Research Toward a Cure and Immune-Based Therapies

By Richard Jefferys

INTRODUCTION

The research effort to cure HIV infection has continued to expand over the past year. The National Institute of Allergy and Infectious Diseases (NIAID) at the U.S. National Institutes of Health (NIH) announced the funding of six new Martin Delaney Collaboratorys (up from three funded previously), which are collaborative research enterprises focused on discovering an HIV cure named after the renowned activist and founder of Project Inform.[1] The grants run for five years, with each awardee tackling the challenge from slightly different angles. The recipients are:

- BEAT-HIV: Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy - Wistar Institute, Philadelphia
- BELIEVE: Bench to Bed Enhanced Lymphoctye Infusions to Engineer Viral Eradication - George Washington University, Washington, D.C.
- Collaboratory of AIDS Researchers for Eradication (CARE) - University of North Carolina, Chapel Hill
- Combined Immunologic Approaches to Cure HIV-1 - Beth Israel Deaconess Medical Center, Boston
- defeatHIV: Cell and Gene Therapy for HIV Cure - Fred Hutchinson Cancer Research Center, Seattle
- Delaney AIDS Research Enterprise to Cure HIV - University of California, San Francisco (UCSF)

Details on each Collaboratory were presented by the lead investigators at the 2016 NIAID Strategies for an HIV Cure Workshop, and these presentations are available online as part of the archived meeting videocast.[2]

The most recent data on global financing of HIV cure research—collected by the International AIDS Society Towards an HIV Cure Initiative, AVAC, and the HIV Vaccines & Microbicides Resource Tracking Working Group—demonstrates progressive growth.[3] Total support in 2015 was $201.8 million, up from $160.8 million in 2014. The NIH remains by far the largest contributor, accounting for more than three quarters of the total. According to a presentation by Paul Sato from the Office of AIDS Research (OAR) at an advisory council meeting last fall, research specifically identified as pertaining to an HIV cure now represents 6% of the total NIH HIV/AIDS research budget.[4] Sato noted that this percentage does not include all of the substantial support for HIV basic science research, which generates many critical clues relevant to the pursuit of a cure. The proportion of NIH HIV/AIDS funding dedicated to cure research is certain to increase as grants expire in areas that are now considered to be low priority.[5]

Scientific progress has been significant, but incremental. There remains only one individual considered to be cured of HIV infection, Timothy Ray Brown, who in early 2017 celebrated ten years since his receipt of the stem cell transplants that led to his being cured of both a serious cancer (acute myelogenous leukemia) and HIV.[6] Attempts to duplicate the outcome in other HIV-positive individuals requiring stem cell transplants for cancers are ongoing, but no similar successes have yet been reported.[7] There have, however, been two additional reports of individuals experiencing a transient state of no detectable HIV activity in the absence of antiretroviral therapy (ART).

In one case presented by Nathan Cummins from the Mayo Clinic in Rochester, the HIV reservoir was greatly diminished as a result of cancer therapy, including a stem cell transplant, and there was a period of 288 days after ART was discontinued before HIV viral load reappeared and treatment was reinitiated.[8]

The second case involved an individual in whom HIV infection was detected extraordinarily early, as it occurred during a short window between screening for a pre-exposure prophylaxis (PrEP) program and starting the first dose of PrEP. The individual was switched from PrEP to ART in a matter of days (when the baseline HIV test results became available), and HIV rapidly became undetectable by multiple measures, including assessments of virus reservoirs. A careful interruption of ART was later undertaken and no HIV was subsequently detectable for 220 days, at which point a rebound in viral load occurred and ART was restarted. This latter case, initially described by Hiroyu Hatano from UCSF prior to the ART interruption,[9] has not yet been formally presented, but was briefly cited by Jintanat Ananworanich in a cure research plenary delivered at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI).[10]

These two individuals join the Mississippi baby[11] and two Boston patients[12] as examples of prolonged HIV remission. The number of cases is small, but they offer important evidence that dramatically reducing or limiting the size of the HIV reservoir can lead to a significant delay in the reemergence of the virus. A key challenge for the cure research field is to shrink the HIV reservoir to the point where viral load rebound is delayed for life in most individuals—mathematical modeling indicates this will likely require reductions of greater than 10,000-fold (>99.99%).[13] Although the number of clinical trials of interventions that may have reservoir-reducing potential continues to increase (see Table 1), the largest declines in HIV reservoir measures that have been reported thus far are on the order of 40%,[14] emphasizing the fact that the research is still at an early stage. Alternative strategies that don't necessarily rely on reservoir depletion—such as those that attempt to induce immune control of HIV and/or protect vulnerable cells with gene therapy—continue to be evaluated, with some recent hints of progress (see below for combination approaches).

Significant advances have occurred in understanding how HIV persists despite ART. Controversy has long surrounded the question of whether ART completely suppresses HIV replication in most recipients, but data has emerged over the past year that strongly favors the conclusion that it does.[15,16] These studies found no evidence of HIV evolving during ART in adherent individuals, indicating that ongoing HIV replication is not a major mechanism of viral persistence. The results are likely to lessen interest in intensifying ART with additional antiretrovirals in cure research trials.

Focus is instead shifting to the role of proliferation of CD4 T cells containing latent HIV in maintaining viral reservoirs in the face of treatment; a growing body of evidence suggests that this phenomenon may be of central importance.[17] Proliferation is part of the normal life and times of CD4 T cells, and can be driven by nonspecific signaling from immune system proteins (such as cytokines and chemokines) or by a specific response to an antigen recognized by the CD4 T cell (such as an influenza protein). Recent studies have demonstrated that CD4 T cells latently infected by HIV generate daughter cells containing a copy of the same virus when they proliferate, thereby expanding the number of cells harboring latent HIV.[18] Although many HIV copies are defective,[19] it is now well documented that proliferation of latently infected CD4 T cells can also increase the number of replication-competent viruses.[20,21,22] These findings have spurred interest in studying the potential of anti-proliferative interventions to reduce or limit the HIV reservoir—an example of how basic science research can generate leads to translate into therapeutic trials.

Another potential breakthrough that has recently emerged from the realm of basic science is the identification of a cell surface marker, CD32a, which is expressed by a significant proportion of CD4 T cells that contain latent HIV.[23] This finding, if confirmed, should make it far easier to isolate latently infected CD4 T cells from individuals on ART so that they can be studied in the laboratory. In addition, the marker may offer a means of targeting the latent reservoir for elimination more specifically.

Scientists are also beginning to investigate population-specific differences in HIV persistence that may be relevant to the development of a cure. A project supported by amfAR recently debuted results showing

that the HIV reservoir may generate less viral genetic material in women than in men,[24] perhaps as a consequence of interactions between estrogen and estrogen receptors on CD4 T cells.[25] The first study comparing HIV reservoir measures in an African versus North American setting was published in May 2017;[26] the researchers found that the levels of replication-competent HIV were about threefold lower in a cohort of individuals on ART in the Rakai District Uganda compared with counterparts in Baltimore, USA. One possibility is that environmentally driven immune activation in the African setting[27] shortens the lifespan of CD4 T cells that might otherwise harbor latent HIV long-term, but further investigations are required to understand the reason for the results.

Interest in developing therapies for use in conjunction with ART has waned considerably in recent years. This is largely the result of the impressive efficacy and tolerability of modern ART regimens, which are associated with life expectancies for many HIV-positive people that are increasingly comparable to similar HIV-negative individuals.[28] Concerns persist, however, regarding populations whose residual risk of HIV-associated morbidity and mortality remains elevated despite ART.[29] These include people with a history of injection drug use and those who experience poor immune reconstitution despite HIV suppression (dubbed immunologic non-responders, INRs[30]), a problem that is associated with late initiation of ART and older age.[31] Inflammation and immune senescence (age-related dysfunction of immune cells) can also persist despite ART and may be linked to earlier onset of age-related morbidities such as frailty, neurocognitive impairment, and cardiovascular disease.[32]

The pipeline of approaches that may address these concerns and further reduce risk of morbidity and mortality when added to ART is not completely dry, but is currently comprised of intermittent drips. Academic investigators primarily drive the research in this area, with little contribution from pharmaceutical companies (likely as a result of uncertainty about the potential market). Efforts are ongoing to pry open the spigot and promote a more robust flow of candidates for populations who might stand to benefit.

Table 1. Research Toward a Cure 2017: Current Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
ADOPTIVE IMMUNOTHERAPY				
Reconstitution of HIV-specific immunity against HIV	T cell therapy	NCT02563509	Guangzhou 8th People's Hospital	Phase I/II
HXTC: HIV 1 antigen expanded specific T cell therapy	HIV 1 antigen expanded specific T cell therapy	NCT02208167	University of North Carolina, Chapel Hill	Phase I
ANTIBODIES				
Vedolizumab	Anti-$\alpha_4\beta_7$ integrin antibody	NCT03147859	Ottawa Hospital Research Institute	Phase II
VRC01	Broadly neutralizing monoclonal antibody	NCT02664415 (closed to enrollment)	National Institute of Allergy and Infectious Diseases (NIAID)	Phase II
3BNC117	Broadly neutralizing monoclonal antibody	NCT02446847 (closed to enrollment)	Rockefeller University	Phase I/II
3BNC117	Broadly neutralizing monoclonal antibody	NCT02588586 (closed to enrollment)	Rockefeller University	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
10-1074	Broadly neutralizing monoclonal antibody	NCT02511990 (closed to enrollment)	Rockefeller University	Phase I
3BNC117 + 10-1074	Broadly neutralizing monoclonal antibodies	NCT02825797	Rockefeller University	Phase I
PGT121	Broadly neutralizing monoclonal antibody	NCT02960581 (enrolling by invitation only)	International AIDS Vaccine Initiative	Phase I
Vedolizumab	Anti-$\alpha_4\beta_7$ integrin antibody	NCT02788175	NIAID	Phase I
VRC01LS	Long-acting broadly neutralizing monoclonal antibody	NCT02840474	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody in acute HIV infection	NCT02591420	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody	NCT02471326 (closed to enrollment)	NIAID	Phase I
ANTI-FIBROTIC				
Losartan	Angiotensin receptor blocker	NCT01852942	University of Minnesota	Phase II
Telmisartan	Angiotensin receptor blocker	NCT02170246	Yale University	Phase I
ANTI-INFLAMMATORY				
Canakinumab	IL-1β inhibitor	NCT02272946	University of California, San Francisco	Phase II
Metformin	Antidiabetic	NCT02659306	McGill University Health Center	Phase I
ANTIRETROVIRAL THERAPY				
Dolutegravir in reservoirs		NCT02924389	Emory University	Phase N/A
HIV reservoir dynamics after switching to dolutegravir in patients on a PI/r based regimen	Switching from ritonavir-boosted protease inhibitor to dolutegravir	NCT02513147	Hospital Universitari Vall d'Hebron Research Institute	Phase IV
ABX464	Inhibitor of HIV RNA export	NCT02735863	Abivax S.A.	Phase II
ABX464	Inhibitor of HIV RNA export	NCT02990325	Abivax S.A.	Phase I/II
ANTIRETROVIRAL THERAPY IN HIV CONTROLLERS				
Emtricitabine + rilpivirine + tenofovir		NCT01777997 (closed to enrollment)	AIDS Clinical Trials Group/NIAID	Phase IV
COMBINATIONS				
Maraviroc, dolutegravir, dendritic cell vaccine, auranofin, nicotinamide		NCT02961829 (closed to enrollment)	Federal University of São Paulo	Not listed
Perturbing of HIV reservoir with immune stimulation: Fluarix, Pneumovax vaccines		NCT02707692	University of California, San Diego	Not listed

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
Impact of Sirolimus and maraviroc on CCR5 expression and the HIV-1 reservoir in HIV+ kidney transplant recipients		NCT02990312	University of Maryland	Phase IV
ROADMAP: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody	NCT02850016	Rockefeller University	Phase IIa
eCLEAR: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody	NCT03041012	Aarhus University Hospital	Phase II
Panobinostat + pegylated interferon-alpha2a	HDAC inhibitor + cytokine	NCT02471430	Massachusetts General Hospital	Phase II
Research In Viral Eradication of HIV Reservoirs (RIVER): ART, ChAdV63. HIVconsv and MVA. HIVconsv vaccines, vorinostat	Therapeutic vaccines + HDAC inhibitor	NCT02336074 UK CPMS18010 (closed to enrollment)	Imperial College London	Phase II
SB-728mR-T + cyclophosphamide	Autologous CD4 T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02225665 (closed to enrollment)	Sangamo BioSciences	Phase I/II
SB-728-T + cyclophosphamide	Autologous CD4 T cells gene-modified via adenovirus vector to inhibit CCR5 expression + transient chemotherapy	NCT01543152 (closed to enrollment)	Sangamo BioSciences	Phase I/II
AGS-004 + vorinostat	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens + HDAC inhibitor	NCT02707900	NIAID	Phase I
DCV3 + pegylated interferon	Dendritic-cell-based vaccine pulsed with autologous heat-inactivated HIV + cytokine	NCT02767193 (not yet open for enrollment)	Judit Pich Martínez, Fundació Clínic per la Recerca Biomèdica	Phase I
MVA.HIVconsv + romidepsin	Therapeutic vaccine + HDAC inhibitor	NCT02616874 (closed to enrollment)	IrsiCaixa	Phase I
SB-728mR-T + cyclophosphamide	Autologous CD4 T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02388594	University of Pennsylvania	Phase I
CD4-ZETA ± interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	Phase I
GENE THERAPIES				
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)	ACTRN12615000763549	Calimmune	Phase I/II
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)	NCT01734850 (closed to enrollment) NCT02390297 (long term safety phase)	Calimmune	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
VRX496	Autologous CD4 T cells modified with an antisense gene targeting the HIV envelope	NCT00295477 (closed to enrollment)	University of Pennsylvania	Phase I/II
SB-728mR-HSPC	Autologous hematopoietic stem/progenitor cells gene-modified to inhibit CCR5 expression	NCT02500849	City of Hope Medical Center	Phase I
MazF-T	Autologous CD4 T cells gene-modified with MazF endoribonuclease gene to inhibit HIV	NCT01787994 (closed to enrollment)	Takara Bio/University of Pennsylvania	Phase I
C34-CXCR4	Autologous CD4 T cells gene-modified to express HIV-inhibiting peptide C34	NCT03020524	University of Pennsylvania	Phase 0
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS				
Gene therapy in treating patients with human-immunodeficiency-virus-related lymphoma receiving stem cell transplant	Stem cells gene-modified with CCR5 shRNA/ TRIM5alpha/TAR decoy	NCT02797470	AIDS Malignancy Consortium	Phase I/II
HIV-resistant gene-modified stem cells and chemotherapy in treating patients with lymphoma and HIV infection	Stem cells gene-modified to abrogate CCR5 expression and encode an HIV entry inhibitor C46	NCT02343666	Fred Hutchinson Cancer Research Center	Phase I
Gene-modified HIV-protected stem cell transplant in treating patients with HIV-associated lymphoma	Stem cells gene-modified to abrogate CCR5 expression and encode an HIV entry inhibitor C46	NCT02378922 (suspended)	Fred Hutchinson Cancer Research Center	Phase I
Safety of transplantation of CRISPR CCR5 modified CD34+ cells in HIV-infected subjects with hematological malignances	Stem cells gene-modified to abrogate CCR5 expression using CRISPR technology	NCT03164135	307 Hospital of PLA (Affiliated Hospital of Academy to Military Medical Sciences)	Not listed
Gene therapy and combination chemotherapy in treating patients with AIDS-related non-Hodgkin lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ)	NCT02337985	City of Hope Medical Center	Not listed
Busulfan and gene therapy after frontline chemotherapy in patients with AIDS-related non-Hodgkin lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ) + cyclophosphamide conditioning	NCT01961063	City of Hope Medical Center	Not listed

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
Gene-therapy-treated stem cells in patients undergoing stem cell transplant for intermediate-grade or high-grade AIDS-related lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ)	NCT00569985 (closed to enrollment)	City of Hope Medical Center	Not listed
HORMONES				
Somatotropin	Human growth hormone	NCT03091374	McGill University Health Center	Phase II
IMAGING STUDIES				
Radiolabeled broadly neutralizing anti-HIV antibody 3BNC117 + Copper-64 radio isotope followed by MRI/PET scanning to detect HIV in vivo		NCT03063788	Bayside Health	Phase I
IMMUNE CHECKPOINT INHIBITORS				
Durvalumab in solid tumors	Anti-PD-L1 antibody	NCT03094286	Spanish Lung Cancer Group	Phase II
Pembrolizumab	Anti-PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms	NCT02595866	National Cancer Institute (NCI)	Phase I
Nivolumab + ipilimumab	Anti-PD-1 antibody + anti-CTLA-4 antibody in people with advanced HIV-associated solid tumors	NCT02408861	National Cancer Institute (NCI)	Phase I
IRON CHELATORS				
Deferiprone		NCT02456558 (closed to enrollment)	ApoPharma	Phase I
JANUS KINASE INHIBITORS				
Ruxolitinib		NCT02475655	NIAID	Phase II
LATENCY-REVERSING AGENTS				
Chidamide	HDAC inhibitor	NCT02513901	Tang-Du Hospital	Phase I/II
Poly-ICLC	TLR-3 agonist	NCT02071095 (closed to enrollment)	Nina Bhardwaj, MD/Campbell Foundation/Oncovir, Inc.	Phase I/II
Romidepsin	HDAC inhibitor	NCT01933594	AIDS Clinical Trials Group/NIAID/Gilead	Phase I/II
Vesatolimod in ART-treated HIV controllers	TLR-7 agonist	NCT03060447	Gilead Sciences	Phase Ib
Vesatolimod (formerly GS-9620)	TLR-7 agonist	NCT02858401	Gilead Sciences	Phase Ib
ALT-803	Recombinant human super agonist interleukin-15 complex	NCT02191098	University of Minnesota - Clinical and Translational Science Institute	Phase I
Kansui	Traditional Chinese medicine containing ingenols	NCT02531295 (suspended)	UCSF	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
OBSERVATIONAL STUDIES				
ACTG A5321	Decay of HIV-1 reservoirs in subjects on long-term antiretroviral therapy: The ACTG HIV reservoirs cohort (AHRC) study	Not listed yet, see ACTG website entry for information	AIDS Clinical Trials Group	N/A
Analytic treatment interruption (ATI) to assess HIV cure	Antiretroviral treatment interruption	NCT02437526 (enrolling by invitation only)	Mayo Clinic	N/A
Biomarkers to predict time to plasma HIV RNA rebound	Antiretroviral treatment interruption	NCT03001128	AIDS Clinical Trials Group	N/A
CLEAC	Comparison of late versus early antiretroviral therapy in HIV-infected children	NCT02674867 (not yet open for enrollment)	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A
CODEX (the "Extreme" cohort)	Long term non-progressors and HIV controllers	NCT01520844	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A
Effects of dolutegravir-based regimen on HIV-1 reservoir and immune activation	Effects of dolutegravir-based regimen on HIV-1 reservoir and immune activation	NCT02557997	University Hospital, Strasbourg, France	N/A
EPIC4	Early pediatric treatment initiation cohort study	CTN S 281	Canadian Institutes of Health Research (CIHR)/ Canadian Foundation for AIDS Research (CANFAR)/ International AIDS Society (IAS)	N/A
Establish and characterize an acute HIV infection cohort in a high-risk population	Establish and characterize an acute HIV infection cohort in a high-risk population	NCT00796146	Southeast Asia Research Collaboration with Hawaii/ Armed Forces Research Institute of Medical Sciences/ Thai Red Cross AIDS Research Centre	N/A
EURECA	Exploratory study of cellular reservoirs in blood	NCT02858414	Centre Hospitalier Universitaire de Besancon	N/A
HEATHER	HIV reservoir targeting with early antiretroviral therapy	UK CPMS17589	University of Oxford/Medical Research Council/British HIV Association	N/A
HIV-STAR	HIV sequencing after treatment interruption to identify the clinically relevant anatomical reservoir	NCT02641756 closed to enrollment	University Hospital, Ghent	N/A
Host and viral factors associated with HIV elite control		UK CPMS16146	University College London Hospitals NHS Foundation Trust	N/A
HSCT-HIV	Allogeneic hematopoietic stem cell transplantation in HIV-1-infected patients	NCT02732457	Kirby Institute	N/A
Identification and quantification of HIV CNS latency biomarkers	Identification and quantification of HIV CNS latency biomarkers	NCT02989285	St Vincent's Hospital, Sydney	N/A
ImmunoCo27	Co-adaptation between HIV and CD8 cellular immunity	NCT02886416	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A
Impact of ART adherence on HIV persistence and inflammation		NCT02797093	University of Colorado, Denver	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
ISALA	Analytical treatment interruption in HIV-positive patients	NCT02590354	Institute of Tropical Medicine, Belgium	N/A
LoViReT	Low viral reservoir treated patients	NCT02972931	IrsiCaixa	N/A
Post-analytic treatment interruption study		NCT02761200 (closed to enrollment)	South East Asia Research Collaboration with Hawaii	N/A
Predictors of time to viremia with an analytic treatment interruption	Predictors of time to viremia with an analytic treatment interruption	NCT03033017	University of Minnesota - Clinical and Translational Science Institute	N/A
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans	Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans	NCT02154035	NIAID	N/A
TESOVIR	Tracking and exploring the source of viral rebound (ART interruption)	NCT03117985	Centre Hospitalier Régional d'Orléans	N/A
The use of leukapheresis to support HIV pathogenesis studies		NCT01161199	University of California, San Francisco	N/A
mTOR INHIBITORS				
Everolimus	Impact of everolimus on HIV persistence post kidney or liver transplant	NCT02429869	UCSF	Phase IV
Sirolimus	Safety and efficacy of sirolimus for HIV reservoir reduction in individuals on suppressive ART	NCT02440789	ACTG	Phase I/II
PROTEASOME INHIBITORS				
Ixazomib		NCT02946047	Nathan W. Cummins, M.D.	Phase I/II
STEM CELL TRANSPLANTATION				
BMT CTN 0903	Allogeneic transplant in individuals with chemotherapy-sensitive hematologic malignancies and coincident HIV infection	NCT01410344 (closed to enrollment)	National Heart, Lung, and Blood Institute (NHLBI)/ National Cancer Institute (NCI)/ Blood and Marrow Transplant Clinical Trials Network	Phase II
Maraviroc in HIV-1+ individuals requiring allogeneic hematopoietic cell transplant	Maraviroc in HIV-1+ individuals requiring allogeneic hematopoietic cell transplant	NCT03118661 (not yet open for enrollment)	Washington University School of Medicine	Phase I
HIVECT	HIV eradication through cord-blood transplantation	NCT02923076	Puerta de Hierro University Hospital	N/A
IMPAACT P1107	Cord blood transplantation using CCR5-Δ32 donor cells for the treatment of HIV and underlying disease	NCT02140944	IMPAACT/NIAID/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	N/A
THERAPEUTIC VACCINES				
iHIVARNA-01	TriMix & HIV antigen naked messenger RNA	NCT02888756	Rob Gruters, Erasmus Medical Center	Phase IIa

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
GTU-multiHIV + LIPO-5	DNA + lipopeptide vaccines	NCT01492985 (closed to enrollment)	French National Institute for Health and Medical Research/French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	Phase II
GTU-MultiHIV B-clade + MVA HIV-B	DNA + viral vector vaccines	NCT02972450 (not yet open for enrollment)	Inserm/ANRS	Phase II
VAC-3S	Peptide-based vaccine	NCT02041247 (closed to enrollment)	InnaVirVax	Phase II
VAC-3S	Peptide-based vaccine	NCT02390466 (closed to enrollment)	InnaVirVax	Phase I/ IIa
Tat Oyi	Tat protein vaccine	NCT01793818 (closed to enrollment)	Biosantech	Phase I/II
THV01	Lentiviral-vector-based therapeutic vaccine	NCT02054286 (closed to enrollment)	Theravectys S.A.	Phase I/II
Ad26.Mos.HIV + MVA-Mosaic	Adenovirus and modified Vaccinia Ankara strain vectors encoding mosaic HIV antigens	NCT02919306 (closed to enrollment)	Janssen Vaccines & Prevention B.V.	Phase I
Recombinant adenovirus type 5 vaccine	Viral vector vaccine	NCT02762045	Centers for Disease Control and Prevention, China	Phase I
iHIVARNA-01	TriMix and HIV antigen naked messenger RNA vaccine	NCT02413645 (closed to enrollment)	Biomedical Research Institute August Pi i Sunyer (IDIBAPS)	Phase I
MAG-pDNA + rVSVIN HIV-1 Gag	DNA + viral vector vaccines	NCT01859325 (closed to enrollment)	NIAID/Profectus Biosciences, Inc.	Phase I
TRADITIONAL CHINESE MEDICINE				
Triptolide wilfordii		NCT02219672	Peking Union Medical College	Phase III
TREATMENT INTENSIFICATION/EARLY TREATMENT				
LEOPARD: Latency and Early Neonatal Provision of Antiretroviral Drugs Clinical Trial	Combination antiretroviral therapy	NCT02431975	Columbia University	Not listed
New Era Study: Treatment with multi–drug class (MDC) HAART	Combination antiretroviral therapy	NCT00908544 (closed to enrollment)	MUC Research GmbH	Not listed
Antiretroviral regime for viral eradication in newborns	Combination antiretroviral therapy	NCT02712801 (not yet open for enrollment)	National Center for Women and Children's Health, China CDC	Phase IV
DGVTRU: Immediate initiation of antiretroviral therapy during 'hyperacute' HIV infection	Combination antiretroviral therapy	NCT02656511	UCSF	Phase IV
DIORR: Dolutegravir Impact on Residual Replication	Combination antiretroviral therapy	NCT02500446	University of Melbourne	Phase IV

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
DRONE: Impact of starting a dolutegravir-based regimen on HIV-1 proviral DNA reservoir of treatment-naive and experienced patients	Combination antiretroviral therapy	NCT02370979	University Hospital, Strasbourg, France	Phase IV
AAHIV: antiretroviral therapy for acute HIV infection	Combination antiretroviral therapy	NCT00796263	South East Asia Research Collaboration with Hawaii	Phase III
tenofovir/ emtricitabine + dolutegravir or tenofovir/ emtricitabine + darunavir/cobicistat	Combination antiretroviral therapy	NCT02987530 (not yet open for enrollment)	Inserm/ANRS	Phase III
VIRECURE: Impact of extremely early ART to reduce viral reservoir and induce functional cure of HIV infection	Combination antiretroviral therapy	NCT02588820	David Garcia Cinca, Hospital Clinic of Barcelona	Phase III
EIT: Early Infant HIV Treatment in Botswana	Combination antiretroviral therapy	NCT02369406	Harvard School of Public Health	Phase II/III
EARLIER: Early ART to limit infection and establishment of reservoir	Combination antiretroviral therapy	NCT02859558	AIDS Clinical Trials Group	Phase II
Peginterferon alfa-2b	Cytokine	NCT02227277	The Wistar Institute	Phase II
Peginterferon alfa-2b	Cytokine	NCT01935089 (closed to enrollment)	University of Pennsylvania/Wistar Institute	Phase II
IMPAACT P1115: Very early intensive treatment of HIV-infected infants to achieve HIV remission	David Garcia Cinca, Hospital Clinic of Barcelona	NCT02140255	IMPAACT/NIAID/NICHD	Phase I/II

Shaded entries represent additions since the 2016 Pipeline Report. For a listing including completed trials related to cure research, with 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.

COMBINATION APPROACHES

An increasing number of trials are exploring the effects of combinations of agents on the HIV reservoir. At the 2017 CROI, results from a study combining therapeutic vaccination with a drug capable of reversing HIV latency—the so-called 'kick & kill' approach—drew considerable attention due to evidence that the interventions may have enhanced control of viral load after an ART interruption. The results were presented by Beatriz Mothe from IrsiCaixa in Barcelona.[33]

Mothe and colleagues conducted a two-part trial. In the initial phase, 24 HIV-positive individuals who had started ART within three months of infection received a series of immunizations with chimpanzee adenovirus (ChAdV63) and modified Vaccinia Ankara strain (MVA) vaccine vectors, both encoding antigens designed to focus T cell responses on highly conserved parts of HIV, including elements from the Gag, Pol, Env and Vif proteins. Mothe had previously reported that receipt of these vaccines shifted HIV-specific T cell responses toward the intended conserved targets, but did not have a measurable effect on the size of the HIV reservoir.[34]

The second phase enrolled 15 participants from the first trial and administered booster immunizations with the MVA vector before and after three infusions of the HDAC inhibitor romidepsin. Eight weeks after the final MVA dose, all participants interrupted ART, with a requirement to restart if viral load increased to more than 2,000 copies/ml.

Data were available from 13 individuals at the time of Mothe's CROI presentation: eight quickly met the criteria to reinitiate ART, but the remaining five had controlled viral load to low levels for several months, with follow up ongoing (the longest duration is a little over six months). Based on Mothe's slide presentation, three appeared to have viral loads below the limit of detection of the assay used (20 copies/ml), whereas the other two fluctuated between the limit of detection and ~2,000 copies/ml. Mothe highlighted that the frequency of viral load containment in the cohort (~38%) was higher than had been observed in any studies involving early initiation of ART, where rates had varied from 0–15%.[35,36] The researchers are investigating whether correlates of viral load control can be identified, with a particular focus on vaccine-induced T cell responses.

The contribution of the different interventions may be difficult to tease out, as this was an open-label, uncontrolled study in which all participants received the MVA vaccine and romidepsin. Evidence of a latency-reversing effect of romidepsin was documented, with viral load transiently increasing after each infusion. Viral load blips were also observed after MVA immunizations in 60% of participants, suggesting that the vaccine may have been stimulating production of virus from latently infected CD4 T cells specific for HIV antigens.[37] There was no evidence of a decrease in measures of the HIV reservoir.

Romidepsin infusions were associated with an array of side effects that are known to be caused by HDAC inhibitors—primarily grade 1 and grade 2 headaches, fatigue and nausea—and the drug also caused precipitous, but transient, declines in peripheral blood CD4 T cell counts of around 300 cells. One participant developed the serious complication of sepsis after the final romidepsin dose.

Two trials that have been initiated during the past year (ROADMAP and eCLEAR, see Table 1) are evaluating a variation of the kick & kill approach, combining romidepsin with the broadly neutralizing antibody (bNAb) 3BNC117. This bNAb was discovered by the laboratory of Michel Nussenzweig at Rockefeller University and has been shown to have potent antiretroviral activity in a Phase I trial.[38] The rationale for combining 3BNC117 with a latency-reversing agent in people on ART is derived from an experiment in the humanized mouse model, which found that the approach was associated with a diminution of the HIV reservoir and reduced viral load rebound after ART interruption.[39] A potential mechanism of action is antibody-mediated cellular cytotoxity (ADCC): when latent HIV is stimulated to

make proteins by a latency-reversing agent, these appear on the outside of the cell, and bNAbs such as 3BNC117 can bind to the Env protein and recruit immune cells to destroy the HIV-infected target via a part of the antibody called the Fc receptor.[40]

An ongoing trial in Brazil is testing a combination of interventions that includes the gold-based anti-proliferative drug auranofin. The laboratory of Andrea Savarino pioneered the study of auranofin in the SIV/macaque model, reporting that it contributed to control of SIV replication after an ART interruption.[41] This research now seems prescient given the new appreciation of the role of CD4 T cell proliferation in sustaining the HIV reservoir. The regimens administered in the macaque study were complex, as is the case in the clinical trial, which involves ART intensification with maraviroc and/or dolutegravir, a dendritic-cell-based therapeutic HIV vaccine, nicotinamide (an HDAC inhibitor), and auranofin. The effects on various measures of HIV persistence will be assessed. The principal investigator is Ricardo Sobhie Diaz of the Federal University of São Paulo.

A concern that has emerged from studies of bNAbs given as single agents is that HIV can rapidly develop resistance. The first trial of a bNAb combination, 3BNC117 and 10-1074, is now underway at Rockefeller University. The activity of the bNAbs will be assessed in multiple groups of participants, including individuals that are off ART and those that are undergoing an ART interruption.

The US Military HIV Research Program (US MHRP) is collaborating with Janssen Vaccines & Prevention B.V. to study a combination of two therapeutic vaccines in individuals who initiated ART during acute HIV infection in Bangkok, Thailand. The vaccines are an adenovirus serotype 26 (Ad26) vector and an MVA vector, both of which encode mosaic HIV antigens designed to induce immune responses capable of recognizing diverse viral strains. The aim is to eventually combine these vaccines with an agonist of toll-like receptor (TLR) 7 developed by Gilead Sciences, as promising results obtained in a macaque study showed that the combination was associated with control of SIV viral load after ART interruption.[42]

TOLL-LIKE RECEPTOR AGONISTS

TLRs are proteins that have an important role in innate immunity by recognizing certain shared features that are common to many pathogens. Stimulating TLR signaling with TLR agonists has long been of interest in cure research, as there is evidence that it may contribute to both reversing HIV latency and promoting antiviral immune responses.[43] In addition to the planned collaboration with US MHRP, Gilead Sciences is sponsoring two ongoing trials of their TLR7 agonist vesatolimod (formerly known as GS-9620). One involves individuals on ART and aims to assess the safety and effects on measures of HIV persistence, the second is recruiting ART-treated HIV controllers—people who initiated ART despite relatively low viral loads—and includes an analytical ART interruption to investigate whether vesatolimod influences viral load rebound.

The research group of Ole Søgaard at Arhus University in Denmark has been investigating a TLR9 agonist, MGN1703, after an exploratory analysis of a trial in which a similar compound was used as a vaccine adjuvant in people on ART suggested that it was associated with a slight decline in the HIV reservoir.[44] In a recently published paper, the researchers report results from a small trial that administered MGN1703 subcutaneously to 15 individuals on ART, twice weekly for four weeks.[45] They observed increased activation of natural killer cells and CD8 T cells, indicating a potential enhancement of cellular immunity. Evidence of activation of plasmacytoid dendritic cells and elevated production of alpha interferon was also documented, along with upregulation of interferon-stimulated genes. In 6 of the 15 participants, viral load became transiently detectable, consistent with MGN1703 stimulating virus production by latently infected cells, although there was no significant change in measurements of the HIV reservoir. The researchers believe the results are promising and that MGN1703 should be considered for inclusion in future studies of combination strategies targeting the reservoir.

GENE THERAPIES

A number of clinical trials of gene therapies are ongoing, but little news has emerged from this research over the past year. While not specific to HIV, Jennifer Adair from the laboratory of Hans-Peter Kiem at the Fred Hutchinson Cancer Research Center published a description of an approach that aims to address concerns about the potential accessibility of gene therapies. Dubbed "gene therapy in a box," the method potentially allows for the creation of gene-modified stem cells at the point of care, rather than at high-tech facilities.[46]

Two new gene therapy trials have recently begun. One involves the infusion of CD4 T cells that have been gene modified to express an HIV-inhibiting protein, C34, fused to part of CXCR4, a cell surface protein that can serve as a co-receptor for HIV entry. The idea is to bring the C34 protein to the sites where HIV infects vulnerable cells. The approach has shown broad and potent inhibition of diverse HIV isolates—both CXCR4-tropic and CCR5-tropic—in laboratory experiments.[47]

The AIDS Malignancy Consortium has initiated a gene therapy study for HIV-positive individuals with lymphoma who require stem cell transplants. This Phase I/II trial will modify transplanted stem cells with a triple combination of anti-HIV genes developed by researchers at the University of California, Davis.[48] The primary goal is to assess the magnitude and persistence of the gene-modified cells after transplantation.

CRISPR/Cas9, a relatively new technology derived from the primitive immune system of bacteria, has generated considerable excitement because of its vaunted ability to reliably target and modify genes of interest. The research group of Kamel Khalili at Temple University has spearheaded the use of the approach as a means to excise the HIV genome from latently infected cells, reporting encouraging results in preclinical experiments.[49,50] The media coverage of this work has at times been guilty of glossing over the challenges associated with translating the approach for use in the human body—for example, the fact that a bacterial protein is involved raises concern that the approach could induce anti-bacteria immune responses that might hamper efficacy (this has been observed in mice[51]). But the apparent promise of the approach for multiple diseases means that many different research groups are working to develop ways to deliver CRISPR/Cas9 as a therapy.[52]

In the meantime, a group of Chinese researchers have become the first to use the technology in an HIV trial. CRISPR/Cas9 will be used ex vivo to delete the CCR5 gene from stem cells in the laboratory, with the modified cells being subsequently administered to HIV-positive individuals requiring stem transplants for hematological cancers.

IXAZOMIB

The first study of a proteasome inhibitor, ixazomib, as a potential intervention in cure research is being conducted by Nathan Cummins from the Mayo Clinic in Rochester. The drug is an FDA-approved treatment for multiple myeloma. Cummins and colleagues have a longstanding interest in manipulating cell death pathways as a means of preferentially promoting the demise of CD4 T cells that are latently infected with HIV, and proteasome inhibitors are among the candidates that they have identified.[53] The trial represents the first step toward translating this work into the clinic.

BROADLY NEUTRALIZING ANTIBODIES

The International AIDS Vaccine Initiative (IAVI) is sponsoring a first-in-human trial of the potent bNAb PGT121, recruiting both HIV-positive and HIV-negative individuals. Of particular interest from the perspective of cure research, PGT121 has been shown to mediate protection against a simian-human

immunodeficiency virus (SHIV) challenge in macaques by promoting clearance of infected cells from tissues.[54] The antibody also strongly suppressed SHIV replication when delivered in the therapeutic context.

Researchers in Australia plan to combine the bNAb 3BNC117 with a radiolabel to facilitate imaging studies of the locations in the body in which 3BNC117 binds to the HIV envelope protein. The first step will be to assess safety in HIV-negative individuals before moving on to HIV-positive individuals that are either off ART or on ART with suppressed viral loads.

THERAPEUTIC VACCINES

The idea of using naked DNA as a vaccine platform has been around for some time. The approach involves injecting DNA comprising the genes for the protein antigens of interest; the DNA is transcribed into RNA, which is then translated into protein. But results using this approach have, overall, been disappointing compared with what was observed in initial experiments in small animals.

In recent years, technological advances have made it possible to employ naked RNA as the delivery vehicle, and this approach has generated strong interest, particularly in the field of cancer.[56] A consortium of investigators is now exploring the potential of an RNA vaccine designed to induce immune responses to HIV. Named iHIVARNA-01, the vaccine uses messenger RNA to deliver HIV antigens combined with TriMix, an adjuvant cocktail consisting of three proteins involved in the activation of antigen-presenting cells: CD40L, CD70, and TLR4. The vaccine is delivered intranodally (into the lymph nodes). Positive preclinical results have been reported[57], and the vaccine is now the subject of a Phase IIa trial led by Rob Gruters from the Erasmus Medical Center in the Netherlands.

ABX464

ABX464 is an antiretroviral with a novel mechanism of action: it interferes with the process by which HIV RNA is spliced to assemble new virions during the viral life cycle. In studies in the humanized mouse model, administration of ABX464 was associated with a reduced HIV viral load rebound after treatment cessation compared with standard ART[58] (although it has been suggested that this may have been an artifact of the model system[59]), and a preliminary trial in humans has reported that the drug was relatively well tolerated, with a hint of antiretroviral activity observed at the highest dose.[60]

A Phase II placebo-controlled trial combining ABX464 with darunavir and ritonavir or darunavir and cobicistat, followed by an analytical treatment interruption, is now ongoing. A recent press release regarding this study from the manufacturer, Abivax, trumpeted: "First ever evidence of treatment-induced reduction in HIV reservoirs" and reported that 7 of 14 participants who received ABX464 showed a decline in HIV DNA levels averaging around 40%.[61] Contrary to the company's claims, a very similar HIV DNA reduction has been reported in a study that combined romidepsin with the therapeutic vaccine Vacc-4x, and it was not associated with a delay in HIV viral load rebound when ART was interrupted.[62] The Abivax press release states that their study results will be submitted to scientific conferences and it is unfortunate that the company decided to promote them before a formal presentation has occurred. The mechanism by which ABX464 might have an effect on the latent HIV reservoir is as yet unclear.

Table 2. Immune-Based Therapy Pipeline 2017

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Canakinumab	IL-1β inhibitor	University of California, San Francisco	Phase II
Isotretinoin	13-cis retinoic acid	NIAID	Phase II
Lactobacillus casei shirota	Probiotic	University of Sao Paulo General Hospital	Phase II
Losartan	Angiotensin II receptor antagonist, anti-inflammatory	Minneapolis Medical Research Foundation	Phase II
Methotrexate (low dose)	Anti-inflammatory	NIAID	Phase II
Niacin	Vitamin B3	McGill University Health Center/ Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network	Phase II
Visbiome	Probiotic	University Health Network, Toronto/ CIHR Canadian HIV Trials Network	Phase II
Dipyridamole	Phosphodiesterase type 5 inhibitor, anti-inflammatory	Sharon Riddler, University of Pittsburgh/ NIAID	Phase I/II
tocilizumab	IL-6 blockade	Case Western Reserve University	Phase I/II
Tripterygium wilfordii Hook F	Traditional Chinese medicine, anti-inflammatory	Beijing 302 Hospital Peking Union Medical College	Phase I/II
Vorapaxar	Thrombin receptor (PAR-1) antagonist	Kirby Institute/NIAID/University of Minnesota – Clinical and Translational Science Institute/University of Melbourne/Merck	Phase I/II
Arabinoxylan rice bran supplementation (BRM4)	A product derived from rice bran treated with extracts from three mushrooms	University of Southern California	Not specified

As outlined in the introduction to this chapter, research into potential immune-based adjuncts to ART now represents a rather quiet backwater compared with the expanding sea of cure research. An antibody that inhibits the pro-inflammatory cytokine IL-1β, canakinumab, straddles both fields to some degree—an ongoing trial is primarily studying the effects on inflammation individuals on ART, but will also measure HIV reservoirs as a secondary endpoint. The study is being conducted by Priscilla Hsue from UCSF, who presented results of a pilot evaluation of canakinumab in ten HIV-positive individuals on ART at the 2017 CROI.[63]

The data were encouraging, with significant declines being observed in several inflammatory biomarkers, including IL-6 (levels fell by 30%) and high sensitivity C-reactive protein (41%). Imaging studies also revealed a 10% reduction in arterial inflammation. There was no evidence of an alteration in CD4 counts, so it is unclear whether canakinumab might benefit INRs. The larger trial is aiming to enroll 110 participants.

Benigno Rodriguez at Case Western Reserve University is leading a study investigating tocilizumab, an antibody against the proinflammatory cytokine IL-6, in individuals on ART. Effects on inflammatory biomarkers and the turnover of central memory CD4 T cells (measured by the cycling marker Ki67) will be assessed. The trial ended in January 2017 and results are pending.

A scattering of studies involving probiotics have been published over the past year,[64,65] continuing to suggest benefits without providing much in the way of guidance for HIV-positive people regarding their use. The CIHR Canadian HIV Trials Network is attempting to help fill the information gap by conducting two prospective, double-blinded, randomized, placebo-controlled, multicenter pilot studies of the probiotic Visbiome.[66] One trial will enroll individuals initiating ART, whereas the other is recruiting INRs with CD4 counts below 350 cells despite ART.

A cautionary report regarding the potential dangers of probiotic use also appeared in the literature, describing a case of Lactobacillus acidophilus bacteraemia in an individual with AIDS that was associated with excessive consumption of probiotic-enriched yogurt.[67]

Efforts to bring some clarity and coordination to the pursuit of probiotic research in HIV have received a boost with the initiation of an annual HIV Microbiome Workshop sponsored by Virology Education.[68] The third meeting is scheduled to take place from October 19–20, 2017 in Washington DC.

The only other new trial for INRs that has appeared in the clinicaltrials.gov database over the past year involves the nutritional supplement BRM4, which contains extracts from rice bran and shiitake mushrooms. The study is being conducted at the University of Southern California and is looking to enroll around 24 individuals on ART with CD4 T cell counts between 100 and 350.

A few short years ago, it appeared that the cytokine IL-7—which has shown promise for promoting immune reconstitution[69]—was likely to be studied for efficacy in a large randomized trial that would have measured the effect on morbidity and mortality in INRs. But the manufacturer, Cytheris, went bankrupt, and when surveying the current state of immune-based therapy research, it appears extremely unlikely that any candidate will undergo that type of rigorous evaluation in the near future.

CONCLUSION

The cure research endeavor maintains a productive diversity, with many leads currently under investigation and constant recalibration occurring as new information emerges. The expansion in the number of Martin Delaney Collaboratories is a particularly encouraging development, particularly given that the five-year funding period offers hope that they will outlast the current US President. But at the current time, it is still not possible to predict when a broadly accessible cure might be developed. Updates on the field will be provided at the International AIDS Society HIV Cure & Cancer Forum, which takes place from July 22–23, 2017 in Paris, and the biannual HIV Persistence Meeting held on December 12–15, 2017 in Miami.

Immune-based therapy research has dwindled to a point where a pipeline barely exists, and it will require ongoing engagement of activists and other stakeholders to try and ensure that work continues in this area.

An overarching threat to all of the research described in this and other chapters is the strong anti-science bias of the Trump administration, which is proposing massive cuts to the National Institute Health, the global leader in science funding. Although there is reason to hope that the US Congress will prevent their desired decimation, ongoing vigilance will be essential to ensure that the work described in this report continues.

RECOMMENDATIONS

- Continue to increase funding for cure-related research and protect extant funding from the anti-science efforts of the Trump administration to slash the NIH budget.
- Broaden the global scope of HIV cure research to gain a better understanding of geographic and population-specific differences in HIV reservoirs.
- Work to promote and facilitate participation of diverse populations in clinical trials.
- Support social science research aiming to gain insights into how HIV cure research is perceived and understood.
- Further enhance community education on HIV cure research to both facilitate community involvement in the effort and provide accurate context for media coverage of the topic.
- Support and promote dialogue between regulators, researchers, funders, and community stakeholders on trial design issues, particularly regarding the use of analytical ART interruptions.
- Develop more user-friendly technologies for monitoring HIV rebound in individuals experiencing HIV remission to avert or lessen the risks associated with a rapid return of viral replication.
- Address the engineering challenges associated with making potentially complex interventions such as gene therapy more convenient, accessible, and affordable.
- Improve communication on concepts of HIV remission, and be clear that the maintenance of low viral load in the absence of ART may not necessarily be equivalent to suppression of HIV by ART in terms of long-term health outcomes.
- Support webcasting for all cure-related scientific conferences to facilitate greater global sharing of information.
- Remain alert for any indications that candidates studied in the cure context might have benefits as adjunctive therapies in addition to ART, for example, to enhance immune reconstitution in INRs.
- Advocate for enhanced research and development efforts to address the needs of INRs.

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