Research Toward a Cure and Immune-Based and Gene Therapies

By Richard Jefferys

INTRODUCTION

The pursuit of a cure for HIV infection has become a central plank of the overall research portfolio, and this has been officially underpinned by the revised HIV/AIDS priorities announced by the U.S. National Institutes of Health (NIH) in 2015.[1,2] The NIH has cited the goal of developing a cure for HIV/AIDS as one of five high-priority areas for HIV/AIDS research, and only grant applications that address these priorities will be considered for funding from 2016 onwards.

The NIH will soon announce the funding of several new Martin Delaney Collaboratorys, which are research collaborations specifically focused on discovering a cure (the total number that will be supported is unknown, but may be as many as five or six). The grants for the current Martin Delaney Collaboratorys—the Collaboratory of AIDS Researchers for Eradication (CARE), Delaney AIDS Research Enterprise (DARE), and the Delaney Cell and Genome Engineering Initiative (defeatHIV)—expire in mid-2016. The non-profit organization amfAR continues to invest heavily in cure research, announcing last December the creation of the amfAR Institute for HIV Cure Research, which is based at the University of California, San Francisco (UCSF).[3]

At the global level, the International AIDS Society (IAS) has embraced cure research as a key element of their mission with the long-running Towards an HIV Cure initiative. At the upcoming AIDS 2016 conference in Durban, IAS will issue an update to the Towards an HIV Cure: Global Scientific Strategy Recommendations that were originally published in 2012.[4]

The number of clinical trials and observational studies related to the effort to cure HIV has expanded further over the past year (see table 1). However, this work remains largely exploratory; among the main lines of research being pursued, investigators are probing a variety of possible means to try and diminish the reservoir of HIV that persists in the body despite antiretroviral therapy (ART). Strategies for inducing containment of the virus when ART is interrupted are also being explored, including gene therapies and immune-based therapies (particularly therapeutic vaccines). These are early-stage tests, and it is important to appreciate that there is no prospect of study participants being cured; the hope is that the information gleaned will guide scientists toward curative approaches.

The one current area of research where there might be a slim possibility of a cure being achieved is limited to HIV-positive individuals with life-threatening cancers requiring stem cell transplantation. Several projects are looking to treat people in this situation using stem cells from donors who are homozygous for the CCR5-Δ32 mutation (which abrogates expression of the CCR5 co-receptor that most forms of HIV use to enter target cells), in hopes of recapitulating the experience of Timothy Brown, who remains the lone individual considered to be cured of HIV infection.[5]

Brown received stem cell transplants from a CCR5-Δ32 homozygote as part of a grueling series of treatments for acute myelogenous leukemia nearly a decade ago, and no trace of replication-competent HIV has been detected in his body since that time, despite the discontinuation of ART.[6] At least six individuals have since been reported who underwent similar procedures, but all of them died as a result of either the underlying cancers or complications from the transplantation procedure.[7] One new case was described in a poster at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI), and the preliminary signs appear

encouraging: the cancer is in remission and HIV cannot be detected using multiple techniques.[8] However, ART had not yet been interrupted at the time of the presentation, so it is too early to know whether this may represent a second example of an HIV cure.

Research into therapies that might offer benefits as adjuncts to ART is dwindling, and it would be a stretch to describe the candidates in this area as moving through a pipeline. Academic investigators have initiated the clinical trials that are being conducted, and there are currently no pharmaceutical companies attempting to usher interventions along a pathway toward approval. The only trial of sufficient size to assess the efficacy of an adjunctive approach is the NIH-sponsored REPRIEVE study, which is evaluating whether pitavastatin can reduce the incidence of cardiovascular disease in people on ART.[9]

Despite the fallowness of this field, there does remain a need for therapies capable of addressing the elevated risk of morbidity and mortality faced by individuals who experience a poor immunologic response to ART.[10] The single most important risk factor for becoming an immunologic non-responder (INR) is late initiation of ART, and the most recently available surveillance data from the U.S. Centers for Disease Control and Prevention indicate that this remains a problem despite efforts to promote early diagnosis: in 2013, 41,661 individuals were newly diagnosed with HIV infection, and 23.6% had progressed to AIDS at the time of diagnosis.[11] TAG is currently collaborating with other activists to explore whether candidate treatments for INRs might be considered as orphan drugs, a U.S. Food and Drug Administration (FDA) designation intended to spur the development of treatments for disorders that are relatively rare.

Table 1. Research Toward a Cure 2016: Current Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
ADOPTIVE IMMUNOTHERAPY				
Early ART in combination with autologous HIV-specific cytotoxic T lymphocyte (CTL) infusion	T cell therapy	NCT02231281	Yongtao Sun, MD, PhD, Tangdu Hospital, the Fourth Military Medical University	Phase III
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				
VRC01	Broadly neutralizing monoclonal antibody	NCT02664415 (not yet open for enrollment)	National Institute of Allergy and Infectious Diseases (NIAID)	Phase II
3BNC117	Broadly neutralizing monoclonal antibody	NCT02446847	Rockefeller University	Phase I/II
3BNC117	Broadly neutralizing monoclonal antibody	NCT02588586	Rockefeller University	Phase I/II
10-1074	Broadly neutralizing monoclonal antibody	NCT02511990	Rockefeller University	Phase I
Vedolizumab	Anti-$\alpha 4\beta 7$ integrin antibody	NCT02788175 (not yet open for enrollment)	NIAID	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
ANTIBODIES (continued)				
VRC01	Broadly neutralizing monoclonal antibody in acute HIV infection	NCT02591420 (not yet open for enrollment)	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody	NCT02471326 (closed to enrollment)	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody	NCT02411539 (closed to enrollment)	NIAID	Phase I
CHERUB 001	Intravenous immunoglobulin in primary HIV infection	No clinicaltrials.gov entry	CHERUB (Collaborative HIV Eradication of viral Reservoirs: UK BRC)	N/A
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
CC-11050	Phosphodiesterase-4 inhibitor	NCT02652546	NIAID	Phase I
Metformin	Antidiabetic	NCT02659306 (not yet open for enrollment)	McGill University Health Center	Phase I
ANTIRETROVIRAL THERAPY				
HIV reservoir dynamics after switching to dolutegravir in patients on a PI/r based regimen		NCT02513147	Hospital Universitari Vall d'Hebron Research Institute	Phase IV
ANTIRETROVIRAL THERAPY IN HIV CONTROLLERS				
Emtricitabine + Rilpivirine + Tenofovir		NCT01777997 (closed to enrollment)	AIDS Clinical Trials Group/ NIAID	Phase IV
COMBINATIONS				
Perturbing of HIV reservoir with immune stimulation: Fluarix, Pneumovax vaccines		NCT02707692 (not yet open for enrollment)	University of California, San Diego	Not listed
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	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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
COMBINATIONS (continued)				
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
Vacc-4x + romidepsin	HDAC inhibitor + peptide-based therapeutic vaccine	NCT02092116 (closed to enrollment)	Bionor Immuno AS/Celgene	Phase I/II
AGS-004 + vorinostat	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens + HDAC inhibitor	NCT02707900 (not yet open for enrollment)	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	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 NCT02390297 (long term safety phase)	Calimmune	Phase I/II
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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS				
High-dose chemotherapy with transplantation of gene-modified stem cells for high-risk AIDS-related lymphoma	Stem cells gene-modified to express an HIV entry inhibitor C46	NCT00858793 (suspended)	Universitätsklinikum Hamburg-Eppendorf	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 (not yet open for enrollment)	Fred Hutchinson Cancer Research Center	Phase I
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's 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
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
IMMUNE CHECKPOINT INHIBITORS				
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				
MGN1703	Toll-like receptor 9 (TLR-9) agonist	NCT02443935 (enrolling by invitation only)	University of Aarhus	Phase Ib/IIa

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
LATENCY-REVERSING AGENTS (continued)				
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
GS-9620	TLR-7 agonist	No clinicaltrials.gov entry	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 (not yet open for enrollment)	UCSF	Phase I
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
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		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		NCT00796146	Southeast Asia Research Collaboration with Hawaii/ Armed Forces Research Institute of Medical Sciences/ Thai Red Cross AIDS Research Centre	N/A
HEATHER	HIV reservoir targeting with early antiretroviral therapy	UK CPMS17589	University of Oxford/Medical Research Council/British HIV Association	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
OBSERVATIONAL STUDIES (continued)				
HIV-STAR	HIV sequencing after treatment interruption to identify the clinically relevant anatomical reservoir	NCT02641756 (enrolling by invitation only)	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
ISALA	Analytical treatment interruption in HIV-positive patients	NCT02590354	Institute of Tropical Medicine, Belgium	N/A
Post analytic treatment interruption study		NCT02761200 (closed to enrollment)	South East Asia Research Collaboration with Hawaii	N/A
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans		NCT02154035	NIAID	N/A
The use of leukapheresis to support HIV pathogenesis studies		NCT01161199	University of California, San Francisco	N/A
Tat protein vaccine	Roll-over observational study for extended follow-up of volunteers in the ISS T-003 trial	NCT02712489 (closed to enrollment)	Barbara Ensoli, MD, Istituto Superiore di Sanità/Italian Ministry of Foreign Affairs	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
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
Immune response after stem cell transplant in HIV-positive patients with hematologic cancer		NCT00968630	Fred Hutchinson Cancer Research Center	Phase II
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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
THERAPEUTIC VACCINES				
AGS-004	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens	NCT01069809 (closed to enrollment)	Argos Therapeutics	Phase II
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
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
GTU-MultiHIV B Clade Vaccine	DNA vaccine	NCT02457689	Imperial College London	Phase I/II
AGS-004	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens	NCT02042248	University of North Carolina at Chapel Hill/Argos Therapeutics/U.S. National Institutes of Health (NIH)	Phase I/II
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
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	Biomedical Research Institute August Pi i Sunyer (IDIBAPS)	Phase I
HIVAX	Lentiviral-vector-based therapeutic vaccine	NCT01428596	GeneCure Biotechnologies	Phase I
MAG-pDNA + rVSV$_{IN}$ 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

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
TREATMENT INTENSIFICATION/EARLY TREATMENT (continued)				
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
DRONE: Impact of starting a dolutegravir-based regimen on HIV-1 proviral DNA reservoir of treatment naïve 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
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
Viral suppression after analytic treatment interruption in Thai patients who initiated HAART during acute HIV infection		NCT02614950	South East Asia Research Collaboration with Hawaii	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
Alpha interferon intensification	Cytokine	NCT01295515	NIAID	Phase I/II
IMPAACT P1115: Very early intensive treatment of HIV-infected infants to achieve HIV remission	Combination antiretroviral therapy	NCT02140255	IMPAACT/NIAID/NICHD	Phase I/II

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

The number of trials combining agents to target the HIV reservoir has increased since 2015. A leading strategy is known as "kick and kill" and combines drugs that may have the potential to reverse HIV latency (latency-reversing agents or LRAs) with immune-based interventions intended to facilitate the elimination of latently infected cells that have been prompted to express viral proteins by LRAs. At CROI 2016, Ole Søgaard from the University of Aarhus in Denmark presented preliminary data from an ongoing trial of this type of

two-pronged approach, involving a combination of the HDAC inhibitor romidepsin with Vacc-4x, a therapeutic vaccine comprised of several epitopes from the HIV Gag protein delivered with a GM-CSF adjuvant.[12]

In a previous pilot study, Søgaard and colleagues administered romidepsin alone to six individuals on ART with suppressed viral loads; as covered in last year's *Pipeline Report*, evidence of latency-reversing activity was documented in the form of detectable increases in HIV RNA after drug administration. There were no significant changes in the size of the HIV reservoir. These results were presented at the 2014 International AIDS Conference and subsequently published in *PLoS Pathogens* in September 2015.[13]

In the new trial, a series of six immunizations with Vacc-4x and GM-CSF adjuvant were administered, followed by three infusions of romidepsin, to 17 participants on ART. Levels of total HIV DNA, one possible surrogate measure of the reservoir, showed a statistically significant decline of 39.7%. An alternate assay measuring HIV DNA that is integrated into the genome of CD4 T cells also documented a slight reduction, but this did not reach statistical significance. Replication-competent HIV was detectable in six participants at baseline using a viral outgrowth assay, and levels fell significantly after the interventions by around 38%.

In the final stage of the study, 16 participants underwent an ART interruption. Despite the evidence of a small decline in HIV reservoir size, there was no delay in viral load rebound in any participant. In his CROI presentation, Søgaard concluded that the data offer some support for the idea of combining LRAs with therapeutic vaccines, but improvements are needed to enhance the magnitude of the effect.

Additional insights into the potential of kick and kill strategies should emerge from other ongoing trials of different combinations of HDAC inhibitors and therapeutic vaccines (see table 1). These include:

- The multicenter RIVER trial in the UK, investigating vorinostat together with two viral-vector-based HIV vaccines derived from chimpanzee adenovirus and a modified Vaccinia Ankara strain (MVA).
- A study at the IrsiCaixa institute in Spain looking at romidepsin and an MVA-based HIV vaccine.
- A combination of vorinostat with AGS-004, a dendritic-cell-based vaccine that is personalized to present HIV antigens obtained by sampling viral sequences from each intended recipient, which is being tested at the University of North Carolina.

Other types of combinations are also being explored, with several new protocols being launched or imminent since last year. Among them is a trial of the HDAC inhibitor panobinostat and the cytokine pegylated interferon-α2a that is being conducted at Massachusetts General Hospital by Dan Kuritzkes, Mathias Lichterfeld, and Rajesh Gandhi. The rationale derives from a previously published study of panobinostat that reported that a small subset of participants appeared to experience a diminution of the HIV reservoir that correlated with a delay in viral rebound after ART interruption.[14] An analysis led by Mathias Lichterfeld found that this response was partly linked to interferon-stimulated genes,[15] suggesting that interferon may be able to potentiate the effects of panobinostat on the HIV reservoir.

Pegylated interferon is also being assessed as a means to enhance responses to a dendritic-cell-based HIV vaccine in an upcoming trial in Spain. Felipe García's research group has conducted two previous trials with the vaccine, which uses heat-inactivated HIV isolated from each participant as the source of antigens. The results demonstrated induction of HIV-specific T cell responses and a significant, albeit transient, lowering of HIV viral load during an ART interruption.[16] An inverse correlation was also reported between HIV-specific T cell responses and measures of integrated HIV DNA, suggesting a possible effect on the HIV reservoir.[17]

David Smith and colleagues at the University of California, San Diego are exploring whether influenza and pneumococcus vaccines can perturb the HIV reservoir in individuals on ART. Latent HIV resides in resting memory CD4 T cells, and vaccination might be a means of stimulating these cells and awakening the virus,

particularly if the latently infected CD4 T cells recognize antigens contained in the vaccines. At least one published study has reported the presence of latent HIV infection in influenza-specific CD4 T cells.[18]

Immune Checkpoint Inhibitors

Over the past decade or so, scientists have discovered a family of receptors that are involved in dampening or switching off immune responses; examples include PD-1 and CTLA-4. These "immune checkpoint" receptors have an important role in restraining immune responses that might otherwise attack body tissues causing autoimmune disease (the immunological equivalent of friendly fire). Sometimes, however, immune checkpoint receptors can curtail responses to viruses or cancerous tissues, impeding activities of the immune system that would be helpful rather than harmful. This has led to the development of immune checkpoint inhibitors that aim to revive beneficial immune responses, particularly against cancers. Several immune checkpoint inhibitors are now FDA approved, having shown significant efficacy against a variety of cancers, including the anti-PD-1 antibodies nivolumab (trade name Opdivo) and pembrolizumab (Keytruda) and the anti-CTLA-4 antibody ipilimumab (Yervoy).[19]

There is longstanding interest in studying immune checkpoint inhibitors in the context of HIV cure research, stemming from evidence that expression of the receptors PD-1, CTLA-4, and TIGIT increases as disease progresses and is associated with exhaustion of HIV-specific T cell immunity.[20,21,22] Furthermore, latently infected CD4 T cells preferentially express several immune checkpoint receptors, including PD-1, LAG-3, and TIGIT[23,24], and antibodies against PD-1 have been reported to reverse HIV latency in laboratory studies.[25] The major hurdle to evaluating the approach is the potential for the induction of autoimmunity, which has occurred in a minority of participants in cancer trials and, in rare cases, can be fatal.[26]

Earlier this year, Joe Eron from the University of North Carolina debuted data from the first trial of an antibody targeting the PD-1 pathway in people with HIV. The antibody in question is manufactured by Bristol-Myers Squibb and does not bind to PD-1, but rather to a ligand that it interacts with, PD-L1. The original intent was to study single infusions of various, escalating doses in people on suppressive ART; however, only the lowest dose (0.3 mg/kg) was administered due to an unexpected concern about the potential for retinal toxicity that emerged from animal experiments.

A total of six individuals received the antibody, and two showed clear evidence of increased HIV Gag-specific CD8 T cell responses (measured both by interferon gamma production and expression of CD107a, a marker of cytotoxicity), but the overall average change compared to a control group of two placebo recipients did not reach statistical significance. An assay that can measure HIV RNA levels down to a single copy did not reveal significant changes associated with the treatment, but one individual experienced a tenfold decline in levels of cell-associated HIV RNA, and Eron noted that this was the person who experienced the greatest increase in Gag-specific CD8 T cell responses. This individual also had the highest baseline expression of PD-1, hinting that perhaps they had started with the most exhausted HIV-specific T cell response and were therefore best able to respond to the antibody.

In terms of safety, no evidence of the retinal toxicity that stymied plans to escalate dosing was observed. However, one person developed autoimmune pituitary insufficiency nine months after the infusion, and, although the relationship to the anti-PD-L1 antibody is uncertain, the fact that it was an autoimmune phenomenon raises serious concerns about whether further studies of antibodies targeting the PD-1 pathway will be possible in otherwise healthy HIV-positive people.

An alternate approach to investigating immune checkpoint inhibition in HIV is to conduct trials limited to HIV-positive individuals with cancers that are unresponsive to standard therapies, and this is the tack that has been taken by Thomas Uldrick at the National Cancer Institute. The primary goal of Uldrick's phase I study of the

anti-PD-1 antibody pembrolizumab is to assess whether the cancers can be successfully treated, but secondary analyses will measure the effect on the HIV reservoir and HIV-specific immune responses.

Lakshmi Rajdev of the AIDS Malignancy Consortium at the National Cancer Institute is conducting a multicenter trial of a combination of the anti-CTLA-4 antibody ipilimumab with the anti-PD-1 antibody nivolumab in HIV-positive people with advanced, HIV-associated solid tumors that are refractory to standard care. The primary endpoint is safety, but the study will also look at efficacy against cancer and several HIV-related parameters, including viral load and HIV-specific T cell immunity.

Another potential source of information is case reports on HIV-positive people with cancer who have received approved immune checkpoint inhibitors as part of their medical care. One such report has been published on an individual with HIV and metastatic melanoma who received the anti-CTLA-4 antibody ipilimumab and, interestingly, there was evidence of transient increases in cell-associated HIV RNA after infusions, suggestive of latency-reversing activity.[27] In parallel, HIV RNA levels measured by a single copy assay declined over time, from 60 to 5 copies/ml. The report has spurred interest in conducting further research, but it is currently uncertain whether ipilimumab can be studied outside of the cancer setting; results from other ongoing trials and experiments in animal models should help to ascertain if this will be possible.

Gene Therapies

Two new gene therapy trials were initiated last summer. At the City of Hope Medical Center in Los Angeles, enrollment began in a study that is extracting stem cells from participants, genetically modifying them with a zinc finger nuclease technology that is designed to abrogate expression of the CCR5 coreceptor, then reinfusing them with the aim of generating new immune cells that are resistant to HIV. The research represents a collaboration between Sangamo BioSciences (the developer of the zinc finger nuclease technology), City of Hope, and the Keck School of Medicine at the University of Southern California, supported by the California Institute for Regenerative Medicine (CIRM). As discussed in a plenary presentation at CROI 2016 by Paula Cannon (available online via webcast), Sangamo's approach has shown some promise when applied to CD4 T cells, with a subset of recipients displaying evidence of lowered viral loads after ART interruption.[28]

The company Calimmune is also pursuing a strategy involving gene modification of stem cells. Their approach uses a lentiviral vector designed to both downregulate CCR5 expression and introduce a gene that encodes an HIV fusion inhibitor, designated C46.[29] Results are pending from an ongoing phase I trial in the U.S., and recruitment began earlier this year for another small study in Australia that is being conducted by Anthony Kelleher at the Kirby Institute.

A possible gene therapy candidate that has generated intense interest recently involves the use of the gene-editing tool CRISPR/Cas9 to try and excise the HIV genome from latently infected cells. CRISPR/Cas9 is derived from bacteria, where it evolved as a defense mechanism against invading viruses. Researchers have reported some success in using CRISPR/Cas9 to delete HIV genes from cells[30] and small animals[31] in laboratory studies, but it has also emerged that viruses can rapidly become resistant to its effects.[32,33,34] Although some scientists have made optimistic predictions that human trials may begin in the next few years, it is not yet known whether it will be feasible to deliver CRISPR/Cas9 into the human body.

Ruxolitinib

Ruxolitinib is an FDA-approved treatment for myelofibrosis (a type of bone marrow cancer) that targets a cellular signaling pathway with a complicated name: the Janus activating kinase–signal transducer and activator of transcription (JAK-STAT) pathway. Studies have shown that this pathway is activated in HIV-infected

macrophages and lymphocytes, creating an inflammatory environment that favors viral replication and persistence.[35,36] In laboratory experiments, ruxolitinib countered this environment and inhibited HIV,[37] leading researchers at the National Institute of Allergy and Infectious Diseases (NIAID) to launch a clinical trial of the drug in individuals on ART. Endpoints include safety, anti-inflammatory activity, and impact on the HIV reservoir.

Anti-inflammatories

The question of whether suppressing inflammation can reduce the HIV reservoir is being probed in several other studies. At the University of California, San Francisco, Priscilla Hsue and colleagues are testing canakinumab, an antibody that blocks the inflammatory cytokine interleukin-1β (IL-1β), primarily to assess whether it can beneficially modulate markers of cardiovascular disease risk, but measures of the HIV reservoir are among the secondary endpoints.

CC-11050 is a novel compound that inhibits phosphodiesterase-4; other drugs in this class have been found to be useful against inflammatory diseases such as asthma and psoriasis.[38] Researchers at NIAID have initiated a study to evaluate CC-11050 in HIV-positive individuals on ART, including any effects on HIV persistence.

Jean-Pierre Routy and colleagues at McGill University in Canada are investigating the antidiabetic drug metformin, which has recently been shown to also have an anti-inflammatory mechanism of action.[39] The primary goal of the trial, named the Lilac Study, is to measure if the drug reduces the size of the HIV reservoir.

Vedolizumab

The monoclonal antibody vedolizumab is an FDA-approved treatment for ulcerative colitis and Crohn's disease. It binds to a molecule expressed on CD4 T cells, α4β7 integrin, that is involved in the trafficking of cells to the gut. As there is evidence that HIV can interact with the α4β7 integrin in a manner that enhances transmission and viral replication,[40,41] researchers at NIAID are on the verge of initiating a trial that will evaluate whether vedolizumab administration can suppress viral load during an ART interruption. The approach has shown activity in the SIV/macaque model,[42] but some laboratory experiments have suggested that the capacity to bind to the α4β7 integrin is uncommon among HIV isolates;[43] the NIAID study should reveal whether there is a relationship between HIV and α4β7 integrins that can be targeted therapeutically.

Protein Kinase C (PKC) Agonists

Many laboratory studies have identified PKC agonists as having the potential to reverse HIV latency.[44,45] Recently, results of the first human trial of the PKC agonist bryostatin-1 were published, demonstrating that a single, low dose of the drug appears to be safe in individuals on ART, but the study did not show activity against the latent HIV reservoir.[46] The researchers now aim to explore the effects of multiple doses and combinations with other candidate LRAs.

Sulggi Lee and colleagues at the University of California, San Francisco are hoping to soon launch a trial of a plant extract used in traditional Chinese medicine, kansui, on the basis that it contains PKC agonists with latency-reversing activity known as ingenols.[47] The product is delivered as a tea made from powder extracted from the plant *Euphorbia kansui*.

Broadly Neutralizing Antibodies

An increasing number of highly potent antibodies that are capable of neutralizing a broad array of differing HIV isolates (broadly neutralizing antibodies, or bNAbs) are becoming available for use in both prevention and cure research. In the latter context, there is interest in investigating whether bNAbs can promote clearance of HIV-infected cells via effector functions such as antibody-mediated cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP).[48,49]

At CROI 2016, two presentations debuted data from trials of the bNAb VRC01 in HIV-positive people undergoing ART interruptions. Katherine Bar from the University of Pennsylvania described results from a trial involving three infusions of VRC01, given before and after an interruption of ART to assess whether viral load rebound would be delayed.[50] The antibody was safe and well tolerated, but there was only a slight hint of a short-term delay in the return of detectable viral load compared with historical controls, which evanesced by eight weeks of post-interruption follow up. Bar highlighted the need to better understand the relationship between HIV neutralization measured in laboratory assays and antibody potency in people, and suggested that combinations of different bNAbs will likely be required to improve results. Another similar trial conducted by Tae-Wook Chun at the NIAID was presented at CROI 2016 as a poster, reporting broadly consistent findings.[51] Results from several trials of newer bNAbs that appear to be more potent than VRC01 are pending.

Deferiprone

Several years ago there was a wave of media coverage regarding a study suggesting that ciclopirox, an antifungal drug, or deferiprone, an iron chelator that is used to treat thalassemia, might be able to promote the apoptotic death of HIV-infected cells.[52] In May of 2016, results of a small pilot trial of deferiprone in ART-naive HIV-positive people in South Africa were published, claiming evidence of mild antiretroviral activity in a small number of individuals with deferiprone levels above a certain threshold.[53] A variety of side effects were also reported, including elevations in transaminases and serum liver enzymes, and over a third of participants assigned to the highest dose did not complete the study. The researchers nevertheless continue to investigate the approach, and a second, larger trial—also conducted in South Africa—is now in follow up.

Table 2. Immune-Based Therapy Pipeline 2016

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Losartan	Angiotensin II receptor antagonist, anti-inflammatory	Minneapolis Medical Research Foundation	Phase II
Lubiprostone	Apical lumen CIC-2 chloride channel activator	Ruth M. Rothstein CORE Center/Chicago Developmental Center for AIDS Research	Phase II
Methotrexate (low dose)	Anti-inflammatory	NIAID	Phase II
Metformin	Biguanide antidiabetic	University of Hawaii/National Institute of General Medical Sciences	Phase II
Niacin	Vitamin B3	McGill University Health Center/Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network	Phase II
VSL#3	Probiotic	Virginia Commonwealth University/ Bill & Melinda Gates Foundation University Health Network, Toronto/ CIHR Canadian HIV Trials Network	Phase II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Lactobacillus sasei shirota	Probiotic	University of Sao Paulo General Hospital	Phase II
Isotretinoin	13-cis retinoic acid	NIAID	Phase II
Dipyridamole	Phosphodiesterase type 5 inhibitor, anti-inflammatory	Sharon Riddler, University of Pittsburgh/NIAID	Phase I/II
Mesenchymal stem cells	Allogenic adult mesenchymal stem cells from adipose tissue	Iniciativa Andaluza en Terapias Avanzadas – Fundación Pública Andaluza Progreso y Salud	Phase I//II
***Tripterygium wilfordii* Hook F**	Traditional Chinese medicine, anti-inflammatory	Beijing 302 Hospital Peking Union Medical College	Phase I/II
Umbilical cord mesenchymal stem cells	Adult stem cells originating from the mesenchymal and connective tissues	Beijing 302 Hospital	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
Aprepitant	Neurokinin 1 receptor antagonist	University of Pennsylvania	Phase I
HLA-B*57 cell transfer	Cell infusion	NIH Clinical Center	Phase I

As explained in the introduction, the pursuit of immune-based adjuncts to ART now represents a small niche in the HIV research portfolio with essentially no significant industry interest. Much of the work in this area involves probiotic supplements, which are available over the counter, but are typically expensive, and, despite some evidence of beneficial effects, the data are unfortunately insufficient to offer a great deal of guidance as to how best they might be used.

Over the past year, two additional probiotic studies have been published that appear somewhat consistent with findings from a randomized trial of *Saccharomyces boulardii*[54] that was described in the 2015 *Pipeline Report*. Birgitte Stiksrud and colleagues from Oslo University Hospital in Norway conducted a small trial of multistrain probiotics delivered in the form of fermented skimmed milk supplemented with *Lactobacillus rhamnosus GG, Bifidobacterium animalis* subsp. *lactis* B-12 and *Lactobacillus acidophilus*. A total of 32 HIV-positive people on ART with CD4 T cell counts below 500 participated and were randomly assigned to receive the intervention (15), placebo (9), or to serve as untreated controls (8). After eight weeks, a significant 33% decline in levels of D-dimer—a coagulation biomarker that is associated with risk of mortality[55]—was observed, along with falls in levels of the inflammatory biomarkers C-reactive protein and IL-6, which did not quite crest the threshold for statistical significance.

The second study was performed by Gabriella d'Ettorre and colleagues from the University of Rome, and administered a probiotic containing *Streptococcus salivarius* ssp. *Termophilus*, Bifidobacteria represented by *B. breve, B. infantis*, and *B. longum, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus delbrueckii* ssp. *Bulgaricus*, and *Streptococcus faecium*. The supplement was taken for 48 weeks, twice a day. A total of 20 HIV-positive participants on suppressive ART were enrolled together with 11 HIV-negative controls. The researchers documented significant declines in levels of immune activation markers on CD4 T cells, high-sensitivity C-reactive protein and lipopolysaccharide binding protein (LBP). In contrast to the Norwegian study, D-dimer levels did not change significantly.

The reason for listing the multifarious species of bacteria used in these trials is to highlight the daunting complexity that lies behind the deceptively simple term probiotic. With relatively little else on offer to address

the residual inflammation and immune activation that can persist despite ART, there is a need to try and pull together the scattered data suggesting that probiotics could be helpful and to design research that could provide clear guidance as to how best they might be used. TAG's recommendation is that a research funder—perhaps the Bill & Melinda Gates Foundation, who are co-sponsoring an ongoing trial of the probiotic VSL#3 in HIV-positive individuals—convene a workshop for investigators to generate a scientific agenda for resolving uncertainties about the value of probiotics as adjuncts to ART.

CONCLUSION

The expansion of clinical research into curing HIV infection continues in 2016; seen in light of Mao's view on the benefits of many blooming flowers, this offers reasons for optimism that encouraging data is likely to emerge from at least some trials. A counterbalancing cause for caution is that, thus far, the HIV reservoir that persists despite ART is proving stubbornly difficult to reduce. The latest news on the state of the field can be expected to emerge from the IAS Towards an HIV Cure Symposium that will take place in Durban, South Africa, July 16–17, and the NIH-sponsored Strategies for an HIV Cure workshop, which is scheduled for November 14–16 in Bethesda, Maryland, U.S.A.

Efforts to develop immune-based enhancements to ART remain on the backburner, at least relatively speaking. But activists and researchers are seeking ways to ensure that the work carries on, as there is evidence that an effective intervention could address residual risks of morbidity and mortality, particularly in immunologic non-responders. It is possible that the strategies being studied in the context of curing HIV will turn out to have potential as additions to ART, and it is important that results from trials are viewed with this possibility in mind to avoid potential therapies being discarded prematurely.

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