Research Toward a Cure and Immune-Based and Gene Therapies

By Richard Jefferys

Introduction

The rise to prominence of cure research has continued over the past year, with every major scientific conference on HIV now featuring sessions and presentations on the topic. The U.S. National Institute of Allergy and Infectious Diseases (NIAID) sponsors a biannual workshop with the most recent, Strategies for an HIV Cure, taking place in Bethesda in October 2014. The NIAID meeting alternates years with another more longstanding event known as the International HIV Persistence Workshop, which debuted in 2003 and will convene for the seventh time in December 2015. In addition, the International AIDS Society (IAS) sponsors a two-day symposium, Towards an HIV Cure, every year in July.

The proliferation of meetings and workshops reflects the expansion of the research effort and the resultant data, which are presented and discussed at these events. Since the publication of the *2014 Pipeline Report*, many new clinical trials have been initiated (see table 1), and important results from early human studies of candidate HIV latency-reversing agents have been presented and published.

The most significant development has been a disappointment: the child once known as the Mississippi baby, considered possibly cured of HIV infection, experienced a viral-load rebound and had to restart antiretroviral therapy (ART). The news was announced July 10, 2014,[1] and a case report published in the *New England Journal of Medicine* in February of this year.[2] ART had been initiated shortly after the child's birth and then interrupted around 18 months later; the child subsequently went 27 months with no detectable viral load or replication-competent HIV before the rebound occurred. An International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network trial based on the case, P1115, has gone ahead and will attempt to evaluate whether similar or longer periods of remission can be obtained by immediate treatment of newborns infected with HIV because their mothers did not receive appropriate prevention of mother-to-child transmission.

With the return of HIV in the Mississippi child, Timothy Brown once again became the lone individual considered cured (he recently celebrated reaching eight years with this unique status). Gero Hütter, the doctor who identified a stem cell donor homozygous for the CCR5-Δ32 mutation for Brown and performed the transplantation procedures, recently reviewed six other documented cases of people with HIV and cancers who received stem cell transplants from CCR5-Δ32 homozygotes. In a stark and unhappy illustration of the challenges associated with the approach, all six died within a few months, due to either the underlying cancers or complications from the transplantation procedures such as graft-versus-host-disease.[3] In one case, HIV had become undetectable, but ART was not discontinued to evaluate the potential for viral-load rebound, and the individual died from the cancer three months posttransplant.[4] The high mortality has raised some concerns, as recent reports indicate a superior survival rate, of 47%, among HIV-positive individuals receiving stem cell transplants from donors lacking the CCR5-Δ32 mutation.[5,6] Two ongoing trials in the United States continue to attempt to identify CCR5-Δ32 homozygous donors for people with HIV who need stem cell transplants to treat cancers (see table 1), and a similar effort is under way in Europe led by the IrsiCaixa Institute for AIDS Research in Spain.[7]

Clearly, hopes have significantly diminished that additional cases of cures might result in the near term from immediate ART in infants or CCR5-negative stem cell transplants for people with HIV and cancers. While more cases would have been encouraging for the field, they would not necessarily have aided in the design of more broadly relevant approaches. The majority of current clinical trials represent attempts to create stepping stones toward a cure or the intermediate outcome of extended ART-free remission.

On the funding front, a report from the HIV Vaccines and Microbicides Resource Tracking Working Group (in partnership with AVAC and the Towards an HIV Cure initiative) estimates that global investment in HIV cure research was US$102.7 million in 2013, up from US$88.1 million in 2012[8] – still a very small proportion of overall spending on HIV research. More recently, amfAR, the Foundation for AIDS Research, announced a further expansion of its cure research program, to the tune of US$100 million over the next several years,[9] and NIAID has announced a request for funding applications that will lead to the support of three or four Martin Delaney Collaboratories focused on the development of an HIV cure starting in mid-2016 (after the current grants supporting the Collaboratory of AIDS Researchers for Eradication (CARE), Delaney AIDS Research Enterprise, and defeatHIV, the Delaney Cell and Genome Engineering Initiative expire). A little over US$22 million will be allocated in FY 2016, primarily from NIAID with contributions from the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke.[10] Notably, when the director of the U.S. National Institutes of Health (NIH), Francis Collins, asked the Office of AIDS Research Advisory Council to identify the key priorities for future funding, the pursuit of a cure was ranked prominently among them.[11]

For the most part, immune-based and gene therapies have become integrated into the cure research effort. There is now relatively little exploration of approaches that might be added to ART in order to reduce the residual risk of illness that can persist in some individuals, particularly those who experience poor recovery of CD4+ T cells despite effective viral-load suppression (referred to as immunologic nonresponders, or INRs). Immunologic nonresponse to ART and more subtle manifestations of persistent immune dysregulation such as elevated levels of inflammatory biomarkers and low CD4:CD8 ratios have been associated with a significantly increased risk of morbidity and mortality.[12,13] In the absence of immune-based interventions, evidence indicates that the best approach to minimizing risk is to address modifiable lifestyle factors such as smoking, diet, and exercise. Excercise has been reported to have positive immunologic effects including lowering markers of immune senescence.[14,15]

There is one very large clinical endpoint trial of a possible adjunct to ART that has been launched this year. Known as the REPRIEVE trial, it will assess whether the statin drug pitavastatin can reduce the incidence of cardiovascular disease in people on ART; it aims to recruit 6,500 participants.[16] In addition to lipid-lowering effects, some statins have been reported to reduce inflammatory and immune activation biomarkers in HIV-positive individuals.[17,18] Changes in the inflammatory biomarkers RP, Lp-PLA2, and sCD163 will be evaluated in a REPRIEVE substudy.[19]

Table 1. Research Toward a Cure 2015: Current Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
ADOPTIVE IMMUNOTHERAPY				
Early ART in combination with autologous HIV-specific cytotoxic T-lymphocyte (CTL) infusion	T-cell therapy	NCT02231281	Yong-Tao Sun, Tangdu Hospital, Fourth Military Medical University	Phase III
HXTC	HIV-1 antigen–expanded specific T-cell therapy	NCT02208167	University of North Carolina (UNC) at Chapel Hill	Phase I
ANTIBODIES				
3BNC117	Broadly neutralizing monoclonal antibody	NCT02018510	Rockefeller University	Phase I
BMS-936559	Anti-PD-L1 antibody	NCT02028403 (suspended)	U.S. National Institute of Allergy and Infectious Diseases (NIAID)	Phase I
VRC01	Broadly neutralizing monoclonal antibody + ART interruption	NCT02463227 (not yet open for enrollment)	NIAID	Phase I

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
VRC01	Broadly neutralizing monoclonal antibody	NCT02411539 (not yet open for enrollment)	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody	NCT01950325	NIAID	Phase I
CHERUB 001	Intravenous immunoglobulin in primary HIV infection	No clinicaltrials.gov entry yet	CHERUB (Collaborative HIV Eradication of viral Reservoirs: UK BRC)	N/A
ANTIFIBROTICS				
ACE inhibitors		NCT01535235	University of California, San Francisco/amfAR	Phase IV
losartan	Angiotensin receptor blocker	NCT01852942	University of Minnesota	Phase I
ANTIRETROVIRAL THERAPY IN HIV CONTROLLERS				
emtricitabine + rilpivirine + tenofovir		NCT01777997 (closed to enrollment)	AIDS Clinical Trials Group (ACTG)/ NIAID	Phase IV
COMBINATIONS				
RIVER (Research In Viral Eradication of HIV Reservoirs): ART + ChAdV63.HIVconsv & MVA.HIVconsv vaccines + vorinostat	Therapeutic vaccines + HDAC inhibitor	NCT02336074 (not yet open for enrollment)	Imperial College London	Phase II
SB-728mR-T + cyclophosphamide	Autologous CD4+ T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02225665	Sangamo BioSciences	Phase I/II
SB-728-T + cyclophosphamide	Autologous CD4+ T cells gene-modified via adenovirus vector to inhibit CCR5 expression + transient chemotherapy	NCT01543152	Sangamo BioSciences	Phase I/II
Vacc-4x + romidepsin	HDAC inhibitor + peptide-based therapeutic vaccine	NCT02092116	Bionor Immuno AS/Celgene	Phase I/II
CD4-ZETA +/− interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	Phase I
SB-728mR-T + cyclophosphamide	Autologous CD4+ T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02388594	University of Pennsylvania	Phase I
GENE THERAPIES				
Cal-1: Dual anti-HIV gene transfer construct	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 + fusion inhibitor (C46)	NCT01734850 NCT02390297 (long-term safety phase)	Calimmune	Phase I/II
VRX496	Autologous CD4+ T cells modified with an antisense gene targeting the HIV envelope	NCT00295477 (closed to enrollment)	University of Pennsylvania	Phase I/II
MazF-T	Autologous CD4+ T cells gene-modified with MazF endoribonuclease gene to inhibit HIV	NCT01787994	Takara Bio/University of Pennsylvania	Phase I

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS				
High-dose chemotherapy with transplantation of gene-modified stem cells for high-risk AIDS-related lymphoma	Stem cells gene-modified to express an HIV entry inhibitor C46	NCT00858793 (suspended)	Universitätsklinikum Hamburg - Eppendorf	Phase I/II
HIV-resistant gene-modified stem cells and chemotherapy in treating patients with lymphoma and HIV infection	Stem cells gene-modified to delete CCR5 and express an HIV entry inhibitor C46	NCT02343666	Fred Hutchinson Cancer Research Center	Phase I
Gene-modified HIV-protected stem cell transplant in treating patients with HIV-associated lymphoma	Stem cells gene-modified with LVsh5/C46 (Cal-1)	NCT02378922 (not yet open for enrollment)	Fred Hutchinson Cancer Research Center	Phase I
Gene therapy and combination chemotherapy in treating patients with AIDS-related non-Hodgkin's lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ)	NCT02337985 (not yet open for enrollment)	City of Hope Medical Center	Not listed
Busulfan and gene therapy after frontline chemotherapy in patients with AIDS-related non-Hodgkin's lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ)	NCT01961063	City of Hope Medical Center	Not listed
Gene therapy–treated stem cells in patients undergoing stem cell transplant for intermediate-grade or high-grade AIDS-related lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ)	NCT00569985	City of Hope Medical Center	Not listed
LATENCY-REVERSING AGENTS				
MGN1703	Toll-like receptor 9 (TLR-9) agonist	NCT02443935	University of Aarhus	Phase Ib/IIa
poly-ICLC	TLR-3 agonist	NCT02071095	Nina Bhardwaj/Campbell Foundation/Oncovir	Phase I/II
romidepsin	HDAC inhibitor	NCT01933594	ACTG/NIAID/Gilead Sciences	Phase I/II
vorinostat	HDAC inhibitor	NCT01319383	UNC at Chapel Hill/NIAID/Merck	Phase I/II
ALT-803	Recombinant human superagonist interleukin-15 complex	NCT02191098 (not yet open for enrollment)	University of Minnesota – Clinical and Translational Science Institute	Phase I
bryostatin-1	PKC agonist	NCT02269605 (closed to enrollment)	Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal	Phase I
GS-9620	TLR-7 agonist	Not entered in clinicaltrials.gov (closed to enrollment)	Gilead Sciences	Phase I
OBSERVATIONAL STUDIES				
ACTG A5321	Decay of HIV-1 reservoirs in subjects on long-term antiretroviral therapy: the ACTG HIV reservoirs cohort (AHRC) study	Not listed	ACTG	N/A
Analytic Treatment Interruption (ATI) to Assess HIV Cure	Antiretroviral treatment interruption	NCT02437526 (enrolling by invitation only)	Mayo Clinic	N/A
CHERUB 003	Prospective cohort study evaluating the effects of chemotherapy on the HIV reservoir	NCT01902693 (closed to enrollment)	Imperial College London/CHERUB	N/A

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
CODEX (the "Extreme" cohort)	Long-term nonprogressors and HIV controllers	NCT01520844	French National Institute for Health and Medical Research/ French National Agency for Research on AIDS and Viral Hepatitis (INSERM/ANRS)	N/A
EPIC4	Early Pediatric ART Initiation: Canada Child cure Cohort Study	Not listed	Canadian Institutes of Health Research/Canadian Foundation for AIDS Research/International AIDS Society	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, Thailand/Thai Red Cross AIDS Research Centre	N/A
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans		NCT02154035	NIAID	N/A
Use of leukapheresis to support HIV pathogenesis studies		NCT01161199	University of California, San Francisco	N/A
ULTRASTOP/ERAMUNE-03 (Towards HIV Functional Cure)	Antiretroviral treatment interruption	NCT01876862	Objectif Recherche VACcin Sida/ Fondation Bettencourt Schueller	N/A
mTOR INHIBITORS				
everolimus	Impact of everolimus on HIV persistence following kidney or liver transplant	NCT02429869 (not yet open for enrollment)	University of California, San Francisco	Phase IV
sirolimus	Safety and efficacy of sirolimus for HIV reservoir reduction in individuals on suppressive ART	NCT02440789 (not yet open for enrollment)	ACTG	Phase I/II
STEM CELL TRANSPLANTATION				
BMT CTN 0903	Allogeneic transplant in individuals with chemotherapy-sensitive hematologic malignancies and coincident HIV infection	NCT01410344	National Heart, Lung, and Blood Institute/National Cancer Institute/Blood and Marrow Transplant Clinical Trials Network	Phase II
Immune response after stem cell transplant in HIV-positive patients with hematologic cancer		NCT00968630	Fred Hutchinson Cancer Research Center	Phase II
IMPAACT P1107	Cord blood transplantation using CCR5-Δ32 donor cells for the treatment of HIV and underlying disease	NCT02140944	IMPAACT/NIAID/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	N/A
THERAPEUTIC VACCINES				
AGS-004	Personalized therapeutic vaccine using patient-derived dendritic cells and HIV antigens	NCT01069809 (closed to enrollment)	Argos Therapeutics	Phase II
GTU-MultiHIV + LIPO-5	DNA + lipopeptide vaccines	NCT01492985	INSERM/ANRS	Phase II
VAC-3S	Peptide-based vaccine	NCT02041247	InnaVirVax	Phase II

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
VAC-3S	Peptide-based vaccine	NCT02390466 (not yet open for enrollment)	InnaVirVax	Phase I/IIa
AGS-004	Personalized therapeutic vaccine using patient-derived dendritic cells and HIV antigens	NCT02042248	UNC at Chapel Hill/Argos Therapeutics/U.S. National Institutes of Health	Phase I/II
GTU-MultiHIV B clade	DNA vaccine	NCT02457689	Imperial College London	Phase I/II
Tat Oyi	Tat protein–based vaccine	NCT01793818 (closed to enrollment)	Biosantech	Phase I/II
THV01	Lentiviral vector–based vaccine	NCT02054286	Theravectys S.A.	Phase I/II
ChAdV63.HIVcons + MVA.HIVconsv	Chimpanzee adenovirus and modified vaccinia Ankara strain (MVA) viral vector vaccines	NCT01712425 (closed to enrollment)	IrsiCaixa/Fundació Lluita contra la SIDA/Hospital Clinic of Barcelona/HIVACAT/University of Oxford	Phase I
D–GPE DNA + M–GPE MVA	DNA and MVA viral vector vaccines	NCT01881581	Centers for Disease Control and Prevention, China	Phase I
HIVAX	Lentiviral vector–based vaccine	NCT01428596	GeneCure Biotechnologies	Phase I
iHIVARNA-01	TriMix + HIV antigen naked messenger RNA	NCT02413645 (not yet open for enrollment)	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Phase I
MAG-pDNA + rVSV$_{IN}$ HIV-1 Gag (DNA + viral vector vaccines)	DNA + vesicular stomatitis virus viral vector vaccines	NCT01859325	NIAID/Profectus Biosciences	Phase I
MVA.HIVconsv	Modified MVA viral vector vaccine	NCT01024842 (closed to enrollment)	University of Oxford/Medical Research Council	Phase I
TRADITIONAL CHINESE MEDICINE				
Triptolide wilfordii		NCT02219672	Peking Union Medical College	Phase III
TREATMENT INTENSIFICATION				
LEOPARD (Latency and Early Neonatal Provision of Antiretroviral Drugs Clinical Trial)	Combination antiretroviral therapy	NCT02431975 (not yet open for enrollment)	Columbia University	Not listed
New Era (treatment with multidrug class HAART)	Combination antiretroviral therapy	NCT00908544 (closed to enrollment)	MUC Research	Not listed
AAHIV (Antiretroviral therapy for Acute HIV infection)	Combination antiretroviral therapy	NCT00796263	South East Asia Research Collaboration with Hawaii	Phase III
EIT (Early Infant HIV Treatment in Botswana)	Combination antiretroviral therapy	NCT02369406	Harvard School of Public Health	Phase II/III
peginterferon alfa-2b		NCT02227277	Wistar Institute	Phase II
peginterferon alfa-2b	Cytokine	NCT01935089	University of Pennsylvania/Wistar Institute	Phase II
alpha interferon intensification	Cytokine	NCT01295515	NIAID	Phase I/II
IMPAACT P1115 (very early intensive treatment of HIV-infected infants to achieve HIV remission)	Combination antiretroviral therapy	NCT02140255	IMPAACT/NIAID/NICHD	Phase I/II

*For more information about a trial, go to clinicaltrials.gov and enter its trial registry identifier in the search bar.

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 Trials" web page at: http://www.treatmentactiongroup.org/cure/trials.

Concepts of Remission

After the return of viral load in the Mississippi child, some leading researchers – including Nobel laureate Françoise Barré-Sinoussi – are advocating more cautious application of the word *cure* and the term *functional cure* (which has never been particularly well defined) and recommending the use of *remission* instead.[20] The concept is intended to refer to the ability to safely interrupt ART for some period; however, various different forms of ART-free remission have been described, and precise criteria have yet to be proposed.

The 27-month remission that occurred in the Mississippi case shows similarities with two adults in Boston whose HIV reservoirs were significantly diminished after they received stem cell transplants for the treatment of cancers; both were able to interrupt ART without a return of detectable viral load or replication-competent HIV for periods of 12 and 32 weeks, respectively.[21] In all three instances, the cause of the remission appears to have been the very small size of the HIV reservoir (in the Mississippi child, this was due to early ART's curtailing the formation of the reservoir). The outcomes are consistent with mathematical modeling studies suggesting that significant shrinkage of the size of the reservoir can delay viral-load rebound, with very large reductions potentially equating to lifelong remission in the absence of ongoing ART.[22]

But while the three cases support the idea that limiting or reducing the viral reservoir – a key goal of the research effort – can be beneficial, so far no reservoir-reducing strategy has shown notable effects, let alone come close to the estimated 3-log reduction that occurred in the Boston patients as a result of stem cell transplantation. The mathematical models indicate that a 5-log drop or greater would be needed to achieve lifelong remission in the majority of HIV-positive individuals, so the research has some way to go if a cure is to be achieved by this strategy alone.

A key shared aspect of the Mississippi and Boston cases is that all three lacked detectable immune responses against HIV: in the child, this was due to ART's suppressing HIV quickly after birth, before the developing immune system was significantly exposed to the virus; in the adults, it was because the stem cell transplants gave rise to a new donor-derived immune system that did not mount a response to HIV because suppressive ART was maintained throughout the procedures and for a long period afterward. So it's important to appreciate that the periods of remission in these individuals were likely a consequence of reservoir depletion alone (as opposed to immunologic suppression of the virus) with the viral-load rebounds caused by the chance reactivation of a latently infected CD4+ T cell.

A more commonly described, less stringently defined type of remission (sometimes referred to as virological remission or posttreatment control) involves control of HIV viral load to very low but not necessarily completely undetectable levels in the absence of ART. The best known example of this phenomenon is the VISCONTI (Viro-Immunologic Sustained CONtrol after Treatment Interruption) cohort, consisting of 20 individuals treated during early infection who interrupted ART after a period of several years and have since maintained very low or undetectable viral loads for an average of nine years at the time of the last report.[23] There have also been various case reports over the years involving individuals who have maintained low or undetectable viral loads after ART interruption; typically, treatment was initiated during acute or early infection, but rare examples in chronic infection exist.[24,25,26,27,28,29,30]

While a relatively small HIV reservoir has been implicated in some of these cases, HIV-specific and innate immune responses are also present and may be contributing. Therefore, it's possible that enhancing or rejuvenating antiviral immunity could lead to this intermediate type of remission while work continues toward the development of interventions capable of reducing the HIV reservoir to the dramatic extent mathematical models suggest is required to achieve a lifelong cure. Several of the trials listed in table 1 are exploring compounds whose mechanisms of action may have immunologic components, and several trials combining latency-reversing agents with therapeutic vaccines are under way or imminent.

A related thread of research is attempting to identify biomarkers that predict a delay in viral load rebound after ART interruption, which would allow candidate therapeutic approaches to be assessed without necessarily requiring study participants to stop treatment. A number of retrospective analyses presented or published over the past year have reported that levels of HIV DNA showed significant associations with time to viral-load rebound[31] or viral-load set point[32] in past clinical trials involving ART interruption. A forthcoming AIDS Clinical Trials Group (ACTG) study (ACTG A5345) plans to prospectively assess whether HIV reservoir measurements can predict the pace of viral-load recrudescence during a carefully monitored break from ART.

The ongoing efforts to define the parameters and predictors of ART-free remission form a backdrop to the entire cure research portfolio.

HIV Remission and Health

One of the challenges in defining remission is that there is evidence that even very low levels of HIV can have negative health consequences. Elite controllers, who naturally control viral load to low or undetectable levels in the absence of treatment, were at one time thought to experience no HIV-related illnesses. But in recent years it has been discovered that elite controllers can show elevated levels of immune activation and inflammation compared with HIV-negative individuals and are not completely protected from eventual CD4+ T-cell decline and progression to AIDS.[33,34] A recent study reported that elite controllers are at increased risk of hospitalization compared with HIV-positive individuals on ART, particularly due to cardiovascular disease,[35] although the extent to which differences in other risk factors (such as smoking) may have contributed is not entirely clear.[36]

If elite controllers are at increased risk of illness compared with their HIV-negative counterparts or HIV-positive people on ART, it raises an important question: what degree of HIV control can actually be considered synonymous with disease-free remission?

The members of the VISCONTI cohort are reported to be healthy, but no one has attempted to prospectively compare the health of posttreatment controllers with HIV-positive people on ART and HIV-negative individuals (such a study would likely be very difficult to conduct given the small numbers). The issue is further complicated by the spectrum of HIV activity that may or may not be detectable in cases described as examples of remission, posttreatment control, or functional cure; this can range from trace amounts of viral genetic material without evidence of replication-competent virus to readily detectable but very low viral load (e.g., <50 copies/mL). There is reason to hope that the extreme low end of this spectrum would be associated with a lack of negative health consequences, but this has not been formally proved. Until these uncertainties are resolved, it should be borne in mind that the terminology used in cure research is not fully clarified, even though it is now quite common for media stories and company press releases to invoke terms like *functional cure*.

Latency-Reversing Agents

Histone Deacetylase (HDAC) Inhibitors

The research group of Ole Søgaard at the University of Aarhus in Denmark continues to pioneer the study of candidate latency-reversing agents in humans. These compounds aim to activate the dormant HIV in latently infected memory CD4+ T cells, which constitute the major reservoir of virus in individuals on ART.[37] Results from a clinical trial of the HDAC inhibitor panobinostat in HIV-positive individuals showed significant induction of HIV RNA expression,[38] and a genetic analysis by Sarah Palmer indicates that the drug activated a diverse pool of latent viruses.[39] Consistent with previously published laboratory research,[40] induction of HIV RNA expression did not lead to a measurable depletion of the HIV reservoir overall.

Four out of the 15 trial participants experienced a persistent decline in HIV DNA levels, ranging from 67% to 84%, and this correlated with a slightly longer time to viral-load rebound during an analytical ART interruption. An analysis presented as a poster by Martin Tolstrup at the 2014 International AIDS Conference suggested that this outcome may have been linked to innate immunity – particularly enhanced natural killer cell activity[41] – but due to the small subset of participants involved the results can be viewed only as exploratory.

Additional findings from the panobinostat trial were that no activation of HIV or inflammation was detectable in the cerebrospinal fluid;[42] cerebrospinal fluid was analyzed due to concerns that latency-reversing agents might provoke virus-associated damage to the brain. In a separate paper, the researchers reported that the drug significantly reduced biomarkers of inflammation and cardiovascular disease in the blood, leading to the suggestion that it might have role as an anti-inflammatory agent.[43]

Also at the 2014 International AIDS Conference, Søgaard presented preliminary results from an ongoing trial of the HDAC inhibitor romidepsin[44] (also currently under study at the ACTG). The results demonstrated induction of HIV RNA to levels detectable using a clinical viral-load test (>20 copies/mL and up to a little over 100 copies/mL in some cases), which has not been documented with any other latency-reversing agent to date. As in other HDAC inhibitor trials, no overall change in HIV DNA or other reservoir measures was observed.

No serious adverse events were documented in the panobinostat or romidepsin trials (side effects were primarily fatigue and gastrointestinal symptoms), although concerns have been raised about the unknown implications of long-term changes in gene expression associated with the receipt of HDAC inhibitors.[45] No evidence of an inhibitory effect of panobinostat or romidepsin on HIV-specific CD8+ T-cell responses was observed,[46] which a previously published laboratory study had suggested might be a problem.[47]

A second part of the romidepsin trial is now testing whether the addition of the therapeutic HIV vaccine candidate Vacc-4x (consisting of several conserved HIV Gag peptides) can invoke immune responses capable of eliminating latently infected CD4+ T cells that are induced to express HIV.

Other combinations of HDAC inhibitors and therapeutic HIV vaccines are also being explored in trials. Researchers at CARE plan to marry the HDAC inhibitor vorinostat with AGS-004, a dendritic cell–based vaccine that incorporates HIV antigens derived from viral RNA sampled from the intended recipient.[48] In the United Kingdom, the Research In Viral Eradication of HIV Reservoirs (RIVER) trial aims to evaluate an HDAC inhibitor along with chimpanzee adenovirus and modified vaccinia Ankara strain (MVA) vaccine vectors encoding HIV antigens selected based on their conservation among diverse viruses.

Disulfiram

The drug disulfiram, better known by its trade name, Antabuse, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcoholism. The potential HIV latency–reversing activity of disulfiram was first identified in a laboratory screen conducted by Robert Siliciano's research group at Johns Hopkins,[49] and a small pilot study was later conducted at the University of California, San Francisco (UCSF).[50] Data from a larger dose-escalation trial recently presented by Steven Deeks of UCSF revealed significant increases in levels of cell-associated HIV RNA, along with a postadministration increase in plasma HIV RNA of around twofold in recipients of the highest dose, 2,000 mg/day.[51] Although there has been some variability in the results, there is interest in continuing to study disulfiram's latency-reversing potential due to its extensive safety record.

Scientists in Spain have completed a small study of disulfiram at a dose of 1,000 mg/day in combination with a therapeutic HIV vaccine, MVA-B (an MVA vector encoding clade B HIV antigens). The vaccine successfully induced HIV Gag-specific T-cell responses and was associated with a very slight delay in viral-load rebound during an analytic ART interruption. Viral-load rebound kinetics were not significantly different among participants receiving disulfiram in addition to MVA-B, and no reduction in HIV DNA levels was observed.[52]

Toll-Like Receptor (TLR) Agonists

TLRs are involved in the recognition of particular patterns common to pathogenic organisms and play a role in the induction of innate and adaptive immunity. Stimulation of TLRs with agonist molecules can have adjuvant and therapeutic effects by modulating the immune response, and several TLR agonists have been reported to activate latent HIV in vitro.[53,54] There is particular interest in the possibility of a dual mechanism of action, as TLR agonists have also been reported to enhance natural killer and CD8+ T-cell activity against HIV.[55]

Two widely publicized presentations at the 2015 Conference on Retroviruses and Opportunistic Infections describe the latency-reversing capacity of GS-9620, a TLR-7 agonist developed by Gilead Sciences. In a study in SIV-infected macaques on ART, GS-9620 caused transient viral-load increases to detectable levels at the highest dose administered. Evidence of increased natural killer cell and CD8+ T-cell activation was also seen, and levels of HIV DNA declined significantly in three of four animals, in both blood and tissues.[56] A separate poster presentation reported that GS-9620 activated latent HIV in CD4+ T cells isolated from HIV-positive individuals on ART.[57] Clinical trials in hepatitis B and C have found GS-9620 to be safe,[58,59] and a phase I exploration of safety and activity in HIV-positive individuals is under way (regrettably, Gilead Sciences has not registered the trial at clinicaltrials.gov).

In addition to its work with HDAC inhibitors and therapeutic vaccination, Søgaard's group has recently launched a trial of a TLR-9 agonist to study its effects on the HIV reservoir. The rationale derives from an exploratory analysis of a trial of a pneumococcal vaccine in HIV-positive individuals on ART in which one arm received a TLR-9 agonist as an adjuvant; levels of HIV DNA among the participants in this arm declined significantly, and this correlated with increases in markers associated with improved CD8+ T-cell function.[60]

An ongoing trial at Rockefeller University is investigating poly-ICLC, a TLR-3 agonist more typically used as a vaccine adjuvant.

Interleukin-15 (IL-15) Superagonist ALT-803

Agents that may have a dual mechanism of action – both reversing HIV latency and enhancing immune responses with the potential to eliminate virus-infected cells – have emerged as a theme this year. Among them is the cytokine IL-15, which has been shown to induce HIV production by latently infected CD4+ T cells[61]

and promote natural killer cell and CD8+ T-cell activity.[62] ALT-803, also known as an IL-15 superagonist, is a modified version of the cytokine with enhanced potency. Recent studies of ALT-803 indicate that it can activate natural killer cells, leading to inhibition of HIV in humanized mice.[63] In laboratory experiments, ALT-803 was found to both stimulate expression of HIV antigens by latently infected CD4+ T cells and enhance their killing by HIV-specific CD8+ T cells.[64] A pilot study of ALT-803 in HIV-positive individuals on ART is due to start soon at the University of Minnesota.

Bryostatin-1/Protein Kinase C (PKC) Agonists

Bryostatin-1 belongs to a class of compounds known as PKC agonists. Laboratory studies have shown that PKC agonists can induce HIV production by latently infected CD4+ T cells[65] and work synergistically with HDAC inhibitors to achieve levels of latency-reversing activity close to those observed with maximal CD4+ T-cell activation.[66,67] Bryostatin-1 has also been reported to interact with TLR-4 and stimulate production of chemokines capable of inhibiting HIV.[68] There are concerns about the potential toxicity of bryostatin-1, which has caused severe myalgias and other grade 3 and 4 adverse events in cancer trials,[69] but a small trial involving low doses is ongoing in Spain. The company supplying the drug, Aphios Corporation, is considering developing a combination latency-reversing agent incorporating bryostatin-1 (or a similar analogue) and an HDAC inhibitor.[70]

Another PKC agonist drawing interest is Ingenol-B, an extract from the sap of the tropical shrub *Euphorbia tirucalli*. Several research laboratories have reported that it has latency-reversing activity,[71,72,73] and there is evidence to suggest that it may be less prone to cause toxicity than other PKC agonists. Clinical trials are in the planning stages.

Broadly Neutralizing Antibodies

New technologies have facilitated the discovery of an increasing number of antibodies capable of broadly neutralizing a diverse array of HIV isolates from across the globe, many with great potency (robust inhibition of HIV is achieved at relatively low antibody concentrations).[74,75,76] Tens of thousands of HIV-specific B cells can now be sampled from HIV-positive individuals and the antibodies they are producing fished from each individual cell and tested for their ability to inhibit viral replication. The broadly neutralizing antibodies (bNAbs) identified with this approach do not necessarily benefit the person they are sampled from, likely due in part to the complex swarm of diverse HIV variants circulating in chronically infected individuals, and the titers of the bNAbs being low compared to the amount of virus present. But the potency and breadth of neutralization of the new generation of bNAbs suggest that they could be beneficial when delivered intravenously or subcutaneously in both preventive and therapeutic contexts (see "Preventive Technologies," page 57).

For cure researchers, there is particular interest in the potential of bNAbs to promote destruction of HIV-infected cells via antibody-mediated cellular cytotoxicity or antibody-mediated cellular phagocytosis.[77] These effector functions involve the binding of the antibody to HIV antigens being expressed by infected cells, followed by the recruitment of natural killer cells or monocytes to destroy the cell (the recruitment is accomplished by a part of the antibody structure known as the Fc region, which interacts with Fc receptors on the effector cells). A study in humanized mice has provided evidence that this type of antibody-mediated activity can work in concert with latency-reversing agents to diminish the HIV reservoir.[78]

Several potent bNAbs are now being manufactured and tested in clinical trials, and this year saw the publication of results from a phase I evaluation of the bNAb 3BNC117 in HIV-positive individuals.[79] At the highest of the four doses administered (30 mg/kg), a single intravenous infusion of 3BNC117 led to a decline in viral load ranging from 0.8 to 2.5 logs, with four of eight recipients remaining below baseline at the last reported follow-up (day 56 postinfusion). There was evidence of 3BNC117-resistant HIV emerging in some participants, and one individual showed high-level resistance to the antibody at baseline. The investigators are currently analyzing whether any recipients developed immune responses against the 3BNC117 antibody; those results are pending.

The confirmation that bNAbs are active against HIV in humans presages a significant expansion of research in this area. VRC01, a bNAb developed by the NIH Vaccine Research Center (VRC), is already undergoing testing (delivered intravenously or subcutaneously)[80] in both HIV-positive and HIV-negative individuals, and several new clinical trials are imminent; these include an assessment of effects on the HIV reservoir and on viral-load rebound after ART interruption. The U.S. Military HIV Research Program will soon launch a study of VRC01 in Thai individuals with acute HIV infection.[81] The VRC has begun manufacture of a longer-acting formulation of VRC01 (VRC01-LS) and an additional long-acting bNAb, VRC07-523-LS.

The research group of Dan Barouch at the Beth Israel Deaconess Medical Center is on the verge of initiating trials of the bNAb PGT121 after obtaining promising results in macaque experiments.[82] If all goes well, future plans include combination studies with other bNAbs and latency-reversing agents.[83]

The researchers responsible for the 3BNC117 trial, led by Sarah Schlesinger at Rockefeller University, are working on several protocols that aim to test the effects of 3BNC117 on the HIV reservoir (either alone or in combination with a latency-reversing agent), the impact on viral rebound after ART interruption, and efficacy in combination with the bNAb 10-1074.[84]

Adoptive Immunotherapy

An alternative approach to therapeutically exploiting immune responses against HIV is to administer CD8+ T cells targeting the virus. The CD8+ T cells are extracted from the intended recipient, stimulated with HIV antigens and expanded in the laboratory, and then reinfused. David Margolis and colleagues from CARE and the University of North Carolina at Chapel Hill are pursuing this strategy – which they have named HIV-1 Antigen Expanded Specific T Cell Therapy (HXTC)[85] – as a means to target the HIV reservoir, and an initial phase I trial investigating safety and efficacy has begun. In laboratory studies, HIV-specific CD8+ T cells generated by their method were able to kill latently infected CD4+ T cells exposed to the latency-reversing HDAC inhibitor vorinostat.[86] Infusions of autologous HIV-specific CD8+ T cells are also being studied in an ongoing trial led by Yong-Tao Sun of the Tangdu Hospital, Fourth Military Medical University in Xi'an, China.

Mammalian Target of Rapamycin (mTOR) Inhibitors

Drugs that inhibit the cellular protein mTOR are under investigation in two trials. The effects of mTOR inhibitors are complex, involving both immune-suppressive and immune-enhancing activity. In a retrospective study of HIV-positive individuals who had undergone kidney transplantation, receipt of the mTOR inhibitor sirolimus was associated with significantly reduced levels of HIV DNA.[87] The ACTG is soon to launch a pilot study to prospectively measure the impact of the drug on the HIV reservoir.

Researchers at UCSF plan to conduct a trial that will add six months of everolimus, a derivative of sirolimus, to the regimens of HIV-positive individuals who have received kidney or liver transplants. The effect on the HIV reservoir will be assessed at several times during and after receipt of the drug.

Gene Therapies

A development in gene therapy that made the news earlier this year was the approval by the FDA of a clinical trial involving genetic modification of stem cells. The project involves collaboration between researchers from City of Hope Medical Center in Los Angeles, the Keck School of Medicine at the University of Southern California, and Sangamo BioSciences, with support from the California Institute for Regenerative Medicine (CIRM). Stem cells will be extracted from individuals, treated with Sangamo's zinc finger nuclease technology to disrupt the CCR5 gene, and then reinfused with the aim of generating CCR5-negative immune cells resistant to HIV. According to a press release from CIRM, the initial study population will be HIV-positive individuals responding poorly to ART.[88] Although some of the headlines described the approach as a "functional cure"[89] or "potential cure,"[90] this is in fact only an exploratory study, and it is wildly premature to suggest that it could be curative; previous trials involving genetic modification of stem cells have generated only low levels of gene-modified CD4+ T cells.[91]

The Fred Hutchinson Cancer Research Center has listed two new gene therapy trials for HIV-positive individuals requiring stem cell transplants for lymphoma. One protocol will genetically modify stem cells with a vector that disrupts CCR5 and encodes the HIV fusion inhibitor protein C46. The vector also encodes a gene (P140K) that enables the engraftment of gene-modified cells to be promoted by the administration of a combination of drugs, O6-benzylguanine and carmustine.[92] Analytic ART interruptions may be performed if sufficient levels of gene-modified cells are achieved. The other trial will alter stem cells with Cal-1, a lentiviral vector developed by Calimmune that encodes a short hairpin RNA that inhibits expression of CCR5 and C46.[93]

Research continues into the use of the Sangamo BioSciences technology to genetically modify CD4+ T cells ex vivo. The CD4+ T cells are extracted from HIV-positive individuals, exposed to the zinc finger nuclease to disrupt the CCR5 gene, then expanded and reinfused. In studies published and presented to date,[94,95] an adenovirus vector was used to deliver the zinc finger nuclease into the CD4+ T cells during the process. The company is now testing a different and potentially more efficient approach in which messenger RNA encoding the zinc finger nuclease is used instead of an adenovirus vector. Over the past year, two clinical trials have opened that will deliver CD4+ T cells modified with this method; both are using transient administration of cyclophosphamide prior to the infusion to enhance the engraftment of the altered cells.

Pediatric Cure Research

In addition to the IMPAACT P1115 clinical trial mentioned in the introduction, there are three other new studies investigating the effect of ART on the HIV reservoir in the context of mother-to-child transmission. The Early Pediatric Initiation: Canadian Child Cure Cohort Study (EPIC4) is an observational cohort study being conducted by Hugo Soudeyns and colleagues under the aegis of the recently established Canadian HIV Cure Enterprise. The aim is to study the HIV reservoir and biomarkers of disease pathogenesis in children and adults who acquired infection at birth and have had varied treatment histories.

The Latency and Early Neonatal Provision of Antiretroviral Drugs (LEOPARD) clinical trial is being led by Louise Kuhn at Columbia University and plans to investigate ART initiated within 48 hours of birth in 60 vertically infected infants in South Africa. The Harvard School of Public Health is sponsoring Early Infant HIV Treatment (EIT) in Botswana, which will assess early ART in two cohorts of infants, one infected antepartum (started on ART within seven days of birth) and the other peripartum (started on ART within 57 days of birth).

Therapeutic Vaccines

New therapeutic vaccines undergoing evaluation include iHIVARNA-01, which uses messenger RNA to deliver HIV antigens along with TriMix, an adjuvant cocktail consisting of three proteins involved in the activation of antigen-presenting cells: CD40L, CD70, and TLR4. The first clinical trial is being launched as part of a collaborative effort involving multiple European institutions coordinated by Felipe García of Barcelona's Institut d'Investigacions Biomèdiques August Pi i Sunyer, with funding support from the European Commission.[96]

Researchers at Imperial College London have initiated a new trial of FIT Biotech's GTU-MultiHIV B clade naked DNA vaccine in HIV-positive individuals on ART. Two different routes of administration will be compared: transcutaneous, or intramuscular with electroporation (which delivers a brief electrical pulse to enhance cellular uptake of the DNA).

Recent published results include those from a completed trial of Barbara Ensoli's HIV Tat protein vaccine, which has been the subject of some controversy over the years, with questions having been raised about the appropriateness of Italian government funding for the research.[97] Ensoli and colleagues' paper, published in the open-access journal *Retrovirology*, reports that the vaccine induced Tat-specific antibody responses and that recipients showed a lowering of HIV DNA levels.[98] However, the trial did not include a placebo control group; instead, comparisons were made with a separate parallel cohort, and this makes the data difficult to interpret. Results from a randomized clinical trial conducted in South Africa are pending.

At the HIV Research 4 Prevention conference in Cape Town in October 2014, Harriet Robinson from GeoVax presented results from a small therapeutic trial of the company's DNA/MVA prime-boost HIV vaccine approach. A total of nine individuals who had started ART within 18 months of seroconversion received the DNA/MVA regimen and underwent a 12-week analytic ART interruption. HIV-specific CD8+ T cells were increased in the majority of participants, but viral-load rebound occurred in all individuals after ART cessation. The levels of HIV viral load were somewhat lower at the end of the ART interruption compared with the pre-ART baseline in five participants, but there was no suggestion of vaccination leading to durable control. A clinical trial is now being planned that will combine the DNA/MVA vaccine with a latency-reversing agent.[99]

Table 2. Immune-Based Therapy Pipeline 2015

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
interleukin-7 (IL-7)	Cytokine	French National Agency for Research on AIDS and Viral Hepatitis (ANRS)/Cognate Biosciences	Phase II
losartan	Angiotensin II receptor antagonist, anti-inflammatory	Minneapolis Medical Research Foundation	Phase II
lubiprostone	Apical lumen ClC-2 chloride channel activator	Ruth M. Rothstein CORE Center/Chicago Developmental Center for AIDS Research	Phase II
methotrexate (low-dose)	Anti-inflammatory	NIAID	Phase II
metformin	Biguanide antidiabetic	University of Hawaii/National Institute of General Medical Sciences	Phase II
niacin	Vitamin B3	McGill University Health Center/Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network	Phase II
VSL#3	Probiotic	Virginia Commonwealth University/Bill & Melinda Gates Foundation University Health Network, Toronto/CIHR Canadian HIV Trials Network	Phase II
dipyridamole	Phosphodiesterase type 5 inhibitor, anti-inflammatory	Sharon Riddler, University of Pittsburgh/NIAID	Phase I/II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Mesenchymal stem cells	Allogenic adult mesenchymal stem cells from adipose tissue	Iniciativa Andaluza en Terapias Avanzadas – Fundación Pública Andaluza Progreso y Salud	Phase I//II
Tripterygium wilfordii Hook F	Traditional Chinese medicine, anti-inflammatory	Beijing 302 Hospital/Peking Union Medical College	Phase I/II
Umbilical cord mesenchymal stem cells	Adult stem cells originating from the mesenchymal and connective tissues	Beijing 302 Hospital	Phase I//II
vorapaxar	Thrombin receptor (PAR-1) antagonist	Kirby Institute/NIAID/University of Minnesota – Clinical and Translational Science Institute/University of Melbourne/Merck	Phase I/II
aprepitant	Neurokinin 1 receptor antagonist	University of Pennsylvania	Phase I
HLA–B*57 cell transfer	Cell infusion	NIH Clinical Center	Phase I
hydroxychloroquine	Antimalarial, antirheumatic, anti-inflammatory	St Stephens AIDS Trust	Phase I

As outlined in the introduction to this chapter, very little is trickling through the immune-based therapy pipeline. A study of the antifibrotic drug pirfenidone in SIV-infected macaques offered support for the idea that repairing lymph node fibrosis, a type of scarring damage that occurs in HIV infection, might promote CD4+ T-cell reconstitution.[100] The immunologic effects of a similar drug, losartan, are being tested in an ongoing clinical trial for HIV-positive individuals on ART at the University of Minnesota.[101]

In a small trial conducted in China, therapeutic administration of umbilical cord–derived mesenchymal stem cells was reported to increase CD4+ T cells and decrease markers of immune activation and inflammation in INRs.[102] An additional trial in INRs is now being launched in Spain; it differs somewhat from the research in China because the mesenchymal stem cells are sourced from adipose (fatty) tissue rather than umbilical cords.[103]

Another relatively unconventional therapy is *Tripterygium wilfordii* Hook F, an extract from a vine used in traditional Chinese medicine. A paper published earlier this year reported that administration to INRs in a small pilot study was associated with an increase in CD4+ T-cell counts;[104] a larger randomized trial that aims to enroll 60 people is under way.[105] An extract of *Tripterygium wilfordii* is also being studied in China for its effects on the HIV reservoir (see table 1).

Interventions with potential anti-inflammatory effects continue to generate interest. A trial with sites in Australia and the United States will test the Merck drug vorapaxar for its effects on D-dimer (a coagulation biomarker that has been associated with mortality in HIV infection)[106] and markers of immune activation.[107] Aprepitant (brand name Emend) is an FDA-approved antiemetic that has been reported to have anti-inflammatory properties in HIV-positive individuals during a short two-week course of treatment.[108] A follow-up trial is now evaluating whether ritonavir-containing ART regimens can increase aprepitant levels and enhance the drug's impact on inflammatory biomarkers over four weeks of administration.[109]

Results from a double-blind, randomized, placebo-controlled trial of the probiotic *Saccharomyces boulardii* were published in March 2015.[110] A total of 44 HIV-positive individuals on ART were enrolled, and significant declines in lipopolysaccharide-binding protein (LBP) and IL-6 were documented in the probiotic recipients. LBP is a marker of microbial translocation (leakage of normally beneficial bacteria from the gut into the systemic circulation), and IL-6 is an inflammatory biomarker that has been associated with the risk of death in HIV-positive people.[111] Three new studies of the probiotic VSL#3 are being undertaken: one sponsored by Virginia Commonwealth University and the Bill & Melinda Gates Foundation that is recruiting Malian women not yet on ART[112] and two by the University Health Network, Toronto, and the Canadian HIV Trials Network – one involving individuals starting ART[113] and the other INRs with CD4+ T-cell counts less than 350/mm^3 despite two years or more of ART.[114]

Hopes that the anti-inflammatory properties of chloroquine might be of benefit to INRs appear to be fading. Results from two clinical trials have become available: researchers in Canada added chloroquine to ART in INRs and found no significant changes in T-cell counts or markers of immune activation and inflammation except for an increase in alpha interferon.[115] An ACTG study of chloroquine in HIV-positive individuals either on or off ART documented no significant differences in immune activation or CD4+ T-cell counts; these results are unpublished but available at clinicaltrials.gov.[116]

Conclusion

The expansion of research toward an HIV cure has continued over the past year. The growing number of clinical trials can be viewed as the tip of the iceberg; below the waterline lies formative basic research and work in animal models aiming to fully delineate the HIV reservoir and refine how to measure and, ultimately, eliminate it. Prominent among the approaches being translated from the basic to clinical realms this year are those with a potential dual mechanism of action: reversing HIV latency and stimulating immune responses against virus-infected cells.

The growing number of cure-related projects and collaborations globally is encouraging, but the decline in funding for the NIH – the world's largest funder of scientific research – is a major concern that must be addressed. As the field increasingly draws media attention, a broader dialogue is needed in order to reach consensus about how the goals of cure research and the terminology are characterized and communicated; the concept of HIV remission is increasingly invoked but is not yet clearly defined.

While the cure research pipeline is swelling, prospects for immune-based adjuncts to ART – interventions for which there remains a need – have dimmed in recent years. This is not due to lack of interest from scientists and clinicians, who are still pursuing small-scale studies of a range of possible therapies, but there is little sign of the industry support that might thrust an approach with promise through the pipeline. On a more hopeful note, although only tangentially related to immune-based therapy, the REPRIEVE trial of statin treatment may offer insight into the feasibility of conducting large-scale clinical evaluations of add-ons to ART.

REFERENCES

Unless noted otherwise, all links were accessed on June 8, 2015.

CROI: Conference on Retroviruses and Opportunistic Infections

1. National Institute of Allergy and Infectious Diseases (U.S.) (Press Release). "Mississippi baby" now has detectable HIV, researchers find. 2014 July 10. http://www.niaid.nih.gov/news/newsreleases/2014/Pages/MississippiBabyHIV.aspx.

2. Luzuriaga K, Gay H, Ziemniak C, et al. Viremic relapse after HIV-1 remission in a perinatally infected child. N Engl J Med. 2015 Feb 19;372(8):786–8. doi: 10.1056/NEJMc1413931.

3. Hütter G. More on shift of HIV tropism in stem-cell transplantation with CCR5 delta32/delta32 mutation. N Engl J Med. 2014 Dec 18;371(25):2437–8. doi: 10.1056/NEJMc1412279.

4. Duarte RF, Salgado M, Sánchez-Ortega I, et al. CCR5 Δ32 homozygous cord blood allogeneic transplantation in a patient with HIV: a case report. Lancet HIV. 2015 June 1;2(6):e236–e242. doi:10.1016/S2352-3018(15)00083-1.

5. Henrich TJ. HIV eradication: is cord blood the answer? Lancet HIV. 2015 June 1;2(6):e219–e220. doi:10.1016/S2352-3018(15)00088-0.

6. Duarte RF, Labopin M, Badoglio M, et al. Allogeneic transplantation in patients with HIV-infection: a pair matched cohort study by the European Society for Blood and Marrow Transplantation (Abstract 007). Bone Marrow Transplant. 2015;50(suppl 1):S5–S6.

7. amfAR (Press Release). HIV cure research gains momentum from new amfAR funding. 2014 July 9. http://www.amfar.org/2.4-million-for-collaborative-efforts-to-pursue-hiv-aids-eradication/.

8. AVAC, IAS Towards an HIV Cure Initiative, HIV Vaccines and Microbicides Resource Tracking Working Group. Global investment in HIV cure research and development in 2013. 2014 July. https://www.iasociety.org/Web/WebContent/File/HIV_Cure_Resource_Tracking_Paper_2013.pdf.

9. amfAR (Press Release). amfAR announces $100 million investment strategy aimed at curing HIV. 2015 February 19. http://www.amfar.org/amfar-announces-100-million-investment-strategy-aimed-at-curing-hiv/.

10. Department of Health and Human Services (U.S.). Martin Delaney Collaboratories for HIV Cure Research (UM1) [Internet]. 2015 May 21. http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-15-029.html.

11. Walensky RP, Auerbach JD; Office of AIDS Research Advisory Council (OARAC) HIV/AIDS Research Portfolio Review Working Group. Focusing National Institutes of Health HIV/AIDS research for maximum population impact. Clin Infect Dis. 2015 Mar 15;60(6):937–40. doi: 10.1093/cid/ciu942.

12. Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. Adv Immunol. 2013;119:51–83. doi: 10.1016/B978-0-12-407707-2.00002-3.

13. Serrano-Villar S, Sainz T, Lee SA, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. PLoS Pathog. 2014 May 15;10(5):e1004078. doi: 10.1371/journal.ppat.1004078.

14. Department of Health and Human Services (U.S.), Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [Internet]. 2015 April 8 (cited 2015 April 8). p. H14. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

15. De Araújo AL, Silva LC, Fernandes JR, Benard G. Preventing or reversing immunosenescence: can exercise be an immunotherapy? Immunotherapy. 2013 Aug;5(8):879–93. doi: 10.2217/imt.13.77.

16. National Institutes of Health (U.S.) (Press Release). NIH launches largest clinical trial focused on HIV-related cardiovascular disease. 2015 April 15. http://www.nih.gov/news/health/apr2015/nhlbi-15.htm.

17. Funderburg NT, Jiang Y, Debanne SM, et al. Rosuvastatin reduces vascular inflammation and T-cell and monocyte activation in HIV-infected subjects on antiretroviral therapy. J Acquir Immune Defic Syndr. 2015 Apr 1;68(4):396–404. doi: 10.1097/QAI.0000000000000478.

18. De Wit S, Delforge M, Necsoi CV, Clumeck N. Downregulation of CD38 activation markers by atorvastatin in HIV patients with undetectable viral load. AIDS. 2011 Jun 19;25(10):1332–3. doi: 10.1097/QAD.0b013e328347c083.

19. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02344290, Evaluating the use of pitavastatin to reduce the risk of cardiovascular disease in HIV-infected adults (REPRIEVE); 2015 January 16 (cited 2015 April 27). https://clinicaltrials.gov/ct2/show/NCT02344290.

20. Tucker JD, Volberding PA, Margolis DM, Rennie S, Barré-Sinoussi F. Words matter: Discussing research towards an HIV cure in research and clinical contexts. J Acquir Immune Defic Syndr. 2014 Nov 1;67(3):e110-1. doi: 10.1097/QAI.0000000000000305.

21. Henrich TJ, Hanhauser E, Marty FM, et al. Antiretroviral-free HIV-1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases. Ann Intern Med. 2014 Sep 2;161(5):319–27. doi: 10.7326/M14-1027.

22. Hill AL, Rosenbloom DI, Fu F, Nowak MA, Siliciano RF. Predicting the outcomes of treatment to eradicate the latent reservoir for HIV-1.Proc Natl Acad Sci U S A. 2014 Sep 16;111(37):13475–80. doi: 10.1073/pnas.1406663111. Erratum in: Proc Natl Acad Sci U S A. 2014 Oct 28;111(43):15598.

23. Rouzioux C, Hocqueloux L, Sáez-Cirión A. Posttreatment controllers: what do they tell us? Curr Opin HIV AIDS. 2015 Jan;10(1):29–34. doi: 10.1097/COH.0000000000000123.

24. Lodi S, Meyer L, Kelleher AD, et al. Immunovirologic control 24 months after interruption of antiretroviral therapy initiated close to HIV seroconversion. Arch Intern Med. 2012 Sep 10;172(16):1252–5. doi: 10.1001/archinternmed.2012.2719.

25. Van Lunzen J, Schulze zur Wiesch J, Schuhmacher U, Hauber I, Hauber J. Functional cure after long term HAART initiated during early HIV infection: a comprehensive case study (Abstract TUPE246). 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2013 June 20–July 3; Kuala Lumpur, Malaysia. http://pag.ias2013.org/Abstracts.aspx?AID=1435.

26. Kinloch S, Dorrell L, Yang H, et al. Aviremia 10-year post-ART discontinuation initiated at seroconversion (Abstract 377). 22nd CROI; 2015 February 23–26; Seattle, WA. http://www.croiconference.org/sessions/aviremia-10-year-post-art-discontinuation-initiated-seroconversion.

27. Salgado M, Rabi SA, O'Connell KA, et al. Prolonged control of replication-competent dual- tropic human immunodeficiency virus-1 following cessation of highly active antiretroviral therapy. Retrovirology. 2011 Dec 5;8:97. doi: 10.1186/1742-4690-8-97.

28. Van Gulck E, Bracke L, Heyndrickx L, et al. Immune and viral correlates of "secondary viral control" after treatment interruption in chronically HIV-1 infected patients. PLoS One. 2012;7(5):e37792. doi: 10.1371/journal.pone.0037792.

29. Feeney ME, Tang Y, Rathod A, Kneut C, McIntosh K. Absence of detectable viremia in a perinatally HIV-1-infected teenager after discontinuation of antiretroviral therapy. J Allergy Clin Immunol. 2006 Aug;118(2):324–30.

30. Uruena A, Mangano A, Arduino R, Aulicino P, Cassetti I. Functional cure and seroreversion after advanced HIV disease following 7-years of antiretroviral treatment interruption (Abstract MOPE016). AIDS 2014. 20th International AIDS Conference; 2014 July 20–25; Melbourne, Australia. http://pag.aids2014.org/EPosterHandler.axd?aid=5607.

31. Williams JP, Hurst J, Stöhr W, et al. HIV-1 DNA predicts disease progression and post-treatment virological control. Elife. 2014 Sep 12:e03821. doi: 10.7554/eLife.03821. [Epub ahead of print]

32. Li JZ, Heisey A, Ahmed H, Wang H, et al. Relationship of HIV reservoir characteristics with immune status and viral rebound kinetics in an HIV therapeutic vaccine study. AIDS. 2014 Nov 28;28(18):2649–57. doi: 10.1097/QAD.0000000000000478.

33. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. J Infect Dis. 2008 Jan 1;197(1):126–33. doi: 10.1086/524143.

34. Olson AD, Meyer L, Prins M, et al. An evaluation of HIV elite controller definitions within a large seroconverter cohort collaboration. PLoS One. 2014 Jan 28;9(1):e86719. doi: 10.1371/journal.pone.0086719.

35. Crowell TA, Gebo KA, Blankson JN, et al. Hospitalization rates and reasons among HIV elite controllers and persons with medically controlled HIV infection. J Infect Dis. 2015 Jun 1;211(11):1692–702. doi: 10.1093/infdis/jiu809. Epub 2014 Dec 15.

36. Karris MY, Haubrich RH. Antiretroviral therapy in the elite controller: justified or premature? J Infect Dis. 2015 Jun 1;211(11):1689–91. doi: 10.1093/infdis/jiu812. Epub 2014 Dec 15.

37. Siliciano JM, Siliciano RF. The remarkable stability of the latent reservoir for HIV-1 in resting memory CD4+ T cells. J Infect Dis. 2015 Apr 15. doi: 10.1093/infdis/jiv219. [Epub ahead of print]

38. Rasmussen TA, Tolstrup M, Brinkmann CR, et al. Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial. Lancet HIV. 2014 Oct 1;1(1): e13–e21.

39. Barton K, Hiener B, Palmer S, et al. Panobinostat broadly activates latent HIV-1 proviruses in patients (Abstract 109). 22nd CROI; 2015 February 23–26; Seattle, WA. http://www.croiwebcasts.org/console/player/25706?mediaType=audio&.

40. Shan L, Deng K, Shroff NS, et al. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. Immunity. 2012 Mar 23;36(3):491–501. doi: 10.1016/j.immuni.2012.01.014.

41. Tolstrup M, Vigano S, Olesen R, et al. Immunological correlates of HIV-1 DNA decline during latency reversal with panobinostat in patients on suppressive cART (Abstract LBPE06). 20th International AIDS Conference; 2014 July 20–25; Melbourne, Australia. http://pag.aids2014.org/Abstracts.aspx?AID=11259.

42. Rasmussen TA, Tolstrup M, Møller HJ, et al. Activation of latent human immunodeficiency virus by the histone deacetylase inhibitor panobinostat: a pilot study to assess effects on the central nervous system. Open Forum Infect Dis. 2015 Mar 30;2(1):ofv037. doi: 10.1093/ofid/ofv037.

43. Høgh Kølbæk Kjær AS, Brinkmann CR, et al. The histone deacetylase inhibitor panobinostat lowers biomarkers of cardiovascular risk and inflammation in HIV patients. AIDS. 2015 Jun 19;29(10):1195–200. doi: 10.1097/QAD.0000000000000678.

44. Søgaard OS, Graversen ME, Leth S, et al. The HDAC inhibitor romidepsin is safe and effectively reverses HIV-1 latency in vivo as measured by standard clinical assays (Abstract TUAA0106LB). 20th International AIDS Conference; 2014 July 20–25; Melbourne, Australia. http://pag.aids2014.org/abstracts.aspx?aid=11267.

45. Elliott JH, Wightman F, Solomon A, et al. Activation of HIV transcription with short-course vorinostat in HIV-infected patients on suppressive antiretroviral therapy. PLoS Pathog. 2014 Nov 13;10(10):e1004473. doi: 10.1371/journal.ppat.1004473.

46. Olesen R, Rasmussen T, Graversen M, et al. In vivo effects of panobinostat and romidepsin on HIV-1-specific CD8 T cell immunity (Abstract 369). 22nd CROI; 2015 February 23–26; Seattle, WA. http://www.croiconference.org/sessions/vivo-effects-panobinostat-and-romidepsin-hiv-1-specific-cd8-t-cell-immunity.

47. Jones RB, O'Connor R, Mueller S, et al. Histone deacetylase inhibitors impair the elimination of HIV-infected cells by cytotoxic T-lymphocytes. PLoS Pathog. 2014 Aug 14;10(8):e1004287. doi: 10.1371/journal.ppat.1004287.

48. Argos Therapeutics (Press Release). NIH funds study of fully personalized immunotherapy AGS-004 combined with a latency reversing therapy for the treatment of HIV. 2015 April 1. http://ir.argostherapeutics.com/releasedetail.cfm?releaseid=904466.

49. Xing S, Bullen CK, Shroff NS, et al. Disulfiram reactivates latent HIV-1 in a Bcl-2-transduced primary CD4+ T cell model without inducing global T cell activation. J Virol. 2011 Jun;85(12):6060–4. doi: 10.1128/JVI.02033-10.

50. Spivak AM, Andrade A, Eisele E, et al. A pilot study assessing the safety and latency-reversing activity of disulfiram in HIV-1-infected adults on antiretroviral therapy. Clin Infect Dis. 2014 Mar;58(6):883–90. doi: 10.1093/cid/cit813.

51. Elliott JH, Lewin S, Deeks SG. Short-term disulfiram to reverse latent HIV infection (Abstract 0301). Keystone Symposia: Mechanisms of HIV Persistence: Implications for a Cure; 2015 April 26–May 1; Boston, MA.

52. Mothe B, Climent N, Plana M, et al. Safety and immunogenicity of a modified vaccinia Ankara-based HIV-1 vaccine (MVA-B) in HIV-1-infected patients alone or in combination with a drug to reactivate latent HIV-1. J Antimicrob Chemother. 2015 Jun;70(6):1833–42. doi: 10.1093/jac/dkv046.

53. Schlaepfer E, Speck RF. TLR8 activates HIV from latently infected cells of myeloid-monocytic origin directly via the MAPK pathway and from latently infected CD4+ T cells indirectly via TNF-α. J Immunol. 2011 Apr 1;186(7):4314–24. doi: 10.4049/jimmunol.1003174.

54. Novis CL, Archin NM, Buzon MJ, et al. Reactivation of latent HIV-1 in central memory CD4+ T cells through TLR-1/2 stimulation. Retrovirology. 2013 Oct 24;10:119. doi: 10.1186/1742-4690-10-119.

55. Schlaepfer E, Speck RF. Anti-HIV activity mediated by natural killer and CD8+ cells after toll-like receptor 7/8 triggering. PLoS One. 2008 Apr 23;3(4):e1999. doi: 10.1371/journal.pone.0001999.

56. Whitney J, Lim SY, Osuna C, et al. Treatment with a TLR7 agonist induces transient viremia in SIV-infected ART-suppressed monkeys (Abstract 108). 22nd CROI; 2015 February 23–26; Seattle, WA. http://www.croiwebcasts.org/console/player/25705?mediaType=audio&.

57. Sloan D, Irrinki A, Tsai A, et al. TLR7 agonist GS-9620 activates HIV-1 in PBMCs from HIV-infected patients on cART (Abstract 417). 22nd CROI; 2015 February 23–26; Seattle, WA. http://www.croiconference.org/sessions/tlr-agonist-gs-9620-activates-hiv-1-pbmcs-hiv-infected-patients-cart.

58. Gane EJ, Lim YS, Gordon SC, et al. The oral Toll-like receptor-7 agonist GS-9620 in patients with chronic hepatitis B virus infection. J Hepatol. 2015 Feb 27. doi: 10.1016/j.jhep.2015.02.037. [Epub ahead of print]

59. Lawitz E, Gruener D, Marbury T, et al. Safety, pharmacokinetics and pharmacodynamics of the oral Toll-like receptor 7 agonist GS-9620 in treatment-naive patients with chronic hepatitis C. Antivir Ther. 2014 Aug 8. doi: 10.3851/IMP2845. [Epub ahead of print]

60. Winckelmann AA, Munk-Petersen LV, Rasmussen TA, et al. Administration of a Toll-like receptor 9 agonist decreases the proviral reservoir in virologically suppressed HIV-infected patients. PLoS One. 2013 Apr 26;8(4):e62074. doi: 10.1371/journal.pone.0062074.

61. Vandergeeten C, Da Fonseca S, Sereti I, Lederman M, Sekaly RP, Chomont N. Differential impact of IL-7 and IL-15 on HIV reservoir persistence (Abstract MOAA0101). 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2011 July 17–20; Rome, Italy.

62. Steel JC, Waldmann TA, Morris JC. Interleukin-15 biology and its therapeutic implications in cancer. Trends Pharmacol Sci. 2012 Jan;33(1):35–41. doi: 10.1016/j.tips.2011.09.004.

63. Seay K, Church C, Zheng JH, et al. In vivo activation of human NK cells by treatment with an interleukin-15 superagonist potently inhibits acute in vivo HIV-1 infection in humanized mice. J Virol. 2015 Jun 15;89(12):6264–74. doi: 10.1128/JVI.00563-15. Epub 2015 Apr 1.

64. Jones RB, Mueller S, O'Connor R, et al. Cytotoxic T-lymphocytes in combination with the IL-15 superagonist ALT-803 eliminate latently HIV-infected autologous CD4+ T-cells from natural reservoirs (Abstract 2008). Keystone Symposia: Mechanisms of HIV Persistence: Implications for a Cure; 2015 April 26–May 1; Boston, MA.

65. Spina CA, Anderson J, Archin NM, et al. An in-depth comparison of latent HIV-1 reactivation in multiple cell model systems and resting CD4+ T cells from aviremic patients. PLoS Pathog. 2013;9(12):e1003834. doi: 10.1371/journal.ppat.1003834.

66. Pérez M, de Vinuesa AG, Sanchez-Duffhues G, et al. Bryostatin-1 synergizes with histone deacetylase inhibitors to reactivate HIV-1 from latency. Curr HIV Res. 2010 Sep;8(6):418–29.

67. Laird GM, Bullen CK, Rosenbloom DI, et al. Ex vivo analysis identifies effective HIV-1 latency-reversing drug combinations. J Clin Invest. 2015 May 1;125(5):1901–12. doi: 10.1172/JCI80142.

68. Ariza ME, Ramakrishnan R, Singh NP, Chauhan A, Nagarkatti PS, Nagarkatti M. Bryostatin-1, a naturally occurring antineoplastic agent, acts as a Toll-like receptor 4 (TLR-4) ligand and induces unique cytokines and chemokines in dendritic cells. J Biol Chem. 2011 Jan 7;286(1):24–34. doi: 10.1074/jbc.M110.135921.

69. Morgan RJ Jr, Leong L, Chow W, et al. Phase II trial of bryostatin-1 in combination with cisplatin in patients with recurrent or persistent epithelial ovarian cancer: a California cancer consortium study. Invest New Drugs. 2012 Apr;30(2):723–8. doi: 10.1007/s10637-010-9557-5.

70. Aphios Corporation (Press Release). Aphios completes enrollment in phase I/II clinical trial towards an HIV cure. 2015 June 2. http://www.businesswire.com/news/home/20150602005569/en/Aphios-Completes-Enrollment-Phase-III-Clinical-Trial.

71. Abreu CM, Price SL, Shirk EN, et al. Dual role of novel ingenol derivatives from Euphorbia tirucalli in HIV replication: inhibition of de novo infection and activation of viral LTR. PLoS One. 2014 May 14;9(5):e97257. doi: 10.1371/journal.pone.0097257.

72. Jiang G, Mendes EA, Kaiser P, et al. Reactivation of HIV latency by a newly modified Ingenol derivative via protein kinase Cδ-NF-κB signaling. AIDS. 2014 Jul 17;28(11):1555–66. doi: 10.1097/QAD.0000000000000289.

73. Pandeló José D, Bartholomeeusen K, da Cunha RD, et al. Reactivation of latent HIV-1 by new semi-synthetic ingenol esters. Virology. 2014 Aug;462–463:328–39. doi: 10.1016/j.virol.2014.05.033.

74. Scheid JF, Mouquet H, Feldhahn N, et al. Broad diversity of neutralizing antibodies isolated from memory B cells in HIV-infected individuals. Nature. 2009 Apr 2;458(7238):636–40. doi: 10.1038/nature07930. Epub 2009 Mar 15.

75. Simek MD, Rida W, Priddy FH, et al. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm. J Virol. 2009 Jul;83(14):7337-48. doi: 10.1128/JVI.00110-09.

76. Wu X, Yang ZY, Li Y, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science. 2010 Aug 13;329(5993):856–61. doi: 10.1126/science.1187659.

77. Bournazos S, Klein F, Pietzsch J, Seaman MS, Nussenzweig MC, Ravetch JV. Broadly neutralizing anti-HIV-1 antibodies require Fc effector functions for in vivo activity. Cell. 2014 Sep 11;158(6):1243-53. doi: 10.1016/j.cell.2014.08.023.

78. Halper-Stromberg A, Lu CL, Klein F, et al. Broadly neutralizing antibodies and viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice. Cell. 2014 Aug 28;158(5):989–99. doi: 10.1016/j.cell.2014.07.043. Epub 2014 Aug 14.

79. Caskey M, Klein F, Lorenzi JC, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature. 2015 Jun 25;522(7557):487–91. doi: 10.1038/nature14411.

80. Graham BS. Update on clinical development of VRC01 and second generation neutralizing CD4 binding site-specific monoclonal antibodies (Abstract SY12.01). HIV Research for Prevention Conference; 2014 October 28–31; Cape Town, South Africa. http://webcasts.hivr4p.org/console/player/25262?mediaType=audio&.

81. Bolton D, Robb M, Michael N, et al. Efficacy of HIV-1 monoclonal antibody immunotherapy in acute SHIV-infected macaques (Abstract 50). 22nd CROI; 2015 February 23–26; Seattle, WA. http://www.croiwebcasts.org/console/player/25576?mediaType=audio&.

82. Barouch DH, Whitney JB, Moldt B, et al. Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. Nature. 2013 Nov 14;503(7475):224–8. doi: 10.1038/nature12744.

83. Barouch D. Broadly neutralizing antibodies for HIV-1 eradication strategies (Abstract 67). 22nd CROI; 2015 February 23–26; Seattle, WA. http://www.croiwebcasts.org/console/player/25642?mediaType=audio&.

84. Schlesinger SJ. Development of 3BNC117 monoclonal antibody. AVAC Webinar: New Frontiers in HIV Prevention, Treatment and Cure. 2015 April 21. http://www.avac.org/blog/new-frontiers-hiv-prevention-treatment-and-cure.

85. Lam S, Sung J, Cruz C, et al. Broadly-specific cytotoxic T cells targeting multiple HIV antigens are expanded from HIV+ patients: implications for immunotherapy. Mol Ther. 2015 Feb;23(2):387–95. doi: 10.1038/mt.2014.207. Epub 2014 Nov 4.

86. Sung JA, Lam S, Garrido C, et al. Expanded cytotoxic T-cell lymphocytes target the latent HIV reservoir. J Infect Dis. 2015 Jan 13. doi: 10.1093/infdis/jiv022. [Epub ahead of print]

87. Stock PG1, Barin B, Hatano H, et al. Reduction of HIV persistence following transplantation in HIV-infected kidney transplant recipients. Am J Transplant. 2014 May;14(5):1136–41. doi: 10.1111/ajt.12699.

88. California Institute for Regenerative Medicine (Press Release). CIRM-funded clinical trial aimed at blocking HIV/AIDS in people gets the go ahead. 2015 March 3. https://www.cirm.ca.gov/about-cirm/newsroom/press-releases/03032015/cirm-funded-clinical-trial-aimed-blocking-hivaids-people.

89. Dovey D. FDA gives HIV 'functional cure' go-ahead for human trials [Internet]. Medical Daily. 2015 March 10. http://www.medicaldaily.com/functional-hiv-cure-step-closer-reality-fda-approval-clinical-human-trials-325048.

90. Leuty R. Study of potential HIV 'cure' wins FDA nod [Internet]. San Francisco Business Times. 2015 March 3. http://www.bizjournals.com/sanfrancisco/blog/biotech/2015/03/hiv-aids-cirm-stem-cells-sangamo-sgmo-usc.html.

91. Mitsuyasu RT, Merigan TC, Carr A, et al. Phase 2 gene therapy trial of an anti-HIV ribozyme in autologous CD34+ cells. Nat Med. 2009 Mar;15(3):285–92. doi: 10.1038/nm.1932.

92. Trobridge GD, Wu RA, Beard BC, et al. Protection of stem cell-derived lymphocytes in a primate AIDS gene therapy model after in vivo selection. PLoS One. 2009 Nov 2;4(11):e7693. doi: 10.1371/journal.pone.0007693.

93. Burke BP, Levin BR, Zhang J, et al. Engineering cellular resistance to HIV-1 infection in vivo using a dual therapeutic lentiviral vector. Mol Ther Nucleic Acids. 2015 Apr 14;4:e236. doi: 10.1038/mtna.2015.10.

94. Tebas P, Stein D, Tang WW, et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. N Engl J Med. 2014 Mar 6;370(10):901–10. doi: 10.1056/NEJMoa1300662.

95. Blick G, Lalezari J, Hsu R, et al. Cyclophosphamide enhances SB-728-T engraftment to levels associated with HIV-RNA control (Abstract 141). 21st CROI; 2014 March 3–6; Boston, MA.

96. IDIBAPS (Press Release). EU Grants a project to test an innovative HIV vaccine candidate in two phase I/IIa clinical trials. 2013 December 9. http://www.idibaps.org/actualitat/en_noticies/13646/eu-grants-a-idibaps-project-to-test-an-innovative-hiv-vaccine-candidate-in-two-phase-iiia-clinical-trials.

97. Cohen J. AIDS research. Feud over AIDS vaccine trials leads prominent Italian researchers to court. Science. 2007 Aug 10:317(5839):738–9. doi: 10.1126/science.317.5839.738.

98. Ensoli F, Cafaro A, Casabianca A, et al. HIV-1 Tat immunization restores immune homeostasis and attacks the HAART-resistant blood HIV DNA: results of a randomized phase II exploratory clinical trial. Retrovirology. 2015 Apr 29;12:33. doi: 10.1186/s12977-015-0151-y.

99. Robinson HL, Thompson M, Heath S, et al. Elicitation of immune responses by a DNA/MVA vaccine in ART treated patients in a treatment interruption trial (Abstract OA05.03). HIV Research for Prevention Conference; 2014 October 28–31; Cape Town, South Africa.

100. Estes JD, Reilly C, Trubey CM, et al. Antifibrotic therapy in simian immunodeficiency virus infection preserves CD4+ T-cell populations and improves immune reconstitution with antiretroviral therapy. J Infect Dis. 2015 Mar 1;211(5):744–54. doi: 10.1093/infdis/jiu519. Epub 2014 Sep 22.

101. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT01852942, Reversing tissue fibrosis to improve immune reconstitution in HIV; 2012 February 20 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/NCT01852942.

102. Zhang Z, Fu J, Xu X, et al. Safety and immunological responses to human mesenchymal stem cell therapy in difficult-to-treat HIV-1-infected patients. AIDS. 2013 May 15;27(8):1283–93. doi: 10.1097/QAD.0b013e32835fab77.

103. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02290041, Treatment with MSC in HIV-infected patients with controlled viremia and immunological discordant response. 2014 November 10 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/NCT02290041.

104. Li T, Xie J, Li Y, Routy JP, et al. Tripterygium wilfordii Hook F extract in cART-treated HIV patients with poor immune response: a pilot study to assess its immunomodulatory effects and safety. HIV Clin Trials. 2015 Mar–Apr;16(2):49–56. doi: 10.1179/1528433614Z.0000000005. Epub 2015 Jan 26.

105. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT01666990, Tripterygium wilfordii Hook F (TwHF) treatment for immune non-responders with HIV-1 infection. 2012 August 15 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/NCT01666990.

106. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008 Oct 21;5(10):e203. doi: 10.1371/journal.pmed.0050203.

107. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02394730, Attenuation of D-dimer using vorapaxar to target inflammatory and coagulation endpoints (ADVICE); 2015 March 16 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/NCT02394730.

108. Tebas P, Spitsin S, Barrett JS, et al. Reduction of soluble CD163, substance P, programmed death 1 and inflammatory markers: phase 1B trial of aprepitant in HIV-1-infected adults. AIDS. 2015 May 15;29(8):931–9. doi: 10.1097/QAD.0000000000000638.

109. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02154360, Pharmacokinetic characteristics and anti-inflammatory effects of aprepitant in HIV-infected subjects (Emend-IV); 2014 May 22 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/NCT02154360.

110. Villar-García J, Hernández JJ, Güerri-Fernández R, et al. Effect of probiotics (Saccharomyces boulardii) on microbial translocation and inflammation in HIV-treated patients: a double-blind, randomized, placebo-controlled trial. J Acquir Immune Defic Syndr. 2015 Mar 1;68(3):256–63. doi: 10.1097/QAI.0000000000000468.

111. French MA, Cozzi-Lepri A, Arduino RC, Johnson M, Achhra AC, Landay A; INSIGHT SMART Study Group. Plasma levels of cytokines and chemokines and the risk of mortality in HIV-infected individuals: a case-control analysis nested in a large clinical trial. AIDS. 2015 Apr 24;29(7):847–51. doi: 10.1097/QAD.0000000000000618.

112. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02448238, Pilot study of oral probiotic bacteria supplementation to reduce chronic immune activation in HIV-infected Malian women; 2015 May 15 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/NCT02448238.

113. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02441244, Probiotic VSL#3 for inflammation and translocation in HIV I (PROOV IT I); 2015 April 23 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/NCT02441244.

114. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02441231, Probiotic VSL#3 for inflammation and translocation in HIV II (PROOV IT II); 2015 April 23 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/NCT02441231.

115. Routy JP, Angel JB, Patel M, et al. Assessment of chloroquine as a modulator of immune activation to improve CD4 recovery in immune nonresponding HIV-infected patients receiving antiretroviral therapy. HIV Med. 2015 Jan;16(1):48–56. doi: 10.1111/hiv.12171.

116. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT00819390, Chloroquine for reducing immune activation in HIV-infected individuals; 2009 January 8 (cited 2015 June 7). https://clinicaltrials.gov/ct2/show/study/NCT00819390.