TAG

Treatment Action Group

RESEARCH TOWARD A CURE & IMMUNE-BASED THERAPIES

PIPELINE REPORT 2018

Dedication

Dedicated to the memories of
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2018 Pipeline Report: Research Toward a Cure and Immune-Based Therapies

Introduction

The research pipeline of candidates that might eventually contribute to the development of a cure for HIV infection—or at least generate data with the potential to accelerate progress toward that goal—continues to expand. When Treatment Action Group first added HIV-cure-related research to our annual Pipeline Report in 2011, there were nine interventional trials listed. As of June 2018, there are 92 interventional trials and 30 observational studies, with 22 of the former and 10 of the latter having been added since the publication of the 2017 Pipeline Report. The global spread of the research has also increased over time (see Table 1).

The diversity of ideas being explored gives reason to hope that advances will be forthcoming. Achievements to date have largely been incremental and, outside of exceptional circumstances such as stem cell transplantations for cancers, no dramatic therapeutic breakthroughs have been reported. In a few instances, researchers have obtained slight reductions in some measures of the HIV reservoir that persists in people on antiretroviral therapy (ART), but these have not been associated with delayed viral load rebound or an improved ability to control HIV after an ART interruption.[1]

Some hints of enhanced suppression of HIV viral load after ART interruption have emerged in the absence of apparent changes in reservoir size, but it's not clear whether the experimental interventions contributed in each case; rare individuals control HIV to low levels for variable periods when ART is stopped, for reasons that are still being investigated (see combination approaches below).

Among the most significant studies in HIV cure research remain those related to a small number of rare individuals who offer evidence that a cure is possible. Timothy Brown is still the lone person considered to be fully cured; last year he passed the milestone of a decade since an arduous series of treatments for a life-threatening cancer, including stem cell transplants from a donor lacking the CCR5 co-receptor typically used by HIV to gain entry into target cells, obliterated any sign of replication-competent virus.

In what might be considered to be a second tier of cases, there are several individuals in whom HIV became undetectable and apparently inactive for an extended period after ART interruption, temporarily raising hopes of additional cures.

These include the Mississippi baby, infected with HIV perinatally, and Clark Hawley, an adult who acquired the virus in a short window between screening for a pre-exposure prophylaxis (PrEP) demonstration project and the first day PrEP was prescribed. In both of these cases, rapid initiation of ART prevented the formation of a detectable

HIV reservoir. Subsequent ART interruptions were followed by a prolonged period before HIV viral load rebounded; 27.6 months in the case of the infant[2] and 7.4 months for Hawley (he is described in the paper about his case as "PrEP Participant A", but recently went public at amfAR's 2017 World AIDS Day HIV Cure Summit in San Francisco).[3]

Three individuals living with HIV who received stem cell transplants to treat concomitant cancers—two known as the Boston patients and another under the care of the Mayo Clinic in Rochester—have had similar experiences. The transplant donors did not lack the CCR5 co-receptor, but nevertheless the transplant procedures resulted in profound reductions in the size of the HIV reservoir. When permission was later obtained to perform an analytical treatment interruption (ATI), HIV remained undetectable, both in terms of viral load and reservoir measures, for 12, 32, and 41 weeks, respectively, before viral load rebounded.[4,5]

The exact mechanism for these periods of remission is unproven, but the evidence suggests that there is a unifying theme to all five of the cases: the HIV reservoir consisted of a very small number of latently infected $CD4^+$ T cells, and these cells remained in a resting state during the period off ART until some unknown event, such as an encounter with a pathogen, caused them to become activated, awakening the latent HIV and triggering the production of new viruses, which went on to infect other cells, spurring the viral load rebound.

The related connecting factor is that none of these five individuals had readily apparent immune responses to HIV; in the cases of the Mississippi baby and Clark Hawley, this is likely a result of the rapid initiation of ART, which suppressed the virus prior to the development of detectable HIV-specific immune responses. The stem cell transplant recipients had developed new immune systems derived from the uninfected stem cell donor, so HIV-specific immune responses were also lacking.

The overarching lesson is that dramatic reductions in the size of the HIV reservoir can be sufficient to cause an extended delay in the return of viral replication after ART interruption in the absence of any active control of the virus by the immune system. Extending that delay for life would represent a cure, but achieving this by reservoir reduction alone appears to be extremely challenging, with modeling studies suggesting that it would require a shrinking of greater than 10,000-fold (>99.99%).[6] The most recent estimate of the size of the replication-competent HIV reservoir in chronic infection puts the total at around 100 million cells.[7]

This brings us to a third tier of cases that researchers are looking at as possible models in cure research: individuals who maintain low or undetectable viral load levels after ART interruption, but typically possess measurable HIV reservoirs. Various terms have been used to describe this state, which can be confusing, but virologic remission and post-treatment control are among the most common.[8]

The idea of maintaining HIV suppression without ART, despite the continued presence of some virus, is sometimes referred to as a functional cure, but this descriptor has fallen out of favor recently, perhaps partly because it is difficult to know whether the low-level presence of HIV might have damaging effects over the long term.

Achieving some degree of post-treatment control is seen as the most realistic near-term goal by many researchers. The desire to test whether interventions might be associated with suppression of HIV viral load after ART withdrawal has prompted increasingly widespread use of ATIs in cure-related research. Currently 26 interventional trials cite an ATI as part of their protocol, although in some cases only if participants meet certain specific criteria. In addition, seven observational studies involve ATIs, primarily with the aim of identifying markers that are predictive of the timing and magnitude of viral load rebound.

Several studies that have been published over the past year offer some reassurance that ATIs do not have lasting effects on HIV reservoir size or immune activation and inflammation.[9,10] But these data do not completely ameliorate concerns about long-term harms that might be difficult to measure in short-term protocols. In an attempt to generate some consensus related to the use of ATIs in HIV cure research, the Ragon Institute of the Massachusetts General Hospital, the Massachusetts Institute of Technology, and Harvard is sponsoring a one-day workshop on July 9, 2018. Treatment Action Group is also conducting a survey of community activists to solicit opinions on the topic, and will publish a report later this year drawing on the responses received.

On the immune-based therapy (IBT) front, evidence continues to accumulate that individuals with poor $CD4^+$ T cell recovery despite HIV suppression by ART—a phenomenon described as suboptimal immune recovery (SIR) or immunologic non-response—are at increased risk for morbidity and mortality compared with counterparts with superior immune reconstitution. A recent large analysis suggested that SIR may be best defined as a failure to increase by ≥100 $CD4^+$ cells per year during the first two years on ART.[11]

A novel finding from researchers in Thailand is that even a subset of people with HIV who start ART extraordinarily early after infection show persistent immunological deficits after HIV viral load is suppressed. A group of 289 individuals who initiated ART a median of 19 days after infection were analyzed, and 11 (3.8%) exhibited $CD4^+$ T cell counts below 350 after 48 weeks, with an additional 44 having counts between 350 and 500. These outcomes were also associated with higher levels of inflammatory biomarkers.[12]

Even though this evidence suggests a role for IBTs in supplementing ART for certain populations of people with HIV, only a meager amount of therapeutic candidates are currently under investigation, and none appear to be on any kind of pathway toward FDA approval.

Table 1. Research Toward a Cure 2018: 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					
Vedolizumab	Anti-α4β7 integrin antibody, ATI	NCT03147859	Ottawa Hospital Research Institute	Canada	Phase II
VRC01	Broadly neutralizing antibody in infants	NCT03208231	NIAID	USA, Botswana, Brazil, Zimbabwe	Phase I/II
10-1074-LS + 3BNC117-LS	Long-acting broadly neutralizing antibodies	NCT03554408	Rockefeller University	USA	Phase I
3BNC117 + 10-1074	Broadly neutralizing antibodies, ATI	NCT03526848 (not yet open for enrollment)	Rockefeller University	USA	Phase I
3BNC117 + 10-1074	Broadly neutralizing antibodies, ATI	NCT02825797	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
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
Vedolizumab	Anti-α4β7 integrin antibody, ATI	NCT02788175	NIAID	USA	Phase I
VRC01LS	Long-acting broadly neutralizing antibody	NCT02840474	NIAID	USA	Phase I
VRC01	Broadly neutralizing antibody in acute HIV infection	NCT02591420	NIAID	USA	Phase I
ANTI-FIBROTIC					
Losartan	Angiotensin receptor blocker	NCT01852942	University of Minnesota	USA	Phase II
Telmisartan	Angiotensin receptor blocker	NCT02170246	Yale University	USA	Phase I
ANTI-INFLAMMATORY					
Canakinumab	IL-1β inhibitor	NCT02272946	University of California, San Francisco	USA	Phase II
High dose vitamin D supplementation	Vitamin	NCT03426592	University of Melbourne	Australia	Phase II

ANTI-PROLIFERATIVE					
mycophenolate mofetil (MMF)	Inosine-5′-monophosphate dehydrogenase inhibitor	NCT03262441	Fred Hutchinson Cancer Research Center	USA	Phase I
ANTIRETROVIRAL THERAPY					
Dolutegravir in reservoirs	Integrase inhibitor	NCT02924389	Emory University	USA	Phase N/A
ABX464	Inhibitor of HIV RNA export	NCT02990325	Abivax S.A.	Spain	Phase I/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
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	Rockefeller University	USA, Denmark, Germany	Phase IIa
Adoptive transfer of haploidentical natural killer cells and IL-2	Natural killer cells + cytokine	NCT03346499	University of Minnesota, Clinical and Translational Science Institute	USA	Phase II
eCLEAR: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody	NCT03041012	Aarhus University Hospital	Denmark	Phase II
Panobinostat + pegylated interferon-alpha2a	HDAC inhibitor + cytokine	NCT02471430	Massachusetts General Hospital	USA	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
Disulfiram + vorinostat		NCT03198559 (suspended for review of adverse events)	The Peter Doherty Institute for Infection and Immunity	Australia	Phase I/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	NCT02972450 (not yet open for enrollment)	Inserm-ANRS	USA, France, Germany, Italy, Spain, Switzerland, UK	Phase I/II

SB-728mR-T + cyclophosphamide	Autologous CD4 T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy, ATI	NCT02225665 (closed to enrollment)	Sangamo BioSciences	USA	Phase I/II
AGS-004 + vorinostat	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens + HDAC inhibitor	NCT02707900	NIAID	USA	Phase I
CD4-ZETA ± interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	USA	Phase I
DCV3 + pegylated interferon	Dendritic-cell-based vaccine pulsed with autologous heat-inactivated HIV + cytokine, ATI	NCT02767193 (not yet open for enrollment)	Judit Pich Martínez, Fundació Clínic per la Recerca Biomèdica	Spain	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	USA	Phase I
Vorinostat + HXTC: HIV-1 antigen expanded specific T cell therapy	HDAC inhibitor + adoptive immunotherapy	NCT03212989	Julia Sung, MD, University of North Carolina, Chapel Hill	USA	Phase I
Vorinostat ± tamoxifen in postmenopausal women	HDAC inhibitor + estrogen receptor modulator	NCT03382834	NIAID	USA	Phase I
CYTOKINES					
Interleukin-2 (IL-2)		NCT03308786 (not yet open for enrollment)	Case Western Reserve University	USA	Phase II
ALT-803	Recombinant human super agonist interleukin-15 complex	NCT02191098	University of Minnesota, Clinical and Translational Science Institute	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
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
C34-CXCR4	Autologous CD4+ T cells gene-modified to express HIV-inhibiting peptide C34, ATI	NCT03020524	University of Pennsylvania	USA	Phase I
Chimeric antigen receptor (CAR) T cell therapy		NCT03240328	Guangzhou 8th People's Hospital	China	Phase I

MazF-T	Autologous CD4+ T cells gene-modified with MazF endoribonuclease gene to inhibit HIV, ATI	NCT01787994 (closed to enrollment)	Takara Bio/ University of Pennsylvania	USA	Phase I
SB-728mR-HSPC	Autologous hematopoietic stem/progenitor cells gene-modified to inhibit CCR5 expression, ATI	NCT02500849	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
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS					
Gene therapy in treating patients with HIV-related lymphoma receiving stem cell transplant	Stem cells gene-modified with CCR5 shRNA/TRIM5alpha/TAR decoy	NCT02797470	AIDS Malignancy Consortium	USA	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	USA	Phase I
Gene-modified HIV-protected stem cell transplant in treating patients with HIV-associated lymphoma	Stem cells gene-modified with Cal-1 to abrogate CCR5 expression and encode an HIV entry inhibitor C46, ATI	NCT02378922 (suspended)	Fred Hutchinson Cancer Research Center	USA	Phase I
Safety of transplantation of CRISPR CCR5 modified CD34+ cells in HIV-infected subjects with hematological malignances	Stem cells gene-modified to abrogate CCR5 expression using CRISPR technology, 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 lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ), ATI	NCT02337985	City of Hope Medical Center	USA	Phase I
Busulfan and gene therapy after frontline chemotherapy in patients with AIDS-related non-Hodgkin lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ) + cyclophosphamide conditioning, 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 (pHIV7-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		NCT03468582	University of Lausanne Hospitals	Switzerland	Phase I
Radiolabeled broadly neutralizing anti-HIV antibody 3BNC117 + Copper-64 radio isotope followed by MRI/PET scanning to detect HIV in vivo		NCT03063788	Bayside Health	Australia	Phase I
IMMUNE CHECKPOINT INHIBITORS					
Durvalumab in solid tumors	Anti-PD-L1 antibody	NCT03094286	Spanish Lung Cancer Group	Spain	Phase II
Nivolumab + ipilimumab	Anti-PD-1 antibody + anti-CTLA-4 antibody in people with advanced HIV-associated solid tumors	NCT02408861	National Cancer Institute (NCI)	USA	Phase I
Pembrolizumab	Anti-PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms	NCT02595866	National Cancer Institute (NCI)	USA	Phase I
Pembrolizumab	Anti-PD-1 antibody, single dose	NCT03239899	National Institute of Neurological Disorders and Stroke (NINDS)	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
Kansui	Traditional Chinese medicine containing ingenols	NCT02531295 (not yet open for enrollment)	UCSF	USA	Phase I
OBSERVATIONAL STUDIES					
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 (not yet open for enrollment)	Inserm-ANRS	France	N/A
APACHE: Monitored antiretroviral pause in chronically infected HIV+ individuals with long-lasting suppressed viremia	ATI	NCT03198325	Ospedale San Raffaele	Italy	N/A
ACTG A5345: Biomarkers to predict time to plasma HIV RNA rebound	ATI	NCT03001128	AIDS Clinical Trials Group	USA	N/A
CLEAC	Comparison of late versus early antiretroviral therapy in HIV-infected children	NCT02674867	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	France	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)	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, Inc.	USA	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)	Canada	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	Thailand	N/A
EURECA	Exploratory study of cellular reservoirs in blood	NCT02858414	Centre Hospitalier Universitaire de Besancon	France	N/A
Genotyping FcɣRs 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 co-infected HIV-HCV patients		NCT03244371	Assistance Publique Hopitaux De Marseille	France	N/A
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	University of Melbourne	Australia	N/A
HIV-STAR	HIV sequencing after ATI to identify the clinically relevant anatomical reservoir	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
Identification and quantification of HIV CNS latency biomarkers		NCT02989285	St Vincent's Hospital, Sydney	Australia	N/A
ImmunoCo27	Co-adaptation between HIV and CD8 cellular immunity	NCT02886416	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	France	N/A
IMPAACT 2015: Evaluation of the HIV-1 reservoir in the CNS of perinatally infected youth and young adults with cognitive impairment		NCT03416790 (not yet open for enrollment)	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	NIAID	USA	N/A
Impact of ART adherence on HIV persistence and inflammation		NCT02797093	University of Colorado, Denver	USA	N/A
ISALA	ATI	NCT02590354	Institute of Tropical Medicine, Belgium	Belgium	N/A
LoViReT	Low viral reservoir treated patients	NCT02972931	IrsiCaixa	Spain	N/A

Post-analytic treatment interruption study		NCT02761200 (closed to enrollment)	South East Asia Research Collaboration with Hawaii	Thailand	N/A
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans		NCT02154035 (closed to enrollment)	NIAID	Uganda	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
mTOR INHIBITORS					
Everolimus	Effect of everolimus on HIV persistence post kidney or liver transplant	NCT02429869 (closed to enrollment)	UCSF	USA	Phase IV
Sirolimus	Safety and efficacy of sirolimus for HIV reservoir reduction in individuals on suppressive ART	NCT02440789 (closed to enrollment)	ACTG	USA	Phase I/II
metformin		NCT02659306 (closed to enrollment)	McGill University Health Center	Canada	Phase I
PROTEASOME INHIBITORS					
Ixazomib		NCT02946047	Nathan W. Cummins, M.D.		Phase I/II
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 (NICHD)	USA	N/A
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	USA	Phase II
Maraviroc in HIV-1+ individuals requiring allogeneic hematopoietic cell transplant	CCR5 inhibitor, ATI	NCT03118661	Washington University School of Medicine	USA	Phase I

THERAPEUTIC VACCINES					
GTU-multiHIV + LIPO-5	DNA + lipopeptide vaccines, ATI	NCT01492985 (closed to enrollment)	French National Institute for Health and Medical Research/French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	France	Phase II
THV01	Lentiviral-vector-based therapeutic vaccine, ATI	NCT02054286 (closed to enrollment)	Theravectys S.A.	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
Ad26.Mos.HIV + MVA-Mosaic	Adenovirus and modified Vaccinia Ankara strain vectors encoding mosaic HIV antigens in people treated during acute HIV infection, ATI	NCT02919306 (closed to enrollment)	Janssen Vaccines & Prevention B.V.	Thailand	Phase I
DNA.HTI + MVA.HTI	DNA + modified Vaccinia Ankara strain vector vaccines	NCT03204617	Aelix Therapeutics	Spain	Phase I
MAG-pDNA + rVSVIN HIV-1 Gag	DNA + viral vector vaccines, ATI	NCT01859325 (closed to enrollment)	NIAID/Profectus Biosciences, Inc.	USA	Phase I
Recombinant adenovirus type 5 vaccine	Viral vector vaccine	NCT02762045	Centers for Disease Control and Prevention, China	China	Phase I
TOLL-LIKE RECEPTOR AGONISTS					
vesatolimod in ART-treated HIV controllers	TLR-7 agonist, ATI	NCT03060447	Gilead Sciences	USA	Phase Ib
vesatolimod (formerly GS-9620)	TLR-7 agonist	NCT02858401 (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	Columbia University	South Africa	Not listed
Antiretroviral regime for viral eradication in newborns	Combination antiretroviral therapy	NCT02712801	National Center for Women and Children's Health, China CDC	China	Phase IV
DGVTRU: immediate initiation of antiretroviral therapy during 'hyperacute' HIV infection	Combination antiretroviral therapy	NCT02656511	UCSF	USA	Phase IV
AAHIV: 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	Inserm/ANRS	France	Phase III
VIRECURE: impact of extremely early ART to reduce viral reservoir and induce functional cure of HIV infection	Combination antiretroviral therapy, ATI	NCT02588820	David Garcia Cinca, Hospital Clinic of Barcelona	Spain	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	USA	Phase II
Peginterferon alfa-2b	Cytokine, ATI	NCT02227277	The Wistar Institute	USA	Phase II
IMPAACT P1115: Very early intensive treatment of HIV-infected infants to achieve HIV remission	Combination antiretroviral therapy, ATI	NCT02140255	IMPAACT/NIAID/ NICHD	Argentina, Brazil, Haiti, India, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, USA, Zimbabwe	Phase I/II

ATI = analytical treatment interruption. In some cases ATIs will only be conducted if study participants meet certain criteria.

Shaded entries represent additions since the 2017 Pipeline Report. For a listing including completed trials related to cure research, with links to published and presented results where available, see TAG's research toward a cure clinical trials web page at: http://www.treatmentactiongroup.org/cure/trials.

Combination Approaches

The most notable cure-related clinical research trend over time is the increasing number of trials involving combinations of different strategies, which is now up to 17.

New studies include an exploration of the combination of the HDAC inhibitor vorinostat and tamoxifen, an FDA-approved drug for the treatment of breast cancer in postmenopausal women. The impetus for the protocol comes from amfAR-supported laboratory research showing that estrogen strongly inhibits the reactivation of HIV from latency in $CD4^+$ T cells from women, and modulating the interaction between estrogen and cellular estrogen receptors with tamoxifen significantly increases the latency-reversing effect of vorinostat *in vitro*.[13] The trial is being conducted by the AIDS Clinical Trials Group (**ACTG**) and co-led by Eileen Scully, whose research focus is on sex-specific differences in the HIV reservoir.[14]

The **ACTG** is a longstanding HIV research network funded by NIAID.

A large collaboration involving researchers in the USA, France, Germany, Italy, Spain, Switzerland, and the UK is launching a placebo-controlled trial combining two therapeutic HIV vaccine candidates with the antibody vedolizumab (trade name Entyvio). The vaccine regimen comprises a DNA construct followed by a modified Vaccinia Ankara strain (MVA) viral vector, both encoding antigens from HIV clade B. Vedolizumab is an antibody targeting α4β7 integrin, a molecule that is preferentially expressed on gut-homing T cells. Interest in vedolizumab, which is FDA approved for the treatment of ulcerative colitis and Crohn's disease, has been prompted by evidence that the α4β7 integrin is involved in facilitating HIV infection of $CD4^+$ T cells,[15,16] and by results in the SIV/macaque model indicating that administration of the antibody led to control of SIV viral load after ART withdrawal.[17]

The trial plans to enroll 192 participants who will be randomly assigned to one of four groups: therapeutic vaccines and vedolizumab, therapeutic vaccines, vedolizumab, or placebo. An ATI will be performed to investigate whether there is any enhancement of control of HIV viral load in the absence of ART.

Researchers at the University of Minnesota are conducting a small pilot test of infusions of natural killer (NK) cells combined with administrations of the cytokine interleukin-2 (IL-2). The NK cells are sourced from donors matched for HLA type to avoid immunological rejection. Just five people with HIV will be recruited for the initial study. There is increasing interest in evaluating whether NK cells may be able to contribute to depleting the HIV reservoir and/or controlling virus replication; a paper published in October 2017 reported that this type of immune response appears to be important in non-pathogenic SIV infection of African green monkeys.[18]

An alternate form of immune cell infusion is being pursued in combination with vorinostat at the University of North Carolina, Chapel Hill. The research group of David Margolis has developed a method they've named HIV-1 Antigen Expanded Specific T Cell Therapy (HXTC), in which T cells are obtained from individuals on ART and expanded in the

laboratory by stimulation with HIV Gag, Pol, and Nef antigens.[19] The resulting cell population, consisting predominantly of $CD8^+$ T cells but with a subset of $CD4^+$ T cells, is then infused into the original donor.

The researchers performed *in vitro* experiments and found that vorinostat reversed HIV latency sufficiently to allow HXTC to recognize and eliminate at least a proportion of the latently infected cells isolated from individuals on ART.[20] This one-two punch represents a variation of the popular 'kick & kill' strategy for targeting the HIV reservoir. A preparatory trial of HXTC alone found the approach to be safe,[21] laying the groundwork for the combination with vorinostat in people with HIV on ART.

Last year there was some tentative excitement about results obtained with a different version of kick & kill: in a trial conducted in Spain and reported at **CROI** 2017 by Beatriz Mothe, 5 of 13 recipients of a regimen combining the candidate latency-reversing agent romidepsin and a therapeutic HIV vaccine displayed low viral loads (<2,000 copies/ml) for several months after an ATI.[22] But the trial did not have a placebo comparator arm, and evidence from a more recent study conducted by researchers at the US National Institute of Allergy and Infectious Diseases (NIAID) suggests that this may have been a significant shortcoming.

CROI is the Conference on Retroviruses and Opportunistic Infections, the largest annual scientific meeting on HIV/AIDS held in the United States.

The NIAID researchers tested an experimental prime-boost vaccine featuring a DNA immunization followed by a recombinant vesicular stomatitis virus (VSV) vector, both of which encoded multiple HIV antigens. The study participants were individuals started on ART during early infection, and they were randomized to receive active vaccines or placebo. After 56 weeks, an ATI was performed to assess whether vaccine-induced immune responses could enhance control of viral load rebound. The results were published in the journal *Science Translational Medicine* in December 2017,[23] revealing that no significant effect of vaccination was observed. The researchers noted, however, that several participants in the placebo arm of the trial exhibited low viral loads for an extended period after ATI, and they specifically compared this outcome to Mothe's study results:

"The importance of having a control arm for such studies is…illustrated by recently reported results of an ongoing single-arm, phase 1 trial of romidepsin combined with therapeutic vaccination in early treated subjects. That study reported that 5 of 13 (38%) subjects exhibited sustained suppression of plasma viremia to <2,000 copies/ml for a median of 14 weeks after treatment interruption, a finding that suggested efficacy of the vaccine regimen when compared with historical controls. However, applying these same virologic criteria to our results, 6 of 15 (40%) subjects in the placebo arm of our trial exhibited suppression to <2,000 copies/ml for at least 16 weeks after treatment interruption."

This finding may not rule out the conduct of single-arm trials for exploratory (and perhaps also cost containment) purposes, but it does argue strongly that conclusions shouldn't be drawn about efficacy in the absence of a control arm.

IMPAACT stands for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network, which is funded by the NIAID, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Institute of Mental Health of the US National Institutes of Health, US Department of Health and Human Services. .

In the pediatric realm, an ongoing trial of immediate ART in HIV-exposed newborns, **IMPAACT** P1115, is evolving into a version 2.0 that will add the integrase inhibitor raltegravir with or without the broadly neutralizing antibody (bNAb) VRC01. The revision was made possible by the FDA approval of raltegravir for newborns in November 2017.[24]

The P1115 protocol is based on the Mississippi baby case and aims to assess whether an extended period of HIV remission or a cure might be achievable in infants born with HIV. Participants are evaluated after 2–4 years of follow up to decide whether a carefully monitored ATI is appropriate. At the current time, eight infants enrolled in version 1.0 of the trial have been followed for over 72 weeks and will soon be eligible for consideration for the ATI phase.[25] The criteria for undergoing an ATI were generated by an expert panel and include:

- >96 weeks on study
- Two consecutive negative fourth-generation HIV ELISA antibody tests
- No detectable HIV RNA after week 48
- No detectable HIV DNA
- CD4 >25% and in the normal age range
- Cessation of breastfeeding

Toll-like receptors (TLRs) are innate immune cell receptors that recognize common features shared among many pathogens. TLR agonists bind to these receptors and can have modulating effects on immunity.

At CROI 2018, encouraging preclinical results were presented for a combination approach involving bNAbs together with a **toll-like receptor** 7 (TLR7) agonist.[26] A research team headed by Dan Barouch at the Beth Israel Deaconess Medical Center started 44 macaques on ART one week after they were infected with the SIV/HIV hybrid virus (SHIV) SHIV-SF162P3. The animals were then divided into 4 groups of 11 and administered the bNAb PGT121, the TLR7 agonist vesatolimod, a combination of PGT121 and vesatolimod, or placebo. When ART was eventually withdrawn, 16 weeks after the last receipt of the interventions, 6 of the 11 macaques in the combination arm maintained viral loads below the limit of detection for 140 days of follow up. The median time to viral load rebound in the group was 112 days, as compared with 21 days in placebo recipients.

Several human trials involving combinations of bNAbs and TLR agonists are now in the works, including one led by Steve Deeks at the University of California San Francisco (UCSF) under the aegis of the amfAR Institute for HIV Cure Research. It is uncertain how well the macaque results might translate; ART was administered to the animals sooner after infection than will be possible in most people, and activity against the SHIV-SF162P3 challenge virus may not necessarily predict similar activity against HIV.

The BELIEVE collaboratory is one of six Martin Delaney Collaboratories funded by NIAID to pursue the development of a cure for HIV infection.

Adoptive Immunotherapy

Immune cell infusion approaches are commonly referred to as adoptive immunotherapy. Researchers affiliated with the **BELIEVE collaboratory** have opened a small phase I trial involving transfer of HIV-specific T cells targeted toward conserved parts of the

virus—specifically elements from the Gag, Pol, and Nef proteins—that have not mutated to escape immune recognition. The name given to the strategy is HIV-specific T cells with non-escaped epitope targeting (HST-NEETs). The plan is to eventually combine HST-NEETs with latency-reversing agents.[27]

Antiretroviral Therapy

ABX464 is a novel antiretroviral drug that inhibits the activity of the HIV protein Rev, thereby interfering with the transcription of HIV RNA. A claim of an 'efficacy signal' related to viral load reduction has been made in an early trial, but no statistically significant effect was documented when all ABX464 recipients were compared with a placebo group.[28] The same study reported generally mild dose-related side effects such as nausea, vomiting, abdominal pain, and headache.

The manufacturer, ABIVAX, believes that ABX464 may help the immune system to recognize HIV-infected cells by promoting the presentation of HIV antigens on the cell's surface, but this theory is unproven. Slight reductions in measures of HIV DNA have been reported in analyses that divide study participants into 'responders' and 'non-responders', but these results have yet to be published.[29]

Toward the end of 2017, results were presented from a Phase II placebo-controlled trial combining ABX464 with darunavir and ritonavir or darunavir and cobicistat, followed by an ATI. Despite the claims of HIV reservoir reductions, no delay in viral load rebound was observed in ABX464 recipients compared to placebo.[30] Additional studies are planned. The company is also testing ABX464 in HIV-negative people as a therapy for moderate-to-severe active ulcerative colitis,[31] due to preclinical research suggesting anti-inflammatory activity in the gut.[32]

Broadly Neutralizing Antibodies

There continues to be strong interest in the potential of bNAbs in the context of HIV cure research.[33] In addition to their direct anti-HIV effects, bNAbs may be able to promote the killing of virus-infected cells via antibody-mediated cellular cytotoxicity (ADCC) or antibody-mediated cellular phagocytosis (ADCP); these mechanisms involve bNAbs binding to HIV Env proteins expressed on the surface of infected cells, thereby flagging them for destruction by NK cells or phagocytes.

Recent evidence also indicates that bNAbs may have the potential to modulate virus-specific T cell responses against HIV; in a macaque experiment in which a short course of two bNAbs, 3BNC117 and 10-1074, was administered, prolonged control of a SHIV was observed in some animals, with virus-specific $CD8^+$ T cell responses appearing to play a key role.[34] A 40-person trial of this bNAb combination in people with HIV on ART, featuring an ATI, will begin enrolling soon at Rockefeller University. Long-acting versions of both bNAbs are also being evaluated.

The International AIDS Vaccine Initiative (IAVI) is sponsoring a preliminary test of a different dual bNAb combination, PGDM1400 and PGT121, in people with and without HIV. PGDM1400 is among the most broadly active and potent bNAbs that have been discovered,[35] and the cocktail with PGT121 has shown efficacy in preclinical prevention studies, protecting macaques from a challenge with a mix of different SHIVs.[36]

A potential shortcoming of bNAbs is that they are delivered via infusion or subcutaneous injection. Several research groups are working on a strategy that draws from gene therapy to try and circumvent the problem: adeno-associated virus (AAV) vectors are outfitted with genes encoding the bNAb of interest and then injected into muscle tissue with the goal of creating a persistent supply in the body. This AAV method has already been used with some success to deliver factor IX to hemophiliacs.

The researcher Ron Desrosiers has recently described some encouraging findings using the strategy in macaques, but they come with a major caveat.[37] AAV vectors were employed to deliver the bNAbs 10E8, 3BNC117, and 10-1074 to four macaques infected with SHIV AD8 and, in terms of achieving suitable bNAb levels, the results were disappointing: 10E8 was low or absent in all animals, 3BNC117 was present in just one, and 10-1074 reached significant levels in three.

Intriguingly, however, the single macaque that had measurable 3BNC117 and 10-1074 levels showed evidence of extremely potent SHIV inhibition. Both viral load and the virus reservoir became undetectable over time, and experiments in which large numbers of cells were transferred into uninfected macaques failed to transmit SHIV infection. For a long period, Desrosiers and colleagues suspected the macaque may have been cured, but very low levels of SHIV AD8 were detected using a quantitative virus outgrowth assay (QVOA) 87 weeks after the AAVs were injected.

The major obstacle to building on this apparent promise lies in the induction of anti-antibody antibodies that target the bNAbs and promote their clearance (also referred to as anti-drug antibodies, ADAs). This problem was found to explain the poor bNAb levels in most of the macaques in the study, and it is a phenomenon that had been documented in earlier work.[38] Desrosiers is now focused on figuring out ways to avert the induction ADAs.[39]

AAV variants are classified into different serotypes. AAV serotype 1 is abbreviated as AAV1. Currently, there are 11 known AAV serotypes.

The first human trial of an AAV-delivered bNAb was sponsored by IAVI in the HIV prevention context, and it ran into the same issue. An **AAV1** vector was engineered to express the bNAb PG9 and administered to HIV-negative men at several different doses. No safety issues were apparent, but none of the participants developed detectable levels of PG9 in serum, and anti-PG9 ADAs were frequent.[40]

Researchers at NIAID recently launched the first trial of an AAV-delivered bNAb in people with HIV on ART. An AAV8 vector encoding VRC07 will be given intramuscularly at one of three doses, with the primary aim of assessing safety and VRC07 levels in serum. Because AAV8 has a particular tropism for the liver, a site favoring induction of immunological tolerance, its use has been proposed as a possible means to reduce the

risk of ADAs. However, this was not the case in preclinical studies in macaques,[41] and it remains to be seen whether there will be any notable difference compared with the results obtained with an AAV1 vector.

IMPAACT 2008 is a newly opened trial investigating the efficacy of the bNAb VRC01 in infants with HIV started on ART within 12 weeks of birth. A total of 68 participants will be randomized to receive ART or ART plus VRC01 given at weeks 0, 2, 6, and 10. The primary aims are to evaluate the safety and pharmacokinetics of VRC01, as well as establish whether addition of the bNAb further reduces the size of the HIV reservoir compared with ART alone. Study locations include the USA, Botswana, Brazil, and Zimbabwe.

Cytokines

The first glimpse of data from an ongoing trial of ALT-803 was presented at CROI 2018. The intervention is a modified form of the cytokine interleukin-15 (IL-15) that is designed to have increased biological activity and a longer half-life in the body.[42] IL-15 has been reported to have multiple effects that could prove useful for the HIV cure field, including latency reversal,[43] enhancement of $CD8^+$ T cell and NK cell responses,[44,45] and direction of virus-specific $CD8^+$ T cells into B cell follicles[46] (an important site of HIV persistence[47]).

In the ongoing trial, ALT-803 was safe and well tolerated, with some injection site rash and adenopathy being observed in participants receiving subcutaneous injections. The researchers reported a 7.6-fold increase in NK cell activation, a 23-fold increase in $CD4^+$ T cell activation, and a 10-fold increase in $CD8^+$ T cell activation in lymph nodes 48 hours after dosing, along with transient low-level plasma viremia suggestive of latency-reversing activity.[48] The data were from the first seven enrollees and final results are pending.

Gene Therapy

Chimeric antigen receptor (CAR) T cells have proven to be potent weapons against cancer and represent a major gene therapy success story. The approach involves the genetic modification of an individual's T cells in the laboratory to endow them with receptors targeting the antigen(s) of interest, followed by expansion and infusion. In August 2017, the US Food and Drug Administration (FDA) approved the first CAR T cell therapy, tisagenlecleucel, for the treatment of certain children and young adults with acute lymphoblastic leukemia. The licensing of a second product for refractory non-Hodgkins lymphomas followed just a few months later. There are some drawbacks, most notably the cost and the risk of serious side effects, such as cytokine release syndrome and neurological problems (researchers continue to work on strategies for reducing these risks).

CAR T cells designed to target HIV antigens were investigated many years ago,[49] but there has been relatively little activity since compared with the cancer field.[50] This is starting to change, with researchers in China having initiated the first cure-related clinical trial of CAR T cells in people with HIV on ART.

The phase I study will test the safety and anti-reservoir activity of VC-CAR-T cells, which are modified with a variable fragment of the bNAb VRC01 to target HIV gp120. In laboratory experiments, VC-CAR-T cells were able to induce killing of HIV-infected cells, including latently infected cells exposed to latency-reversing agents.[51] With a number of other research groups pursuing the development of CAR T cells targeting HIV, more trials are likely in the future.

A variety of other gene therapy trials remain ongoing, with results pending.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors represent another example of FDA-approved cancer therapeutics that are of interest to HIV cure researchers. Immune checkpoint is a term used to refer to a family of immune cell receptors preferentially expressed by T cells that have become exhausted and dysfunctional. Targeting these receptors with antibodies can revive T cell activity, and this has been associated with reduced tumor burden—in some cases even apparent elimination—in a proportion of individuals with certain cancers. The downside of the approach is that T cells recognizing body tissues can get switched on, causing serious, potentially life-threatening autoimmunity.

Ongoing research is exploring the effects of immune checkpoint inhibitors in people with HIV and concomitant cancers for which the therapies are indicated. Preliminary results presented over the past year indicate that the safety profile is similar to that documented in HIV-negative individuals.[52] A secondary goal of these trials is to assess whether measures of HIV persistence are affected, as there is evidence that immune checkpoint inhibitors could have both latency-reversing activity and a beneficial effect on HIV-specific T cell responses.[53]

To date, no consistent alterations in measures of HIV have been reported.[54,55] A single case report of an individual who received the anti-PD1 antibody nivolumab and experienced a significant decline in HIV DNA levels[56] drew widespread media attention toward the end of 2017 (generating some wildly misleading media headlines suggesting that a cure was imminent), but these results must be interpreted cautiously given that no such effect has been documented in four other individuals.

One recently initiated clinical trial at the U.S. National Institutes of Health (NIH) Clinical Center is testing a single dose of the anti-PD1 antibody pembrolizumab in people with HIV on ART who do not have cancer. The main aim is to investigate whether the therapy can promote immune reconstitution in individuals who have poor CD4 recovery despite viral load suppression, but HIV levels will be measured in a subset of participants in both blood and the central nervous system.

Latency-Reversing Agents (LRAs)

The number of trials of LRAs has dwindled somewhat as focus has shifted toward evaluating combinations of different strategies. One new trial has been initiated over the past year, looking at two candidate LRAs: valproic acid and pyrimethamine. The latter drug is better known as an anti-parasitic used in the treatment of toxoplasmosis, but a group of researchers at Erasmus University Medical Center in the Netherlands has reported that it also displays HIV latency-reversing activity as a result of inhibition of cellular components called the BAF chromatin remodeling complex.[57] The clinical trial is designed to discover whether these laboratory results translate to people with HIV on ART.

Chidamide belongs to the class of cancer therapies known as HDAC inhibitors, but is unusual because it was developed in China and is only approved for use in that country. A pilot study at the Tang-Du Hospital investigating chidamide's latency-reversing effects has been completed and a larger, randomized multi-site trial is ongoing in China. Preliminary results are due to be presented at the AIDS 2018 conference in Amsterdam on July 25th.

Therapeutic Vaccines

In recent years, Janssen Pharmaceutical Companies of Johnson & Johnson has made a significant and welcome foray into HIV vaccine development, advancing their lead candidate into a large study of preventive efficacy among women on the African continent.[58] On a smaller scale, the company has also been supporting therapeutic HIV vaccine research, having documented encouraging results in the SIV/macaque model.[59]

The latest trial is a phase I that will assess the safety and immunogenicity of an adenovirus serotype 26 (Ad26) vector encoding **mosaic HIV antigens** followed by a modified Vaccinia Ankara (MVA) vector with the same payload, compared with the Ad26 vector followed by two gp140 protein immunizations (one derived from clade C, the other a mosaic of multiple clades). A total of 26 participants on ART will be randomly assigned to one of the two active vaccine arms or placebo.

As the name suggests, **mosaic antigens** represent an amalgam of components from multiple different HIV clades.

Table 2. Immune-Based Therapy Pipeline 2018

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Status
Canakinumab	IL-1β inhibitor	NCT02272946	University of California, San Francisco	Phase II
Losartan	Angiotensin II receptor antagonist, anti-inflammatory	NCT02049307 NCT01852942	Minneapolis Medical Research Foundation University of Minnesota - Clinical and Translational Science Institute	Phase II
Pyridostigmine	Acetylcholinesterase inhibitor	NCT03312244	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 (AAIT)	Granulocyte colony-stimulating factor (G-CSF)-mobilized donor peripheral blood mononuclear cells (MNCs)	NCT02648516	Beijing 302 Hospital	Phase I/II
Tocilizumab	IL-6 blockade	NCT02049437	Case Western Reserve University	Phase I/II
Vorapaxar	Thrombin receptor (PAR-1) antagonist	NCT02394730	Kirby Institute/NIAID/ University of Minnesota – Clinical and Translational Science Institute/University of Melbourne/Merck	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	University of Southern California	Not specified

At this point in time, it would be a stretch to describe the small number of IBTs under investigation as adjuncts to ART as representing a pipeline. Since Cytheris, the biotech manufacturer of the cytokine IL-7, went out of business several years ago, no manufacturer appears to be developing IBTs with an eye toward licensure. Instead, academic investigators are doing their best to drive the research.

Over the past year, researchers from Mexico have reported that pyridostigmine, an acetylcholinesterase inhibitor used in the treatment of myasthenia gravis, may promote $CD4^+$ T cell increases in individuals with suboptimal immune recovery despite HIV suppression by ART.[60] The data derive from an uncontrolled study of just seven people, however, and are therefore tentative at best. A larger placebo-controlled trial is now underway to provide more definitive insight into whether the approach has promise.

The second new study to open over the past year is the single-dose evaluation of the immune checkpoint inhibitor pembrolizumab (mentioned above). The trial is taking place at the NIH Clinical Center in Bethesda and is recruiting individuals on ART with sustained viral load suppression and $CD4^+$ T cell counts between 100 and 350 cells. The specific aim is to investigate whether the approach might be beneficial to people with suboptimal immune recovery. If the single dose is proven to be safe and tolerable, a larger study will be planned.

A possible mechanism explaining poor $CD4^+$ T cell recovery is scarring damage (fibrosis) in the lymph nodes caused by HIV. Studies have shown that lymph node fibrosis deprives circulating $CD4^+$ T cells of the normal amount of sustenance they need for survival; in essence, lymph nodes act like fueling stations for T cells, and fibrosis reduces the fuel supply.

These findings have prompted multiple studies of drugs that may have anti-fibrotic activity in people with HIV. Results thus far have unfortunately been disappointing. Results from a trial of telmisartan were published in May 2018, reporting no improvement in lymph node fibrosis compared to ART alone.[61] Similarly, a placebo-controlled study of lisinopril found no evidence of anti-fibrotic effects in lymphoid tissues.[62] Two trials investigating losartan remain ongoing.

Conclusion

The growth and diversification of HIV cure research over time is evident, with more clinical trials ongoing in 2018 than ever before. Nevertheless, the field is still wrestling with a number of fundamental questions relating to virus persistence in people on ART and how best to measure the effects of candidate interventions.

Funding support for the work is also increasing, with data from the International AIDS Society Towards an HIV Cure Initiative, AVAC, and the HIV Vaccines & Microbicides Resource Tracking Working Group showing an investment of $268 million in 2016 compared with $201.8 million in 2015.[63] The Office of AIDS Research at the NIH has proposed an additional 3.1% in US government funding for FY 2018 in their Professional Judgment Budget, representing an addition of $7,617,000 to the $243,247,000 enacted in FY 2017.[64]

The IBT field is discouragingly fallow, and this remains a serious concern given that suboptimal immune recovery despite ART is accompanied by an elevated risk of illness. There is a need for more coordinated efforts among researchers, advocates, and regulators to try and spur investment in this area.

A small victory among the ugly and disastrous political events unfolding in the U.S. is the relative protection of scientific research funding from the Luddite, budget-slashing inclinations of the current President's administration. But this situation could change, and broad-based efforts to maintain support for the NIH are essential.

Recommendations

- Continue to increase investments in HIV-cure-related research.
- Develop consensus on the appropriate use of ATIs where possible and work to develop biomarkers that might give insight into therapeutic efficacy without the need for ATIs.
- Support long-term safety follow up of participants in trials involving ATIs.
- Create a database for tracking reported cases of posttreatment control.
- Develop clearer definitions of HIV remission.
- Investigate the consequences of low-level HIV viral load in posttreatment controllers, both for individual health and HIV transmission risk.
- Invest in solving the problem of anti-antibody responses that is hampering bNAb delivery by AAV vectors.
- Continue to broaden the global scope of HIV cure research.
- Recognize the importance of social science research in providing information on how HIV cure research is perceived and understood in different settings and provide funding support for this work.
- Enhance and broaden community education efforts on HIV cure research to better facilitate the involvement and participation of diverse communities.
- Revive research and development efforts to address the needs of individuals experiencing suboptimal immune recovery on ART.

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