics to develop an approach that focuses gene modification on a specific type of immune system cell, T-cell memory stem cells.[64] The hope is to eventually assess the potential to promote CD4+ T-cell reconstitution in people on ART.

## Conclusion

Scientific advances in understanding the nature of the reservoir of HIV that persists in people on ART are placing the cure research field on firmer ground when it comes to informing the development of candidate therapies and monitoring their activity. Progress in this area underscores the importance of supporting basic science in parallel with efforts to move approaches into clinical trials.

Additional HIV cure cases from stem cell transplantation for cancers continue to offer reasons for hope, but there remains a lack of major breakthroughs that might deliver a widely applicable curative intervention. The development of antiretrovirals was revolutionized when triple-combination ART was shown to suppress viral load to undetectable levels, and cure researchers are striving toward a similar milestone — for example, a study in which a substantial proportion of participants show extended post-treatment control of HIV replication. For the time being, only isolated cases have been identified in a few trials.

Improvements on the funding front have been documented in the most recent analysis from the International AIDS Society Towards an HIV Cure Initiative, AVAC, and the Resource Tracking for HIV Prevention Research and Development Working Group.[65] According to the report, financial support increased by 30.3% in 2021 compared with 2020, rising from US$337.4 million to US$439.8 million. As in past years, the U.S. contributed the majority of public funding through the NIH. Prospects for further increases appear uncertain, with President Biden's 2024 budget request for the NIH containing a dispiriting decrease for HIV cure research of US$0.8 million, or −0.4 percent compared with the FY 2023–enacted level of around US$234.5 million.[66]

The prospects for immune-based therapies that might enhance the restorative effects of ART on CD4+ T cells and immune function appear persistently dim, but there are flickers of light in the form of research into fostemsavir and the apparent interest of RORA Biologics in exploring the potential of their gene therapy candidate. Activists are hoping that a recently announced FDA Rare Disease Endpoint Advancement Pilot Program may offer an opportunity to encourage more engagement of industry in pursuing therapies for people with suboptimal CD4 recovery on ART.

## Endnotes


1. Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med. 2009 Feb 12;360(7):692–8.

2. Allers K, Hütter G, Hofmann J, et al. Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation. Blood. 2011 Mar 10;117(10):2791–9.

3. Roberts S. Timothy Ray Brown, first patient cured of H.I.V., dies at 54. New York Times. 2020 September 30.

4. Gupta RK, Abdul-Jawad S, McCoy LE, et al. HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. Nature. 2019 Apr;568(7751):244–8.

5. Gupta RK, Peppa D, Hill AL, et al. Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report. Lancet HIV. 2020 May;7(5):e340–7.

6. Jensen BO, Knops E, Lübke N, et al. Analytic treatment interruption (ATI) after allogeneic CCR5-D32 HSCT for AML in 2013 (Abstract 394). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2019); 2019 March 4–7; Seattle, WA.

7. Jensen BO, Knops E, Cords L, et al. In-depth virological and immunological characterization of HIV-1 cure after CCR5Δ32/Δ32 allogeneic hematopoietic stem cell transplantation. Nat Med. 2023 Mar;29(3):583–7.

8. Highleyman L. Coming out as cured. POZ Magazine. 2023 May 17.

9. Hsu J, Glesby M, Shore TB, et al. CCR5 delta32 cord & haploidentical grafts: allogeneic stem cell transplant for HIV+ /AML patient: a case report from the Impaact P1107 observational study. Blood. 2018;132 (Supplement 1):2184.

10. Hsu J, Van Besien K, Glesby MJ, et al. HIV-1 Remission with CCR5Δ32Δ32 haplo-cord transplant in a US woman: IMPAACT P1107 (Abstract 65). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2022); 2022 February 12–16; Virtual.

11. Hsu J, Van Besien K, Glesby MJ, et al. HIV-1 remission and possible cure in a woman after haplo-cord blood transplant. Cell. 2023 Mar 16;186(6):1115-1126.e8.

12. Dickter J, Weibel S, Cardoso A, et al. The "City of Hope Patient": Prolonged HIV-1 remission without antiretrovirals (ART) after allogeneic hematopoietic stem cell transplantation (alloHCT) of CCR5-Δ32/Δ32 donor cells for acute myelogenous leukemia (AML) (Abstract OALBB0104). Paper presented at: AIDS 2022; 2022 July 29–August 2; Montreal, Canada, and Virtual.

13. Salzman S, Zepeda R. Paul Edmonds, 5th person apparently cured of HIV, steps forward to share his story. ABC News. 2023 April 13.

14. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. Nat Med. 1999 May;5(5):512–7. doi: 10.1038/8394.

15. Crooks AM, Bateson R, Cope AB, et al. Precise quantitation of the latent HIV-1 reservoir: implications for eradication strategies. J Infect Dis. 2015 Nov 1;212(9):1361–5.

16. Gandhi RT, Bosch RJ, Mar H, et al. Varied patterns of decay of intact human immunodeficiency virus type 1 proviruses over 2 decades of antiretroviral therapy. J Infect Dis. 2023 Jun 15;227(12):1376–80.

17. McMyn NF, Varriale J, Lai J, et al. Persistence of inducible replication-competent HIV-1 after long-term ART (Abstract 396). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

18. Lian X, Seiger KW, Parsons EM, et al. Progressive transformation of the HIV-1 reservoir cell profile over two decades of antiviral therapy. Cell Host Microbe. 2023 Jan 11;31(1):83-96.e5.

19. Gandhi RT, Cyktor JC, Bosch RJ, et al. Selective decay of intact HIV-1 proviral DNA on antiretroviral therapy. J Infect Dis. 2021 Feb 3;223(2):225–33.

20. Levy CN, Hughes SM, Roychoudhury P, et al. A highly multiplexed droplet digital PCR assay to measure the intact HIV-1 proviral reservoir. Cell Rep Med. 2021 Apr 12;2(4):100243.

21. Falcinelli SD, Kilpatrick KW, Read J, et al. Longitudinal dynamics of intact HIV proviral DNA and outgrowth virus frequencies in a cohort of individuals receiving antiretroviral therapy. J Infect Dis. 2021 Jul 2;224(1):92–100.

22. Serrano-Villar S, Gala A, Bacchetti P, et al. Circulating immune predictors of intact HIV reservoir decay during long-term ART (Abstract 405). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

23. Chomont N, El-Far M, Ancuta P, et al. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. Nat Med. 2009 Aug;15(8):893-900.

24. Gantner P, Pagliuzza A, Pardons M, et al. Single-cell TCR sequencing reveals phenotypically diverse clonally expanded cells harboring inducible HIV proviruses during ART. Nat Commun. 2020 Aug 14;11(1):4089.

25. Bone BR, Cotugno N, Gao C, et al. HIV-1 reservoirs in young adults after long-term art for congenital infection (Abstract 450). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

26. Roseto IC, Lian X, Seiger K, et al. Distinct integration sites of intact HIV-1 proviruses in post-treatment controllers (Abstract 453). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

27. SenGupta D, Brinson C, DeJesus E, et al. The TLR7 agonist vesatolimod induced a modest delay in viral rebound in HIV controllers after cessation of antiretroviral therapy. Sci Transl Med. 2021 Jun 23;13(599):eabg3071.

28. Liu B, Zhang W, Xia B, et al. Broadly neutralizing antibody-derived CAR T cells reduce viral reservoir in individuals infected with HIV-1. J Clin Invest. 2021 Oct 1;131(19):e150211.

29. Gaebler C, Nogueira L, Stoffel E, et al. Prolonged viral suppression with anti-HIV-1 antibody therapy. Nature. 2022 Jun;606(7913):368–74.

30. Bertagnolli LN, Varriale J, Sweet S, et al. Autologous IgG antibodies block outgrowth of a substantial but variable fraction of viruses in the latent reservoir for HIV-1. Proc Natl Acad Sci USA. 2020 Dec 15;117(50):32066–77.

31. Esmaeilzadeh E, Etemad B, Lavine CL, et al. Autologous neutralizing antibodies increase with early antiretroviral therapy and shape HIV rebound after treatment interruption. Sci Transl Med. 2023 May 10;15(695):eabq4490.

32. 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.

33. Wu HL, Busman-Sahay K, Weber WC, et al. Allogeneic immunity clears latent virus following allogeneic stem cell transplantation in SIV-infected ART-suppressed macaques. Immunity. 2023 May 13. doi: 10.1016/j.immuni.2023.04.019. [Epub ahead of print]

34. Harif M, Weisdorf D, Novitzky N, et al. Special report: Summary of the first meeting of African Blood and Marrow Transplantation (AfBMT) group, Casablanca, Morocco, April 19-21, 2018 held under the auspices of the Worldwide Network for Blood and Marrow Transplantation (WBMT). Hematol Oncol Stem Cell Ther. 2020 Dec;13(4):202–7.

35. Niederwieser D, Baldomero H, Bazuaye N, et al. One and a half million hematopoietic stem cell transplants: continuous and differential improvement in worldwide access with the use of non-identical family donors. Haematologica. 2022 May 1;107(5):1045–53.

36. Chaillon A, Ignacio C, Schanz M, et al. Predictors of HIV rebound after interruption of ART started during primary infection (Abstract 387). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

37. Sáez-Cirión A, Bacchus C, Hocqueloux L, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog. 2013 Mar;9(3):e1003211.

38. Sáez-Cirión A. HIV remission/cure: Just a matter of time?. Paper presented at: 11th IAS Conference on HIV Science (IAS 2021); 2021 July 18–21; Virtual.

39. Ren Y, Huang SH, Patel S, et al. BCL-2 antagonism sensitizes cytotoxic T cell-resistant HIV reservoirs to elimination ex vivo. J Clin Invest. 2020 May 1;130(5):2542–59.

40. Cummins NW, Sainski AM, Dai H, et al. Prime, shock, and kill: priming CD4 T cells from HIV patients with a BCL-2 antagonist before HIV reactivation reduces HIV reservoir size. J Virol. 2016 Mar 28;90(8):4032–48.

41. Chandrasekar AP, Cummins NW, Natesampillai S, et al. The BCL-2 inhibitor venetoclax augments immune effector function mediated by Fas ligand, TRAIL, and perforin/granzyme B, resulting in reduced plasma viremia and decreased HIV Reservoir size during acute HIV infection in a humanized mouse model. J Virol. 2022 Dec 21;96(24):e0173022.

42. Gunst JD, Reikvam DH, McMahon JH, et al. The impact of 3BNC117, 10-1074, and lefitolimod on HIV-1 persistence: the TITAN trial (Abstract 136). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

43. Mothe Pujades B, Curran A, López JC, et al. A placebo-controlled randomized trial of the HTI immunogen vaccine and vesatolimod (Abstract 433). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

44. Tebas P, Azzoni L, Papasavvas E, et al. BEAT2 primary trial outcomes: PEG-IFN-α2b +3BNC117 & 10-1074 in chronic HIV infection (Abstract 431). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

45. Pampena MB, Tebas P, Azzoni L, et al. Evaluation of HIV-specific T cell response in BEAT2 clinical trial (Abstract 319). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

46. Plenn E, Barg FK, Rendle K, et al. Participant experiences in a cure-directed long-term analytic treatment interruption (Abstract 384). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

47. Peluso MJ, Deitchman A, Magombedze G, et al. Rebound dynamics following immunotherapy with an HIV vaccine, TLR9 agonist, and bNAbs (Abstract 435). Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI 2023); 2023 February 19–22; Seattle, WA.

48. EHVA (Press Release). EHVA halts phase II EHVA-T02 clinical trial of a candidate therapeutic HIV vaccine and immunotherapy drug. 2022 November 22.

49. Lefebvre S , Lelievre JD, Rieux V, et al. Refusing to join a HIV cure clinical trial so as not to "break the carefree mindset about the disease". Insights from a French qualitative study. AIDS Impact 2023; 2023 June 12–14; Stockholm, Sweden.

50. Nordstrom JL, Gay CL, Bohac C, et al. In vivo preclinical efficacy of MGD014 and MGD020 (HIV-1 envelope x CD3 DART molecules) and first-in-human phase 1 clinical safety evaluation of MGD014 (Abstract OAA0403). Paper presented at: AIDS 2022; 2022 July 29–August 2; Montreal, Canada, and Virtual.

51. Muvarak N, Li H, Lahusen T, Galvin JA, et al. Safety and durability of AGT103-T autologous T cell therapy for HIV infection in a Phase 1 trial. Front Med (Lausanne). 2022 Nov 14;9:1044713.

52. American Gene Technologies (Press Release). American Gene Technologies® launches new spinoff company "Addimmune™" to focus exclusively on development of HIV cure. 2023 June 9.

53. 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.

54. Grau Expósito J, Rull A, Howard JN, et al. Lauric acid, a natural saturated fatty acid, induces the metabolic reprograming of T cells and reactivates latent HIV, whereas preserves CD8 t cell responses (Abstract CO-16). Paper presented at: XII Congreso Nacional GeSIDA y XIV Reunión Docente de la Red de Investigación de Sida (RIS); 2021 November 29–December 2; Málaga, Spain.

55. Clutton GT, Jones RB. Diverse impacts of HIV latency-reversing agents on CD8+ T-cell function: implications for HIV cure. Front Immunol. 2018 Jun 22;9:1452.

56. 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.

57. Gilead Sciences (Press Release). Gilead Sciences and Gritstone announce collaboration utilizing Gritstone's vaccine platform technology for HIV cure. 2021 February 1.

58. 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.

59. Vigón L, Martínez-Román P, Rodríguez-Mora S, et al. Provirus reactivation is impaired in HIV-1 infected individuals on treatment with dasatinib and antiretroviral therapy. Biochem Pharmacol. 2021 Oct;192:114666.

60. Rodríguez-Agustín A, Casanova V, Grau-Expósito J, Sánchez-Palomino S, Alcamí J, Climent N. Immunomodulatory activity of the tyrosine kinase inhibitor dasatinib to elicit NK cytotoxicity against cancer, HIV infection and aging. Pharmaceutics. 2023 Mar 11;15(3):917.

61. Zhang Z, Fu J, Xu X, et al. Safety and immunological responses to human mesenchymal stem cell therapy in difficult-to-treat HIV-1-infected patients. AIDS. 2013 May 15;27(8):1283-93.

62. Wang L, Zhang Z, Xu R, et al. Human umbilical cord mesenchymal stem cell transfusion in immune non-responders with AIDS: a multicenter randomized controlled trial. Signal Transduct Target Ther. 2021 Jun 9;6(1):217.

63. Lataillade M, Lalezari JP, Kozal M, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. Lancet HIV. 2020 Nov;7(11):e740–51.

64. Case Western Reserve University (Press Release). Case Western Reserve University completes exclusive license agreement with Atlanta-based RORA Biologics Inc. for cancer and HIV therapy technologies. 2023 February 23.

65. 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.

66. Congressional Justification of the NIH request for the fiscal year (FY) 2024 budget. 2023 March.