Pipeline Report » 2019

Research Toward a Cure and Immune-Based Therapies

TAG

Treatment Action Group

Dedication

Dedicated to the pioneering HIV/AIDS treatment education and advocacy organization Project Inform, and all the people who worked and volunteered there over the years.

Thank you to Blythe Terrell for exceptionally sharp-eyed copyediting.

Research Toward a Cure and Immune-Based Therapies Pipeline 2019

By Richard Jefferys

Introduction

For more than a decade, Timothy Ray Brown has been an inspiration for the cure research field, being the only person in the world considered cured of HIV infection. In 2019, news emerged that he might finally have some company: Two people who may have been cured under similarly challenging circumstances were described in March at CROI.[1,2]

CROI is the Conference on Retroviruses and Opportunistic Infections, the largest annual scientific meeting on HIV/AIDS in North America.

Both cases involved stem cell transplants administered because of life-threatening cancer diagnoses that hadn't responded to standard treatments, and antiretroviral therapy (ART) was eventually interrupted after the transplant without any sign of HIV viral load rebound. At the time of CROI, the duration of follow-up off ART was about 18 months for one person and 3.5 months for the other, so researchers are being cautious and using the term remission rather than cure. As with Brown, the stem cell transplants came from donors homozygous for the CCR5Δ32 mutation, which prevents expression of a functional CCR5 receptor on cells, essentially equipping the recipients with a new, HIV-resistant immune system.

Most HIV strains require the CCR5 receptor to enter and infect target cells, although less common variants can use an alternate receptor, CXCR4.

The possibility of additional cure cases is undoubtedly a welcome fillip for the research effort, and the news generated headlines globally, but it remains unclear how much can be learned that might contribute to developing broadly applicable curative interventions. There are some differences in how the stem cell transplants were carried out in these individuals—currently known as the London and Dusseldorf patients—compared with Brown, which may help researchers home in on the key mechanisms underlying the outcomes.[3] For example, Brown received total body irradiation, and there was speculation that this played a role in his HIV cure. But it was not administered in the new cases.

There is widespread agreement that the use of stem cells from donors homozygous for the CCR5Δ32 mutation has been critical to preventing a return of HIV. Evidence for this conclusion comes from three examples of HIV-positive people with cancer diagnoses who received stem cell transplants from donors lacking the mutation. These three subsequently experienced only transient periods of virologic remission (lasting about 3 to 10 months) after an ART interruption.

The central role of CCR5 underpins the part of the cure research pipeline focused on attempting to protect vulnerable cells—particularly CD4+ T cells—from HIV infection. The leading approaches involve the use of gene therapies to abrogate CCR5 expression or introduce other modifications capable of rebuffing the virus from entering or productively infecting cells.

Recently, however, a study has raised concerns about the safety of strategies based on CCR5 deletion. In an analysis of a database of people living in the United Kingdom,

researchers found that being homozygous for the CCR5Δ32 mutation was associated with a reduction in longevity, due to a 21 percent increase in the all-cause mortality rate.[4] In the accompanying news coverage, senior author Rasmus Nielsen stated that this likely reflected a nearly two-year shortening of life span on average.[5] The underlying cause is unproven, but it might be related to the higher risk of mortality from influenza reported among CCR5Δ32 homozygotes.[6] The relevance of these findings to populations outside of the UK will need to be assessed, but they underscore the evidence that the CCR5 receptor has potentially important biological functions (a previously documented example is its role in the immune response to West Nile Virus[7]).

The implications for targeting CCR5 in HIV cure research are somewhat uncertain, but current efforts to ablate the receptor with gene therapies involve modifying CD4+ T cells or stem cells in the laboratory and then infusing them, which creates only a small population of modified cells in the body, and it is considered unlikely that this would mimic what occurs in CCR5Δ32 homozygotes (who lack any functional CCR5 receptors).

For people with HIV and cancers who receive stem cell transplants from donors homozygous for the CCR5Δ32 mutation, the risk/benefit is still likely to be favorable. The risk to life expectancy posed by HIV and the cancer would be greater than that reported in the newly published analysis of CCR5Δ32 homozygotes.

The potentially deleterious impact of CCR5Δ32 homozygosity on life span is directly relevant to one situation: the profoundly unethical effort to create people lacking functional CCR5 receptors by genetically editing embryos, reported by Chinese scientist He Jiankui in the fall of 2018[8] (He's research has since been stopped[9]). There are already multiple reasons why this should not be attempted,[10] and Rasmus Nielsen's results add another.

Beyond the encouraging news of potential new cure cases, a broad spectrum of research is continuing with the aim of generating data that can contribute to the development of scalable curative interventions for the majority of people with HIV (not just those with refractory cancers requiring stem cell transplants). As of June 2019, there are 96 interventional trials listed in clinical trial registries—four of which involve techniques seeking to image HIV or its effects on the body, not therapeutic candidates—and 37 observational studies (see Table 1).

In the summer of 2018, Liz Barr from the Women's HIV Research Collaborative and AIDS Clinical Trials Group Global Community Advisory Board led a landscape analysis of cure-related clinical trials for TAG, with support from the Bill & Melinda Gates Foundation.[11] The findings indicate that over 7,000 people are likely to participate in the current tranche of studies, but—as has been reported by prior analyses[12,13]—there remains a significant lack of diversity among participants, with a notable underrepresentation of women. Addressing this issue will be important to ensure that results are generalizable. There is evidence for potentially significant sex differences in parameters relating to HIV persistence in the body,[14,15] and possibly also in responses to toll-like receptor agonists,[16] which are under investigation as immune modulators in cure research.

Analytical treatment interruptions (ATIs)

Thirty studies cite the inclusion of an analytical treatment interruption (the temporary suspension of ART), although in some cases, this is only triggered if certain criteria are met. As noted in the 2018 Pipeline Report, a meeting was held on July 9, 2018, at the Ragon Institute of the Massachusetts General Hospital, the Massachusetts Institute of Technology, and Harvard to generate consensus guidelines on the use of ATIs in HIV cure research, and the recommendations have now been published in The Lancet HIV[17] (access is free with registration to the journal website). TAG has also surveyed community advocates to solicit their views on the topic and generated a complementary report outlining responses and offering recommendations.[18]

So far, there have been no major therapeutic breakthroughs that would suggest a broadly efficacious curative approach is on the horizon. But there has been progress on several fronts.

The laboratory of Robert Siliciano at Johns Hopkins University has developed an assay that appears to be able to more efficiently distinguish the fraction of the HIV reservoir that is made up of intact, replication-competent virus.[19] This is important because a large proportion of the HIV DNA that can be detected in people on ART is defective, and it has been challenging to discern which cells contain viruses that are functional. The new assay should allow more accurate measurement of the effects of therapeutic interventions.

Researchers have also learned that the proliferation of CD4+ T cells containing HIV plays a key role in sustaining the reservoir in people on ART. CD4+ T cells copy or "clone" themselves as part of the normal maintenance of their numbers, and in the rare cases where HIV has integrated into the genome of a CD4+ T cell, the virus's genetic code is duplicated along with the host cell's. The proliferation of CD4+ T cells containing integrated HIV can be tracked because each copy of the virus is an exact genetic match and is located in the same place within the cell's genome.[20] When HIV is replicating, the copies that get made are genetically varied because the replication process is error-prone.

A mathematical modeling study published in late 2018 reports that CD4+ T cell proliferation may be the primary mechanism that allows the latent HIV reservoir to persist in people on ART and decline only very slowly over time.[21] These findings raise the possibility that anti-proliferative drugs could accelerate the decay of latently infected cells,[22] and the theory is being tested in a small phase I trial of the drug mycophenolate mofetil (MMF) at the Fred Hutchinson Cancer Research Institute (see Table 1).

At the 2018 International AIDS Conference, novel evidence was presented that a substantial portion of the HIV reservoir is formed around the time ART is initiated.[23] The results are preliminary, but they offer a rationale for testing whether anti-reservoir strategies might be more effective if administered when ART is being started. Up until now, candidates have typically been tested in people who have achieved viral load suppression on ART before entering the trials.

The identification of markers that are preferentially expressed by cells containing the reservoir of HIV remains something of a Holy Grail for cure researchers, as it might allow for superior targeting of anti-reservoir approaches. In early 2017, the molecule CD32a was reported to be a contender,[24] but multiple subsequent studies have called the claim into question.[25,26,27,28,29,30,31] A poster presented at CROI 2019 suggested that technical issues may explain the discrepancies,[32] but the debate is as yet unresolved. Combinations of the immune checkpoint molecules PD-1 and TIGIT, together with the integrin α4β1, emerged as potential markers in a study published earlier this year.[33]

University of California, San Francisco

Timothy Henrich's laboratory at **UCSF** has published evidence that CD30 may offer a means to home in on HIV-infected cells.[34] What makes CD30 distinct from the other possibilities is that there is an approved anti-cancer agent, brentuximab vedotin, that targets the molecule because of its expression by tumor cells in Hodgkin's lymphoma and anaplastic large-cell lymphoma. Henrich and colleagues have documented two cases of people with HIV who have received brentuximab vedotin as a cancer therapy, and it appeared to be associated with declines in residual HIV levels.[35] In addition to brentuximab vedotin, there are chimeric antigen receptor (CAR) T cell gene therapies designed to eliminate CD30-expressing cells in early-phase cancer trials,[36] potentially opening up another avenue of investigation.

The immune-based therapy field remains extremely fallow (see Table 2), even though there is a rationale for trying to promote immune recovery in people who do not experience robust CD4+ T cell count increases on ART.[37] The associations that have been documented between inflammatory biomarkers and morbidity and mortality on ART[38] have spurred interest in testing adjunctive anti-inflammatory therapies, but there appears to be little commercial interest, with only one clinical trial sponsored by a small biopharmaceutical company. As has consistently been the case in recent years, academic researchers have initiated the bulk of the research.

By far the largest clinical trial of an anti-inflammatory drug in HIV is the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), which is primarily assessing the effects of pitavastatin calcium (Livalo) on heart disease in 7,500 participants. Statin drugs also lower cholesterol, so they are not strictly immune-based therapies, but the trial—which is now fully enrolled[39]—promises to contribute significantly to understanding the health impact of modulating inflammation in people on ART.

Table 1. Research Toward a Cure 2019: Current Clinical Trials and Observational Studies

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
ADOPTIVE IMMUNOTHERAPY					
HIV-1 specific T-cells for HIV-infected individuals	HIV-specific T cells with non-escaped epitope targeting (HST-NEETs)	NCT03485963	Children's Research Institute	USA	Phase I
ANTIBODIES					
UB-421	Antibody inhibitor of HIV binding to CD4 receptors	NCT03743376 (not yet open for enrollment)	United BioPharma	Taiwan	Phase II
vedolizumab	Anti-α4β7 integrin antibody, ATI	NCT03577782	Hospitales Universitarios Virgen del Rocío	Spain	Phase II
vedolizumab	Anti-α4β7 integrin antibody, ATI	NCT03147859	Ottawa Hospital Research Institute	Canada	Phase II
PGT121 + VRC07-523LS +/- PGDM1400	Broadly neutralizing antibody + long-acting broadly neutralizing antibody	NCT03721510	International AIDS Vaccine Initiative	USA	Phase I/IIa
VRC01	Broadly neutralizing antibody in infants	NCT03208231	NIAID	Botswana, Brazil, Malawi, South Africa, USA, Zimbabwe	Phase I/II
VRC01LS + 10-1074	Long-acting broadly neutralizing antibody + broadly neutralizing antibody in early-treated children, ATI	NCT03707977 (not yet open for enrollment)	NIAID	Botswana	Phase I/II
10-1074-LS +/- 3BNC117-LS	Long-acting broadly neutralizing antibodies	NCT03554408	Rockefeller University	USA	Phase I
10E8.4/iMab	Bi-specific broadly neutralizing antibody	NCT03875209	Aaron Diamond AIDS Research Center	USA	Phase I
3BNC117 + 10-1074	Broadly neutralizing antibodies, ATI	NCT03571204	NIAID	USA	Phase I
3BNC117 + 10-1074	Broadly neutralizing antibodies, ATI	NCT03526848	Rockefeller University	USA	Phase I
3BNC117-LS	Long-acting broadly neutralizing antibody	NCT03254277	Rockefeller University	USA	Phase I
AAV8-VRC07	Broadly neutralizing antibody delivered by adeno-associated virus (AAV) vector	NCT03374202	NIAID	USA	Phase I

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
GS-9722	PGT121-derived broadly neutralizing antibody	Not listed in clinicaltrials.gov	Gilead Sciences	USA	Phase I
PGDM1400 +/- PGT121	Broadly neutralizing antibodies	NCT03205917	International AIDS Vaccine Initiative	USA	Phase I
PGT121	Broadly neutralizing antibody	NCT02960581 (enrolling by invitation only)	International AIDS Vaccine Initiative	USA	Phase I
SAR441236	Tri-specific broadly neutralizing antibody	NCT03705169	NIAID	USA	Phase I
VRC01 + 10-1074	Broadly neutralizing antibodies, ATI	NCT03831945	NIAID	USA	Phase I
VRC01LS, VRC07-523LS	Long-acting broadly neutralizing antibody	NCT02840474 (closed to enrollment)	NIAID	USA	Phase I
VRC01	Broadly neutralizing antibody in acute HIV infection	NCT02591420	NIAID	Kenya, Tanzania, Thailand, Uganda	Phase I
ANTI-INFLAMMATORY					
canakinumab	IL-1β inhibitor	NCT02272946 (closed to enrollment)	University of California, San Francisco	USA	Phase II
CD24Fc	Human CD24 extracellular domain and human IgG1 Fc fusion protein	NCT03960541 (not yet open for enrollment)	OncoImmune	USA	Phase II
ANTI-PROLIFERATIVE					
mycophenolate mofetil (MMF)	Inosine-5′-monophosphate dehydrogenase inhibitor	NCT03262441	Fred Hutchinson Cancer Research Center	USA	Phase II
CANNABINOIDS					
TN-CT11LM, TN-TC19LM	Oral capsules containing Δ9-tetrahydrocannabinol and cannabidiol in two different ratios	NCT03550352 (not yet open for enrollment)	McGill University Health Center	Canada	Phase II
COMBINATIONS					
maraviroc, dolutegravir, dendritic cell vaccine, auranofin, nicotinamide	CCR5 inhibitor, integrase inhibitor, therapeutic vaccine, anti-proliferative + HDAC inhibitor	NCT02961829 (closed to enrollment)	Federal University of São Paulo	Brazil	Not listed
Perturbing of HIV reservoir with immune stimulation: Fluarix, Pneumovax vaccines	Influenza and pneumococcus vaccines	NCT02707692	University of California, San Diego	USA	Not listed

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
Impact of sirolimus and maraviroc on CCR5 expression and the HIV-1 reservoir in HIV+ kidney transplant recipients	mTOR inhibitor + CCR5 inhibitor	NCT02990312	University of Maryland	USA	Phase IV
ROADMAP: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody, ATI	NCT02850016 (closed to enrollment)	Rockefeller University	Denmark, Germany, USA	Phase IIa
TITAN: lefitolimod +/- 3BNC117 + 10-1074	TLR9 agonist +/- broadly neutralizing antibodies, ATI	NCT03837756	University of Aarhus	Denmark, Australia, USA	Phase IIa
eCLEAR: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody	NCT03041012	Aarhus University Hospital	Denmark	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	UK	Phase II
iHIVARNA, MVA vector HIV vaccine, 10-1074, romidepsin, HIVACAR01	Therapeutic vaccines, broadly neutralizing antibody, HDAC inhibitor, ATI	NCT03619278 (not yet open for enrollment)	David Garcia Cinca	Spain	Phase I/IIa
ACTIVATE: panobinostat + pegylated interferon-alpha2a	HDAC inhibitor + cytokine	NCT02471430	Massachusetts General Hospital	USA	Phase II
GTU-MultiHIV B-clade + MVA HIV-B +/- vedolizumab	DNA + viral vector vaccines +/- anti-$\alpha_4\beta_7$ integrin antibody in people who started ART during primary or chronic infection, ATI	NCT02972450 (not yet open for enrollment)	Inserm-ANRS	France, Germany, Italy, Spain, Switzerland, UK, USA	Phase I/II
IMPAACT P1115 v2.0: very early intensive treatment of HIV-infected infants to achieve HIV remission (ART +/- VRC01)	Combination antiretroviral therapy, VRC01 broadly neutralizing antibody, ATI	NCT02140255	IMPAACT/NIAID/NICHD	Argentina, Brazil, Haiti, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, USA, Zambia, Zimbabwe	Phase I/II
haploidentical NK cells + N-803	Adoptive transfer of haploidentical natural killer (NK) cells + recombinant human superagonist interleukin-15 complex	NCT03899480	University of Minnesota - Clinical and Translational Science Institute	USA	Phase I
CD4-ZETA +/- interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	USA	Phase I
chidamide + CAR-T or TCR-T cell therapy	HDAC inhibitor + chimeric antigen receptor T cells	NCT03980691	Guangzhou 8th People's Hospital	China	Phase I

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
DCV3 +/- pegylated interferon	Dendritic-cell-based vaccine pulsed with autologous heat-inactivated HIV +/- cytokine, ATI	NCT02767193	Judit Pich Martínez, Fundació Clínic per a la Recerca Biomèdica	Spain	Phase I
peginterferon alfa-2b + 3BNC117 + 10-1074	Cytokine, broadly neutralizing antibodies, ATI	NCT03588715 (not yet open for enrollment)	Wistar Institute	USA	Phase I
VRC07-523LS + vorinostat		NCT03803605	University of North Carolina, Chapel Hill	USA	Phase I
vorinostat + HXTC: HIV-1 antigen expanded specific T cell therapy	HDAC inhibitor + adoptive immunotherapy	NCT03212989	University of North Carolina, Chapel Hill	USA	Phase I
vorinostat +/- tamoxifen in postmenopausal women	HDAC inhibitor + estrogen receptor modulator	NCT03382834 (closed to enrollment)	NIAID	USA	Phase I
CYTOKINES					
interleukin-2 (IL-2)	Cytokine	NCT03308786	Case Western Reserve University	USA	Phase II
ALT-803	Recombinant human superagonist interleukin-15 complex	NCT02191098	University of Minnesota - Clinical and Translational Science Institute	USA	Phase I
DUAL-AFFINITY RE-TARGETING (DART) MOLECULES					
MGD014	Bi-specific DART molecule targeting the HIV Env protein and CD3-expressing T cells	NCT03570918	MacroGenics	USA	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)	NCT02390297 (long-term safety phase)	Calimmune	USA	Phase I/II
SB-728-T	Autologous CD4+ T cells modified to inhibit CCR5 expression	NCT03666871 (not yet open for enrollment)	Case Western Reserve University	USA	Phase I/II
VRX496	Autologous CD4+ T cells modified with an antisense gene targeting the HIV envelope, ATI	NCT00295477 (closed to enrollment)	University of Pennsylvania	USA	Phase I/II

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
C34-CXCR4	Autologous CD4+ T cells gene-modified to express HIV-inhibiting peptide C34, ATI	NCT03020524 (closed to enrollment)	University of Pennsylvania	USA	Phase I
CD4 CAR + C34-CXCR4 + SB-728mR modified T cells	Autologous CD4+ T cells gene-modified to inhibit CCR5 expression and express the HIV-inhibiting peptide C34 and a chimeric antigen receptor (CAR), ATI	NCT03617198 (not yet open for enrollment)	University of Pennsylvania	USA	Phase I
Chimeric antigen receptor (CAR) T cell therapy	Autologous T cells gene-modified to express a chimeric antigen receptor targeting HIV	NCT03240328	Guangzhou 8th People's Hospital	China	Phase I
SB-728mR-HSPC	Autologous hematopoietic stem/progenitor cells gene-modified to inhibit CCR5 expression, ATI	NCT02500849 (closed to enrollment)	City of Hope Medical Center	USA	Phase I
shRNA-modified CD34+ cells	Infusion of autologous CD34+ cells transduced with short hairpin RNAs targeting CCR5 and the HIV genome	NCT03517631	Shanghai Public Health Clinical Center	China	Phase I
anti-gp120 CAR-T cells	Autologous T cells gene-modified to express a chimeric antigen receptor targeting HIV gp120	ChiC-TR-OPN-17013068 (not yet open for enrollment)	Jinyintan Hospital of WuHan	China	Phase 0
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS					
Stem cells gene-modified with Cal-1 in HIV-1-related high-risk lymphoma	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 and a fusion inhibitor (C46), ATI	NCT03593187	Assistance Publique - Hôpitaux de Paris	France	Phase I/II
Gene therapy in treating patients with HIV-related lymphoma receiving stem cell transplant	Stem cells gene-modified with CCR5 shRNA/ TRIM5alpha/TAR decoy	NCT02797470	AIDS Malignancy Consortium	USA	Phase I/II
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, ATI	NCT03164135	307 Hospital of PLA (Affiliated Hospital of Academy to Military Medical Sciences)	China	Not listed
Gene therapy and combination chemotherapy in treating patients with AIDS-related non-Hodgkin's lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (rHIV7-shI-TAR-CCR5RZ), ATI	NCT02337985 (closed to enrollment)	City of Hope Medical Center	USA	Phase I

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
Busulfan and gene therapy after front-line chemotherapy in patients with AIDS-related non-Hodgkin's lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (rHIV7-shI-TAR-CCR5RZ) + cyclophosphamide conditioning, ATI	NCT01961063 (closed to enrollment)	City of Hope Medical Center	USA	Phase I
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 (rHIV7-shI-TAR-CCR5RZ), ATI	NCT00569985 (closed to enrollment)	City of Hope Medical Center	USA	Phase I
GONADOTROPIN-RELEASING HORMONE (GnRH) AGONISTS					
triptorelin acetate depot		NCT03536234	Immune System Regulation AB	Sweden	Phase II
HORMONES					
somatotropin	Human growth hormone	NCT03091374	McGill University Health Center	Canada	Phase II
IMAGING STUDIES					
123I radiolabeled 3BNC117	Radiolabeled broadly neutralizing antibody	NCT03468582	University of Lausanne Hospitals	Switzerland	Phase I
Imaging immune activation in HIV by PET-MR		NCT03684655	University of California, San Francisco	USA	Phase I
3BNC117 + Copper-64 radio isotope followed by MRI/PET scanning to detect HIV in vivo	Radiolabeled broadly neutralizing antibody	NCT03063788	Bayside Health	Australia	Phase I
Radiolabeled VRC01	Radiolabeled broadly neutralizing antibody	NCT03729752	University of California, San Francisco	USA	Phase I
IMMUNE CHECKPOINT INHIBITORS					
durvalumab in solid tumors	Anti-PD-L1 antibody	NCT03094286 (closed to enrollment)	Spanish Lung Cancer Group	Spain	Phase II
cemiplimab	Anti-PD-1 antibody	NCT03787095	NIAID	USA	Phase I/II
nivolumab + ipilimumab	Anti-PD-1 antibody + anti-CTLA-4 antibody in people with advanced HIV-associated solid tumors	NCT02408861	National Cancer Institute	USA	Phase I

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
pembrolizumab	Anti-PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms	NCT02595866	National Cancer Institute	USA	Phase I
pembrolizumab	Anti-PD-1 antibody, single dose	NCT03239899	National Institute of Neurological Disorders and Stroke	USA	Phase I
LATENCY-REVERSING AGENTS					
chidamide	HDAC inhibitor	NCT02902185 (closed to enrollment)	Tang-Du Hospital	China	Phase II/III
valproic acid + pyrimethamine	HDAC inhibitor, BAF inhibitor	NCT03525730	Erasmus Medical Center	Netherlands	Phase I/II
arsenic trioxide	Chemotherapy	NCT03980665	Guangzhou 8th People's Hospital	China	Phase I
kansui	Traditional Chinese medicine containing ingenols	NCT02531295	University of California, San Francisco	USA	Phase I
OBSERVATIONAL STUDIES					
2000 HIV Human Functional Genomics Partnership Program (2000HIV)		NCT03994835 (not yet open for enrollment)	Radboud University	Netherlands	N/A
Accurate staging of immuno-virological dynamics during acute HIV infection (ACS)		NCT03449706	University Hospital, Ghent	Belgium	N/A
Analytic treatment interruption (ATI) to assess HIV cure	ATI	NCT02437526 (enrolling by invitation only)	Mayo Clinic	USA	N/A
ANRS CO24 OncoVIHAC: immune checkpoint inhibitors in HIV+ individuals with cancers		NCT03354936	Inserm-ANRS	France	N/A
ANRS EP63: a chronological study of the formation of HIV cellular reservoirs through the expression of surface markers on CD4+ T lymphocytes, including CD32a		NCT03298360	Inserm-ANRS	France	N/A
ACTG A5345: biomarkers to predict time to plasma HIV RNA rebound	ATI	NCT03001128	AIDS Clinical Trials Group	USA	N/A

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
CLEAC	Comparison of late versus early antiretroviral therapy in HIV-infected children	NCT02674867 (closed to enrollment)	Inserm-ANRS	France	N/A
CODEX (the 'Extreme' cohort)	Long-term non-progressors and HIV controllers	NCT01520844	Inserm-ANRS	France	N/A
Developing a functional cure for HIV disease: clinical specimen collection from HIV+ individuals	Determination of levels of HIV-reactive CD4+ T cells, possible leukapheresis	NCT03215004	American Gene Technologies International	USA	N/A
EPIC4	Early pediatric treatment initiation cohort study	CTN S 281	Canadian Institutes of Health Research/ Canadian Foundation for AIDS Research/International AIDS Society	Canada	N/A
Establish and characterize an acute HIV infection cohort in a high-risk population		NCT00796146	South East Asia Research Collaboration with Hawaii/ Armed Forces Research Institute of Medical Sciences/Thai Red Cross AIDS Research Centre	Thailand	N/A
FRESH (females rising through education, support, and health)	Early diagnosis, treatment and support for women at high risk for HIV infection	No clinicaltrials.gov entry	Ragon Institute of MGH, MIT and Harvard	South Africa	N/A
FXReservoir: study of the effects of farnesoid X receptor (FXR) ligands on the reactivation of latent provirus		NCT03618862 (not yet open for enrollment)	Hospices Civils de Lyon	France	N/A
Genotyping FcγRs genes		NCT03130296	University Hospital, Strasbourg	France	N/A
HCURE: analysis of the impact of HCV treatment by last generation direct antiviral agents (DAAs) on antiviral Immunity and HIV DNA reservoir in coinfected HIV-HCV patients		NCT03244371	Assistance Publique Hopitaux De Marseille	France	N/A

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
HEATHER	HIV reservoir targeting with early antiretroviral therapy	UK CPMS17589	University of Oxford/Medical Research Council/British HIV Association	UK	N/A
HIV-PRADA: HIV persistence in lymph node and peripheral blood		NCT03426189 (closed to enrollment)	University of Melbourne	Australia	N/A
HIV-STAR: HIV sequencing after ATI to identify the clinically relevant anatomical reservoir	ATI	NCT02641756 (closed to enrollment)	University Hospital, Ghent	Belgium	N/A
Host and viral factors associated with HIV elite control		UK CPMS16146	University College London Hospitals NHS Foundation Trust	UK	N/A
HSCT-HIV: Allogeneic hematopoietic stem cell transplantation in HIV-1-infected patients		NCT02732457	Kirby Institute	Australia	N/A
IciStem	Collaborative project to guide and investigate the potential for HIV cure in HIV+ patients requiring allogeneic stem cell transplantation for hematological disorders	No clinicaltrials.gov entry	amfAR	International	N/A
Identification and quantification of HIV CNS latency biomarkers		NCT02989285	St Vincent's Hospital, Sydney	Australia	N/A
IMPAACT 2015: evaluation of the HIV-1 reservoir in the CNS of perinatally infected youth and young adults with cognitive impairment		NCT03416790 (enrolling by invitation only)	IMPAACT	USA	N/A
Impact of a short-term analytical treatment interruption and re-initiation of antiretroviral therapy on immunologic and virologic parameters in HIV+ individuals	ATI	NCT03225118 (closed to enrollment)	NIAID	USA	N/A
Impact of ART adherence on HIV persistence and inflammation		NCT02797093 (closed to enrollment)	University of Colorado, Denver	USA	N/A

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
Long-term effects of ART in acute HIV infection		ChiCTR1800015006 (not yet open for enrollment)	Key Laboratory of AIDS Immunology of National Health and Family Planning Commission, Department of Laboratory Medicine, The First Affiliated Hospital, China Medical University	China	N/A
LoViReT: Low viral reservoir treated patients		NCT02972931 (closed to enrollment)	IrsiCaixa	Spain	N/A
PembroHIV: treatment with immunological checkpoint inhibitors of HIV+ individuals with cancer		NCT03767465	IrsiCaixa	Spain	N/A
Post-analytic treatment interruption study		NCT02761200	South East Asia Research Collaboration with Hawaii	Thailand	N/A
Primary infection cohort (PRIMO)		NCT03148964	Inserm-ANRS	France	N/A
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans		NCT02154035 (closed to enrollment)	NIAID	Uganda	N/A
RESERVIH32: bioclinical evaluation of two biomarkers of aviremic HIV-1 in CD4 T cells of adults undergoing treatment		NCT03940521 (not yet open for enrollment)	Centre Hospitalier Universitaire de Nîmes	France	N/A
Role of the IL-33/amphiregulin pathway as a potential therapeutic target in HIV infection		NCT03622177 (not yet open for enrollment)	Inserm-ANRS	France	N/A
Specimen repository for HIV immunopathogenesis		NCT03579381	AIDS Healthcare Foundation	USA	N/A
TESOVIR	Tracking and exploring the source of viral rebound after ATI	NCT03117985	Centre Hospitalier Régional d'Orléans	France	N/A
The use of leukapheresis to support HIV pathogenesis studies		NCT01161199	University of California, San Francisco	USA	N/A

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
Thinking and memory problems in people with HIV		NCT01875588	National Institute of Neurological Disorders and Stroke	USA	N/A
PROTEASOME INHIBITORS					
ixazomib		NCT02946047 (closed to enrollment)	Mayo Clinic	USA	Phase I/II
RETINOIDS					
acitretin		NCT03753867 (not yet open for enrollment)	Ottawa Hospital Research Institute	Canada	Phase I
STEM CELL TRANSPLANTATION					
HIVECT: HIV eradication through cord-blood transplantation	ATI	NCT02923076	Puerta de Hierro University Hospital	Spain	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	USA	N/A
HLA-mismatched unrelated donor bone marrow transplantation		NCT02793544 (closed to enrollment)	Center for International Blood and Marrow Transplant Research	USA	Phase II
THERAPEUTIC VACCINES					
p24CE1/2 + p55^gag conserved-element DNA vaccines	DNA vaccines	NCT03560258	NIAID	USA	Phase I/II
PENNVAX-GP or INO-6145 + IL-12 DNA adjuvant (INO-9012)	DNA vaccine + DNA adjuvant	NCT03606213	Steven Deeks, University of California, San Francisco	USA	Phase I/II
Ad26.Mos4.HIV + MVA-Mosaic or clade C gp140 + mosaic gp140	Adenovirus and modified Vaccinia Ankara strain vectors encoding mosaic HIV antigens + Env protein boosts	NCT03307915	Janssen Vaccines & Prevention B.V.	USA	Phase I
DC-HIV04: a1DC + inactivated whole autologous HIV, a1DC + conserved HIV peptides		NCT03758625	Sharon Riddler, University of Pittsburgh	USA	Phase I

Trial	Additional description	Trial registry identifier(s)	Manufacturer/ sponsor(s)	Location(s)	Phase
DNA.HTI + MVA.HTI	DNA + modified Vaccinia Ankara strain vector vaccines	NCT03204617 (closed to enrollment)	Aelix Therapeutics	Spain	Phase I
MAG-pDNA + rVSVIN HIV-1 Gag	DNA + viral vector vaccines, ATI	NCT01859325 (closed to enrollment)	NIAID/Profectus Biosciences	USA	Phase I
MVA.tHIVconsv3 +/- MVA.tHIVconsv4	Viral vector vaccines	NCT03844386	University of North Carolina at Chapel Hill	USA	Phase I
TOLL-LIKE RECEPTOR AGONISTS					
vesatolimod in ART-treated HIV controllers	TLR7 agonist, ATI	NCT03060447 (closed to enrollment)	Gilead Sciences	USA	Phase Ib
TREATMENT INTENSIFICATION/EARLY TREATMENT					
LEOPARD: latency and early neonatal provision of antiretroviral drugs clinical trial	Combination antiretroviral therapy	NCT02431975 (closed to enrollment)	Columbia University	South Africa	Phase IV
Antiretroviral regime for viral eradication in newborns	Combination antiretroviral therapy	NCT02712801	National Center for Women and Children's Health, China CDC	China	Phase IV
DGVTAF: immediate initiation of antiretroviral therapy during 'hyperacute' HIV infection	Combination antiretroviral therapy	NCT02656511	University of California, San Francisco	USA	Phase IV
AAHIV/RV254: antiretroviral therapy for acute HIV infection	Combination antiretroviral therapy	NCT00796263	South East Asia Research Collaboration with Hawaii	Thailand	Phase III
tenofovir/emtricitabine + dolutegravir or tenofovir/emtricitabine + darunavir/cobicistat	Combination antiretroviral therapy	NCT02987530 (closed to enrollment)	Inserm-ANRS	France	Phase III
EIT: early infant HIV treatment in Botswana	Combination antiretroviral therapy	NCT02369406	Harvard School of Public Health	Botswana	Phase II/III
EARLIER: early ART to limit infection and establishment of reservoir	Combination antiretroviral therapy	NCT02859558	AIDS Clinical Trials Group	Malawi, Peru, South Africa, Thailand, USA, Zimbabwe	Phase II

ATI = analytical treatment interruption. In some cases (particularly in trials of gene therapies for HIV-positive people with cancers), ATIs will only be conducted if study participants meet certain criteria.

Shaded entries represent additions since the 2018 Pipeline Report.

For the complete 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.

Combinations

The joint-largest category of cure-related clinical trials comprises evaluations of combinations of candidates with different mechanisms of action. Nineteen studies are ongoing, with four having been launched since the 2018 edition of the Pipeline Report.

Researchers at the University of Aarhus in Denmark are leading TITAN, a randomized controlled trial that will test the toll-like receptor 9 agonist lefitolimod together with two broadly neutralizing antibodies (bNAbs), 3BNC117 and 10-1074, in people on ART. Participants will undergo an ATI to explore whether the interventions influence viral load rebound. Prior assessments of lefitolimod in people with HIV demonstrated positive modulation of innate and adaptive immunity, along with possible latency-reversing activity in a subset of participants.[40,41] The combination of 3BNC117 and 10-1074 has been shown to have potent anti-HIV activity and may have contributed to prolonged control of viral load off ART in two recipients.[42]

Timothy Schacker and colleagues at the University of Minnesota have initiated an evaluation of natural killer (NK) cell infusions combined with N-803, a modified version of the cytokine interleukin-15 (IL-15) designed to have increased biological activity and a longer half-life in the body. The NK cells are obtained from family members of participants to ensure a close genetic match and to reduce the risk of immunological rejection. A phase I trial of N-803 (formerly known as ALT-803) conducted by the same research group found that it was safe and produced evidence of enhanced NK cell activation and HIV latency reversal,[43] providing a rationale for the combination trial. IL-15 has also been reported to enhance NK cell-mediated clearance of HIV-infected cells in laboratory experiments.[44]

Two new trials are exploring variations on the “kick and kill” approach, marrying latency-reversing candidates from the histone deacetylase (HDAC) inhibitor class with immune-based therapies. At the Guangzhou Eighth People’s Hospital in China, the HDAC inhibitor chidamide[45] is being combined with T cells that have been genetically modified to target HIV.[46] Researchers at the University of North Carolina are testing vorinostat in tandem with the bNAb VRC07-523LS.

The goal of these studies is to coax latently infected cells to express HIV antigens, facilitating recognition by the modified T cells or bNAb. In addition to directly inhibiting HIV replication, bNAbs can promote the killing of virus-infected cells via antibody-mediated cellular cytotoxicity or antibody-mediated cellular phagocytosis; the bNAbs bind to HIV Env proteins expressed on the surface of infected cells, thereby flagging them for destruction by NK cells or phagocytes.

Initial results from a clinical trial of a kick and kill combination strategy were presented at the 2018 International AIDS Conference.[47] The Research in Viral Eradication of HIV Reservoirs (RIVER) study is taking place in the UK and randomized 60 male participants with primary HIV infection to receive either ART or ART combined with two therapeutic HIV vaccines and a short course of vorinostat.

No safety issues have emerged, but after 16–18 weeks of follow-up, there were no significant differences in the size of the HIV reservoir between the groups, whether

measured by HIV DNA or using a quantitative virus outgrowth assay that captures replication-competent HIV. While disappointing, the results emphasize the importance of randomized, controlled comparisons for evaluating efficacy. Follow up of study participants is ongoing.

Antibodies

There are also 19 trials of antibodies, eight of which have been registered over the past year.

Three of the new protocols are evaluating combinations of bNAbs that have already been studied individually. Of greater novelty are the first-in-human phase I studies of two candidate multispecific antibodies: 10E8.4/iMab and SAR441236. These constructs are single antibodies that have been engineered to recognize multiple targets.

10E8.4/iMab is a bispecific antibody developed by the Aaron Diamond AIDS Research Center that blends the bNAb 10E8v4 with ibalizumab (trade name Trogarzo), a U.S. Food and Drug Administration-approved antibody that binds the CD4 receptor to inhibit HIV entry.[48] SAR441236 is trispecific, combining the HIV-targeting structures of the bNAbs VRC01, PGDM1400 and 10E8v4.[49] The phase I trial of SAR441236 is the fruit of a collaboration between researchers at NIAID and the pharmaceutical company Sanofi.[50]

The National Institute of Allergy and Infectious Diseases

UB-421 is an antibody manufactured by United BioPharma that blocks the interaction between HIV and the CD4 receptor. Results from a small phase II trial were published this year in the *New England Journal of Medicine*, demonstrating that UB-421 monotherapy maintained viral load suppression after an ART interruption.[51] The company is about to start a randomized trial in Taiwan that will assess whether addition of the antibody reduces the HIV reservoir compared with ART alone.

In 2016, there was excitement about the potential of the antibody therapy vedolizumab to provoke post-treatment control of HIV viral load, based on promising results obtained in the SIV/macaque model.[52] Vedolizumab is an FDA-approved treatment for ulcerative colitis and Crohn's disease that binds to α4β7 integrin, a molecule expressed on T cells involved in guiding trafficking to the gut.

NIAID Director Anthony Fauci presented results from the first clinical trial of vedolizumab in HIV during an overview talk on cure research at the 2018 International AIDS Conference; unfortunately the trial did not recapitulate the SIV/macaque data.[53] After an ATI, there was no consistent evidence of control of viral load, although one or two participants appeared to maintain low levels. At the same conference, Fauci's colleague Michele Di Mascio described a failed attempt to duplicate the original macaque study, revealing that the SIV variant that was used may have led to a misleading outcome.[54] Earlier this year the journal that published the initial SIV/macaque experiment, *Science*, published an editorial expression of concern noting the possible flaws.[55]

Adding to the vedolizumab mystery, a Canadian research group presented a poster outlining interim results from its ongoing trial at CROI 2019, claiming that the antibody

did appear to slow the kinetics of HIV viral load rebound after an ATI.[56] Unfortunately, none of the three vedolizumab studies performed to date (one completed and two still underway) involve randomized controlled comparisons, so it's not clear if further light will be shed on these uncertainties.

Results from a randomized, placebo-controlled trial of the bNAb VRC01 in people with acute HIV infection were published in April 2019 in *Lancet HIV*.[57] Infusions of the antibody during a 24-week ATI proved safe but were not associated with maintenance of viral load below 1,000 copies/mL (the primary endpoint) in 17 of 18 evaluable recipients. The authors suggest that combination approaches will be needed to achieve enhancement of virological control during ATI. This point appears to be supported by the findings from a study that combined the bNAbs 3BNC117 and 10-1074 (noted in the combination section above), in which two of nine recipients did not experience viral load rebound throughout 30 weeks of follow-up.[42]

Latency-Reversing Agents (LRAs)

There is just one new study of an LRA candidate: Researchers at Guangzhou Eighth People's Hospital in China are looking at the effects of arsenic trioxide, which is an approved therapy for low-risk acute promyelocytic leukemia with the trade name Trisenox. The rationale is derived from published evidence of viral reservoir reductions in the SIV/macaque model.[58] The use of arsenic trioxide is likely to raise eyebrows given its potential toxicities.[59]

A long-planned trial of a tea form of the Chinese medicinal herb *Euphorbia kansui* has begun enrolling at the University of Utah. The herb contains ingenol derivatives that have been shown to have latency-reversing activity in laboratory studies.[60,61]

Therapeutic Vaccines

Interest persists in therapeutic HIV vaccines as a potential means to bolster immune responses against virus-infected cells, with a particular eye on developing candidates for use in combination trials with other interventions.

Two trials have opened over the past year: Sharon Riddler's laboratory at the University of Pittsburgh is studying a dendritic cell-based vaccine in tandem with either a whole-killed HIV vaccine or selected HIV peptides. David Margolis's research group at the University of North Carolina at Chapel Hill is testing two modified vaccinia virus Ankara strain (MVA) vectors encoding conserved HIV antigens, either alone or in combination.

At the 2019 Keystone Symposia conference Functional Cures and the Eradication of HIV, Jintanat Ananworanich presented results from a trial of a prime-boost HIV vaccine regimen developed by Janssen Vaccines & Prevention B.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson.[62] The regimen consisted of a priming immunization with an adenovirus serotype 26 (Ad26) vector followed by a boost with an MVA vector, both encoding mosaic HIV antigens designed to induce immune responses against a broad array of viral variants. Participants were Thai adults who had initiated ART during acute HIV infection.

In an analysis including 17 vaccine and nine placebo recipients, successful induction of HIV-specific T cell and antibody responses was demonstrated, but there was no significant difference between the groups in terms of viral load rebound after an ATI. One caveat is that the viral load cutoff for restarting ART during the ATI was 1,000 copies/mL, and some preclinical research has suggested that higher rebounds might need to be allowed in order to optimally activate HIV-specific immunity.[63] A second therapeutic trial involving Janssen's HIV vaccine candidates is ongoing at Beth Israel Deaconess Medical Center in Boston.

Table 2. Immune-Based Therapy Pipeline 2019

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Status
Isoprinosine		NCT03883334	Universidad San Francisco de Quito	Phase IV
Metformin		NCT03774108	Hospital Civil de Guadalajara	Phase IV
Canakinumab	IL-1β inhibitor	NCT02272946 (closed to enrollment)	University of California, San Francisco	Phase II
CD24Fc	Human CD24 extracellular domain and human IgG1 Fc fusion protein	NCT03960541 (not yet open for enrollment)	OncoImmune	Phase II
Pyridostigmine	Acetylcholinesterase inhibitor	NCT03312244 (closed to enrollment)	Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran	Phase II
Visbiome	Probiotic	NCT02441231	University Health Network, Toronto/ CIHR Canadian HIV Trials Network	Phase II
Allogeneic adoptive immune therapy	Granulocyte colony-stimulating factor-mobilized donor peripheral blood mononuclear cells	NCT02648516	Beijing 302 Hospital	Phase I/II
Tocilizumab	IL-6 blockade	NCT02049437 (closed to enrollment)	Case Western Reserve University	Phase I/II
Pembrolizumab	Anti-PD1 antibody, immune checkpoint inhibitor	NCT03367754	National Institutes of Health Clinical Center	Phase I
Arabinoxylan rice bran supplementation (BRM4)	A product derived from rice bran treated with extracts from three mushrooms	NCT02922907 (closed to enrollment)	University of Southern California	Not specified
Natural killer cell infusion	Adoptive immunotherapy with NK cells	ChiCTR1900021008 (not yet open for enrollment)	Beijing Youan Hospital, Capital Medical University	Not specified

The lone immune-based therapy trial with a commercial sponsor is the phase II assessment of CD24Fc, manufactured by OncoImmune. The candidate comprises part of the cell surface glycoprotein CD24 conjugated with elements from a human IgG1 antibody. It is designed to have multiple effects, including inhibition of inflammation. Outside of the context of HIV, CD24Fc is in phase II study for the prevention of acute graft-versus-host disease after stem cell transplantation.

The University of Maryland is undertaking the study, which will investigate the impact of CD24Fc on LDL cholesterol as well as inflammatory and immune activation biomarkers. Measures of the HIV reservoir are also being evaluated.

The remainder of the current research portfolio is being carried out under the aegis of academic researchers and their institutions. Two new trials have begun in Mexico: One is looking at whether the immunomodulatory drug isoprinosine can beneficially affect HIV RNA and/or CD4+ T cell levels in people with detectable low-level viral load (>50 but <200 copies/mL) on ART, while the other is measuring the impact of the antidiabetic drug metformin on inflammatory biomarkers.

In China, Tong Zhang at the Beijing Youan Hospital, Capital Medical University, is planning to test the impact of multiple infusions of allogeneic NK cells on CD4+ T cell counts in people on ART.

Results from a variety of candidates listed in past Pipeline Reports have seen the light of day over the past year, including vorapaxar,[64] dipyridamole,[65] sitagliptin,[66] and CC-11050.[67] For the most part, effects on inflammatory or coagulation biomarkers were either mixed or absent, with the exception of slight reductions in NK cell and IL-8 levels seen with CC-11050, and a more significant diminution in the levels of the chemokine CXCL10 reported for sitagliptin. It appears unlikely that any of these candidates will progress further in HIV.

Conclusion

The cure research endeavor finds itself balancing the optimism induced by the possibility of two new cure cases with the soberingly slow progress toward scalable curative interventions that are applicable to the majority of people with HIV. But there are examples of advances in the preclinical realm, and the portfolio of clinical studies continues to expand and diversify.

Funding support is also still growing, albeit at a slightly slower pace than in past years. A 2018 report from the International AIDS Society Towards an HIV Cure Initiative, AVAC, and the Resource Tracking for HIV Prevention Research and Development Working Group estimates that there was a total global investment of $288.8 million in 2017, an 8 percent increase compared to 2016.[68]

As in past years, the U.S. National Institutes of Health (NIH) contributed the vast majority: $255 million. Under the current U.S. presidential maladministration, NIH funding is constantly under threat, but so far broad support in Congress has staved

off proposals to slash research budgets. For example, the president's FY 2020 budget request contained an arbitrary 16.4% cut to NIH HIV cure research funding,[69] but the House Appropriations Committee has proposed an increase of $149 million for NIH to continue supporting scientific research that could lead to an HIV vaccine or a cure.[70] Close attention will be required to try to ensure that this increase survives the reconciliation process with the Senate and is in the final appropriations bill.

Unfortunately, ideologues that wield influence over the president have been more successful in their efforts to curtail studies involving fetal tissue—this includes the generation of humanized mouse models, which play an important role in preclinical HIV cure research.[71] Scientists within the NIH are now banned from using fetal tissue, and recipients of grants based outside the institutes will be subject to new advisory board reviews when they apply for renewals. Ongoing advocacy by the International Society for Stem Cell Research, TAG and many others is attempting to address the issue.[72,73]

The immune-based therapy pipeline has narrowed to the point of blockage. Arguably, earlier HIV testing and rapid initiation of ART will diminish the number of people at risk for suboptimal immune recovery and/or elevated persistent inflammation in the future, but there is a stark danger of leaving a large extant population without therapeutic options that might improve their long-term prognosis. Efforts to encourage development of immunomodulatory adjuncts to ART must continue, and there are reasons to hope that data from the REPRIEVE trial will provide clues to aid in the design of candidate therapies.

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