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REVIEW ARTICLE

HIV Cure: How Far We Have Come?

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Abstract
Human Immunodeficiency Virus (HIV) is a major global healthcare burden. Current lifelong antiretroviral therapy drastically improves life expectancy but do not cure HIV. Therefore, at the existing growth rates, it is estimated that around 42 million people will be living with HIV by 2030 worldwide. A cure for HIV is need of the hour which could come in the form of remission (durable viral control without ART) or eradication (complete removal of latent replication-competent virus). In this review, we discuss recent advances in basic, applied and clinical aspects of latent HIV reservoirs including its tissue locations, cell types, cell properties, genomic integration sites and its significance, mechanism of reservoir seeding and methods to study the reservoirs. Natural models of functional cure which include elite controllers, viremic controllers, long term non-progressors and post-treatment controllers are discussed. Recent advances towards a functional HIV cure are discussed under headings; CCR5Δ32/Δ32 stem cells transplantation, shock and kill strategy, block and lock strategy, gene therapy and combined strategies.

Keywords HIV · AIDS · HIV cure · Latent reservoir · HIV cure strategies · HIV remission

Introduction

HIV is a retrovirus that transmits through infected blood, semen or vaginal fluids and preferentially destroys CD4 + T cells; compromising cell-mediated immunity and inviting opportunistic infections. Acute HIV stage lasts for few weeks and present with flu-like symptoms. Thereafter, person remains asymptomatic for years until he develops Acquired Immune-Deficiency Syndrome(AIDS). HIV can be detected in blood or oral fluid by antibody-based test (23–90 days after exposure), p24 antigen/antibody-based test (18–45 days after exposure) or nucleic acid test (10–33 days after exposure). No effective vaccine or cure exists for HIV, but Anti-Retroviral therapy (ART) drastically slows disease progression. Various preventive measures includes using condoms during sex, screening blood products, never sharing needles, and HIV prevention medicines such as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). Healthcare workers wear protective equipment (including gowns, gloves and eyewear) while performing any invasive procedures involving HIV patient's blood or body fluids. Recent technologies have shorted HIV treatment frequency from taking traditional ART pills every day orally to once a month or once every two months injection (Cabenuva [1]) and even once in 6 months injection (Sunlenca [2]) following undetectable plasma viral load.

At the existing growth rates, around 42 million people could be HIV positive globally by 2030 [3]. COVID-19 pandemic severely disrupted HIV testing services in 2020 and 2021 [4] and therefore, there are high chances of fuelled HIV transmission from unsuppressed Antiretroviral therapy(ART) naïve PLHIV and re-emergence of AIDS pandemic in post COVID-19 era [5]. Further, Socio-economic condition affects peripheral blood CD4 + cell count among HIV positive adults favoring progression towards AIDS [6, 7]. A cure for HIV is desperately needed to end global HIV/AIDS burden.

The scope of this article includes the evolving mechanisms of HIV latency during anti-retroviral therapy and the concept of functional HIV cure naturally and through experimental interventions (i.e., CCR5Δ32/Δ32 stem cells transplantation, Shock and Kill strategy, Block and Lock strategy, Gene therapy and Combined Strategies); Preventive experimental HIV vaccines is beyond the scope of this article. This article assumes significance as it thoroughly

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explores the recent advances and presents new concepts in understanding HIV reservoirs and functional cures that could accelerate the development and delivery of an HIV cure. An HIV cure could bring tremendous health, economic and social benefits, for example, it will prevent new infections, overcome uneasiness regarding life-long ART treatment, overcome stigma/discrimination, and will ease financial burden of life-long ART.

The Latent Reservoir of HIV

Gut,lymph nodes,spleen,liver and nervous system represents majority of HIV tissue reservoir [8] and cell types includes lymphocytes [9],macrophages [10],dendritic cells [11],astrocytes [12] and adipocytes [13] Fig. 1. HIV is ssRNA virus, however, it gets converted to dsDNA which integrate with host cell DNA Fig. 1. The integrated viral DNA(known as provirus) could remain inactive(latent) for years while the clonal expansion of these provirus harboring cells keep HIV reservoir sustained Fig. 2. Persistence of HIV in these reservoir sites is influenced by cell properties (Response to a specific stimulation, swing from resting state to activated state or vice-versa, transcriptional activity, resistance to immune killing, etc.) and genomic factors (provirus sequence and location, genomic integration site, intact or defective nature of proviruses, etc.). Viral reservoir quantification is usually done by Quantitative Viral Outgrowth Assay [14] and Intact Proviral DNA Assay [15] while genetic characterization of reservoir cells is done by single-cell reservoir profiling techniques(HIV SORT-seq [16]; HIV STIP-seq [17]; ECCITEseq [18]) and full-length individual proviral sequencing.

Compartmentalized proviral population with distinct genotype and phenotype are found in some tissues (eg. Brain) [19]. Overall reservoir decay is sluggish with half-life of around 4 years until seven years of ART and around 19 years afterward [20]. The ability for clonal expansion is different for various CD4 + T cell subsets. Effector memory CD4 + cells are enriched in clonally expanded proviral sequences. Macrophages act as distinctive HIV reservoirs. They express CD4 in low levels [21],reside in every tissue,have long-life and are resistant to elimination by CD8 + cells [22] Fig. 2. In urethral tissue, macrophages are reported to harbor integrated proviruses but CD4 + T cells do not [23].

Replication-competent noninduced provirus with intact genomes and normal LTR function within latent reservoir sites is a barrier to HIV cure. Cells harboring provirus do not behave differently from normal cells, therefore are largely invisible to immune system. CD4 + T cells harboring replication-competent provirus are inherently resistant to killing by CD8 + T cells [24] Fig. 2.

Around 2% proviruses remain genetically intact during long-term ART [25]. Majority of proviruses are defective; they can produce HIV transcripts(eg. novel usHIV-RNAs [26]) or HIV proteins(eg. HIV-1 Gag and Nef proteins [27]) resulting persistent immune activation, but cannot produce new progency virus. Defective provirus levels are unaffected during ART [28].

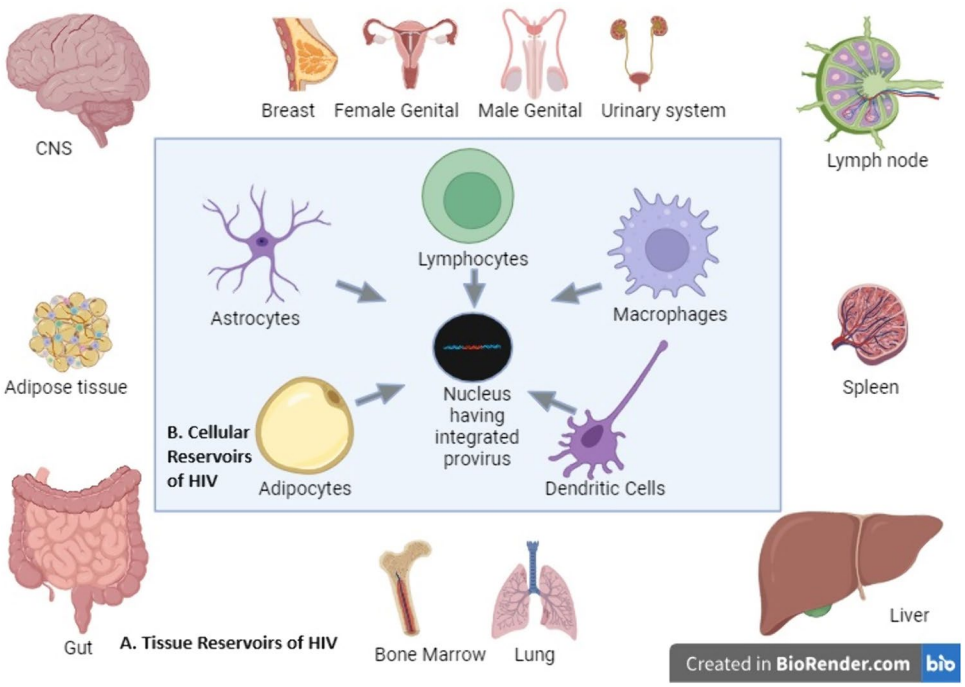

Fig. 1 Various tissue reservoirs and cellular reservoirs of latent HIV proviruses

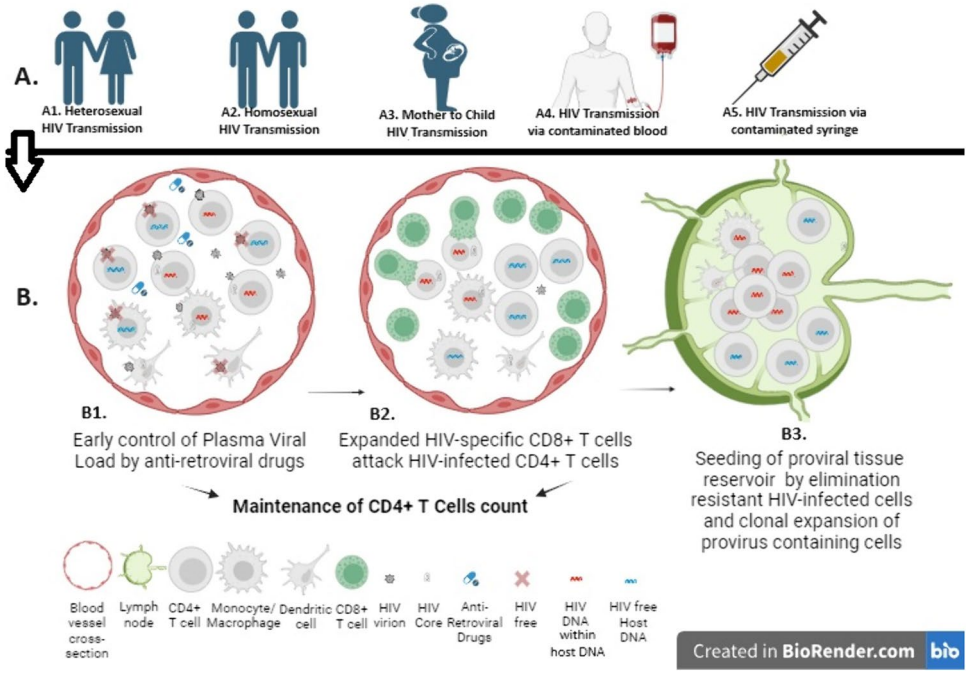

Fig. 2 Mechanism of establishment of HIV latent reservoirs. Following HIV transmission by heterosexual (A1) or homosexual (A2) intercourse with HIV positive partner, mother to child(A3), contaminated blood (A4) or syringe (A5); early initiation of Anti-retroviral drugs drastically controls the plasma viral load and thereby restricting most cells from getting HIV infected (B1). Some cells still get HIV infected and few of these cells are attacked and eliminated by expanded HIV-specific CD8 + T cells (B2). Early initiation of Anti-retroviral drugs together with expanded HIV-specific CD8 + T cells do not allow decline in CD4 + T cells count. Elimination-resistant replication-competent provirus harboring cells get seeded in tissue reservoirs and clonal expansion of these cells keeps the provirus intact for years (B3)

HIV suppression at younger age is linked to smaller HIV DNA level than at higher age [29]. ART started during early stage of HIV infection restricts size of HIV reservoir but do not drastically change proviral landscape [25]. Bulk of proviruses inside viral reservoirs is from latest time point; however,previous proviral variants continue to archive [30]. The extensive diversity of proviral variants within HIV reservoirs challenges HIV eradication or cure. In latently infected cells, the lack of pro-apoptotic viral proteins(HIV Env,protease and Vpr),along with increased host anti-apoptotic(Bcl-2,XIAP) and reduced host pro-apoptotic cell proteins(BAK/Bax),altogether encourage the latent cell survival.

Genomic Sites where virus integrates is critically important in determining the proliferation and persistence of infected cells. HIV integrating within cancer genes encourages expansion of infected cells and slows down virus decay. Provirus containing cells have wider distribution with notable enrichment during cancer metastases [31]. Some integration sites within host genome(eg. KRAB domain-containing ZNF genes for intact proviruses [32]) are more capable to maintain HIV latency in clonally expanded memory CD4 + T cells. Elite controllers have proviruses integration within centromeric satellite DNA which is transcription inactive [33]. Proviruses binding at active transcription sites make HIV infected cells prone to immune elimination.

Natural Models for Functional Cure

Few PLHIVs(Prevalence: 0.5%) are able to sustain undetectable plasma RNA HIV loads for minimum 12 months without ART(Elite controllers). However, around three-fourth of elite controllers experience long-term HIV disease progression and only 17% did not exhibited sign of HIV disease progression after 17 years of follow up [34]. Viremic controllers are similar but bigger subsets of PLHIVs(Prevalence: 3%-4%) who can keep their plasma RNA HIV load suppressed < 2000 copies/ml over a year without ART.

Long term non-progressors are PLHIVs who can maintain CD4 cell counts ≥ 500 cells/μL for ≥ 7 years without ART (Prevalence: 3%-4%). Elite or viremic controllers may classify as long term non-progressors in some cases and vice-versa. Actually, 52% long-term non progressors are reported elite controllers [35]. 30 years survival probability is 0.9 for Elite controllers plus long-term non progressors and 0.7 for viremic controllers plus long-term

non progressors [35]. About 55% Long term non-progressors can maintain their status after 20 years but just 14% after 30 years.

Post-treatment controllers are PLHIVs who can suppress viral load ≤ 400 copies/mL post ≥ 24 weeks of ART interruption. Non-controllers usually have a swift viral rebound in 3–4 weeks after ART discontinuation [36]. Control of HIV after Antiretroviral Medication Pause(CHAMP) study determined the prevalence of Post-treatment controllers as 4% when ART initiated during chronic infection and 13% when ART initiated during early infection [37]. However, only 20% Post-treatment controllers had suppressed viral load after ≥ 5years of ART interruption.

Size of HIV reservoir plays an important role in the natural control of HIV infection in absence of ART. Starting ART during early HIV stage drastically restrict the size of HIV reservoir [38]. A restricted viral reservoir can give long-term advantages in terms of preserving functional cell-mediated immunity and a greater window period to viral rebound. Unlike elite controllers where functional capabilities of cytotoxic T cells are not altered over time when integrated viral DNA gradually increases [38],Post-treatment controllers present with enhanced cytotoxic T cells functional capabilities over time [39]. Defective proviruses may not explain reason for viral control among Elite controllers or Viremic controllers rather than it is through mechanism yet not known.

Strategies for Functional Cure (Fig. 3)

CCR5Δ32/Δ32 Stem Cells Transplantation

HIV-1 entry into CD4 + cells is dependent on co-receptors mainly CCR5 and CXCR4. Homozygous 32-base pair deletion in CCR5 allele(CCR5Δ32/Δ32) block cell-surface expression of CCR5 conferring natural resistance to CCR5-tropic HIV variants(R5) [40]. The frequency of CCR5-Δ32 allele ranges from 16.4% in Norwegian hematopoietic stem cell donors to 0% in Ethiopian donors, however, < 1% are homozygous [41, 42]. However, even if full chimerism is achieved post CCR5Δ32/Δ32 stem cells transplant, donor originated CD4 + cells could still be susceptible to another HIV variant(CXCR4-tropic/X4 variant).

So far, Berlin patient (2008) [43], London patient (2019) [44], City of hope patient (2022)[45], New York patient (2022) [46] and Düsseldorf patient (2023) [47] are presumed cured via CCR5Δ32/Δ32 stem cells transplantation. These five cases were given stem cells transplantation primarily for the treatment of their cancers but no HIV-1 rebound following ART disruption is yet reported. HIV is one of the chronic microbial infections that can be found among cancer patients [48, 49]. Other two patients: Boston patients (2014) [50] and Essen patient (2019) [51] reported viral rebound. Berlin patient died 13 years after transplant due to relapse of acute myeloid leukemia but there was no proof of HIV-1 rebound. Unlike other four male patients, New York patient(2022) is a mixed-race

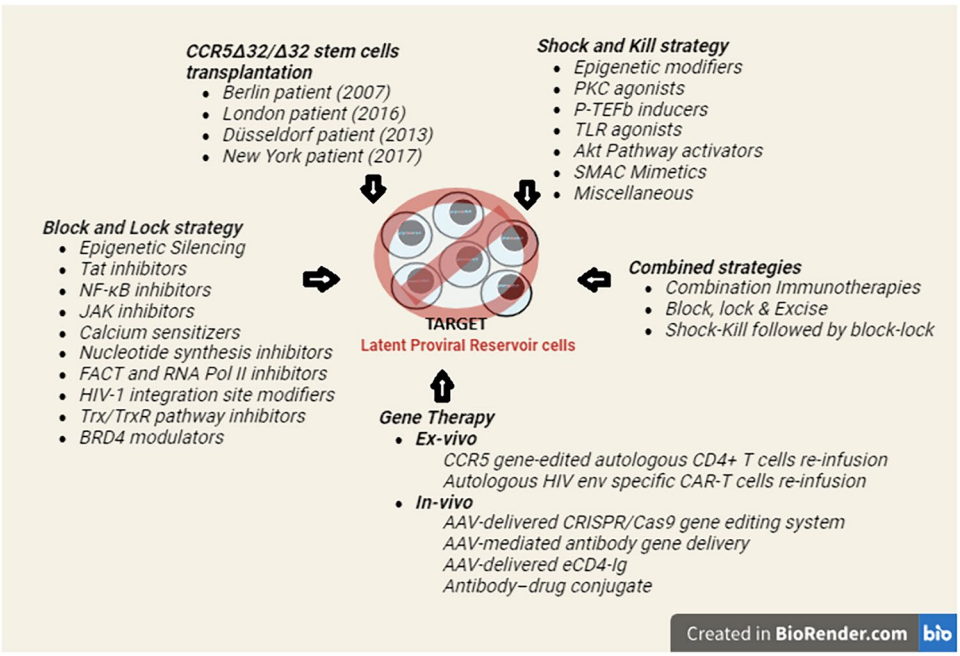

Fig. 3 Different strategies to target latent proviral reservoir cells and thereby achieve functional HIV cure

middle-aged HIV-1 positive woman who received haplocord transplant(CCR5Δ32/Δ32 cord blood cells) for the treatment of acute myeloid leukemia and never developed Graft-versus-host disease [46]. A very close HLA matching of donor and recipient is not required for umbilical cord stem cells transplant unlike haematopoietic stem-cell transplant in other four patients.

Shock and Kill Strategy

In this strategy, drugs classified as latency-reversing agents(LRAs) induce reactivation of the latent proviral transcription ("shock" component). The reactivated cells and virions produced are then supposed to be eliminated by virus induced cell death, immune mediated clearance or anti HIV drugs("kill" component). LRAs are classified based on the host factor they act upon to reactivate latent proviruses and include epigenetic modifiers (HDAC inhibitors, HMT inhibitors, DNA methylation inhibitors), PKC agonists (Ingenol derivatives,prostatin,bryostatin-1), Inducers of P-TEFb release (BETis), TLR agonists (Flagellin, Pam3CSK4,GS-9620, MGN1703), SMAC mimetics (Ciapavir, AZD5582), STAT5 sumoylation inhibitors(HOAt and HODHBt),MAPK agonist(Procyanidin trimer C1),CCR5 antagonist(Maraviroc),Tat vaccine(Tat Oyi vaccine,Tat-R5M4 protein),IL-15 agonist(ALT-803), immune checkpoint inhibitors [anti-PD-1(nivolumab,pembrolizumab),anti-CTLA-4(ipilimumab)] and so on [52].

PKC agonists are potent NF-κB activators. Activated NF-κB bind to NF-κB motifs in the enhancer region of HIV-1 LTR to initiate viral transcription in latent cells [53]. HDACi class-I have specificity for latent reservoirs and minimal inference with PKC agonist [54],therefore, HDACi class-I can have a synergistic combination with PKC agonist(shocktail). The concept of prodrugs can be utilized to transport LRAs to HIV reservoirs at peak concentrations with lesser toxicities. LRAs can be tried with early ART at acute HIV stage(rather than suppressive stage) to disturb latency establishment, reduce reservoir size and facilitate HIV elimination.

Even in case of effective viral reactivation, success in eliminating viral reservoir("kill" component) could be limited by several immunological roadblocks like deficient recognisation, exhaustion, hyperactive cytokines, deficient cytotoxicity, etc. [55–57]. Shock and kill strategy risk damage to neurons if latent HIV-1 reservoirs in central nervous system get reactivated by LRAs. Further, it risks expansion of HIV reservoirs if "kill" part is ineffective. Labeling HIV reservoirs with apoptosis inducers [Bcl-2 inhibitors(eg. Venetoclax, Navitoclax), XIAP antagonists, PI3K/Akt antagonists and RIG-I inducers] after LRA activity can selectively eliminate HIV reservoirs.

Block and Lock Strategy

This strategy aims to achieve permanent silencing of proviral latent reservoir following interruption of antiretroviral therapy. "Block" of sporadic proviral reactivation to "lock" integrated provirus into a deep latency can accomplish a long-term durable HIV remission(functional cure).

HIV silencing can be done by (1) RNA-Induced Epigenetic Silencing [eg. siRNA] (2)Tat inhibition[eg. didehydrocortistatin A(dCA),Tat degradation[eg. Triptolide],CDK9 inhibition[eg. Flavopiridol],transcription factor IIH inhibition[eg. Spironolactone] (3) mTOR inhibition[eg. rapamycin], Akt inhibition[eg. uprosertib], HSP90 inhibition[eg. GV1001] (4) Inhibiting JAK/STAT pathways[eg. filgotinib,ruxolitinib] (5) Calcium sensitization[eg. levosimendan, manidipine] (6) Nucleotide synthesis inhibition[eg. MMF] (7) RNA splicing inhibition[eg. Filgotinib] (8) FACT and RNA Pol II inhibition[eg. curaxin CBL0100] (9) HIV-1 integration site modification[eg. LEDGIN] (10) Trx/TrxR pathway inhibition [eg. tiopronin] (11) BRD4 modulation[eg. ZL0580] [58]

People living with blocked and locked HIV may be fearful for its reactivation. However, fossils of retroviruses are found throughout the human genome(endogenous retroviruses) as they continued to integrate and inherit from millions of years without causing any harm [59]. Block and lock strategy can be combined with shock and kill strategy for a functional cure, although the two look opposite strategies. Since LRAs have limited capability for HIV reactivation at non-toxic concentrations, Shock and kill strategy may first eliminate readily inducible latent reservoirs followed by block and lock strategy to permanently silence the reservoirs which could not reactivated by existing LRAs. Majority of proviruses in latent reservoirs are defective in producing infectious virions, yet they generate viral proteins to cause immune-activation [27, 60]. Block and lock strategy can silence replication-competent as well as replication-defective proviruses. Even a partial silencing can subsequently reduce the reservoir size making it easier to control residual viruses by engineered immune-response.

Gene Therapy

In most Gene therapies, a single-time treatment has lifelong curative capability which can be transformative for PLHIVs. Gene therapy could be done ex-vivo or in-vivo [61]. In ex-vivo strategies,CCR5 co-receptor or HIV provirus are deleted/inactivated in autologous CD4 + cells via CRISPR–Cas9 and recombinases technologies; OR Chimeric antigen receptor(CAR) are employed on autologous T cells to recognize HIV envelope proteins and then re-infused into PLHIVs. The former may reduce but not completely eradicate viral reservoirs due to continuous cloning

of in-vivo CD4 + cells. Infused CAR T cells expand in-vivo only in presence of adequate viral antigen [62] and viral antigens are too low during ART. Therefore,Analytical treatment interruption or potent LRA or exogenous cell-associated HIV envelope may facilitate the expansion of infused CAR T cells. Progress in cancer CAR T cell therapies can benefit HIV cure therapy. Ex-vivo cell modification in automated closed-system equipments at point-of-care will be needed for application in low-resource settings.

Among in-vivo strategies, AAV-delivered CRISPR/Cas9 gene editing construct injected in PLHIV can excise integrated proviral DNA in reservoir cells at all major anatomical sites. EBT-101 is one such construct that is granted Fast Track designation by US-FDA Table 1. AAV-mediated antibody gene delivery (eg. PG9, a potent anti-HIV bnAb) [63], AAV-delivered eCD4-Ig(CD4 mimetics) [64] or CD4 + cell-homing mRNA-LNPs [65], are other promising in-vivo strategies [66]. Novel techniques utilizing Antibody–drug conjugate could act as a biological missile to target proviral reservoirs [67]. Antibody–drug conjugate is made of monoclonal antibody attached to a cytotoxic drug for highly specific killing of target cells.

Ongoing gene therapy based HIV cure clinical trials are summarized in Table 1. While still at an early-stage,in-vivo gene therapy is a promising strategy for HIV cure. Recognizing approaches to drive down the cost of gene therapies will be required for widespread applicability in low and middle income countries and therefore,Global Gene Therapy Initiative was created in 2020 for this purpose [68].

Combined Strategies

- Combination Immunotherapies: Broadly neutralizing antibodies 3BNC117 delay viral rebound following ART interruption [69] and therefore are tested with LRAs in Phase IIa TITAN trial and ROADMAP trial [70, 71]. HIVconsv T cell vaccine combined with romidepsin(HDAC inhibitor) can control viremia and reseeding of viral reservoir after ART interruption [72]. HIVconsv vaccine during early ART induce post-treat-

Table 1 Gene Therapies based ongoing HIV Cure Trials as of May 15, 2024. Source: Treatment action group (https://www.treatmentactiongroup.org/cure/trials/)

Gene therapies	Trial registry identifier(s)	Sponsor(s)	Phase	Estimated end date
EBT-101 (CRISPR/Cas9 targeting HIV provirus)	NCT05144386	Excision BioTherapeutics, San Francisco	Phase I/IIa	March 2025
LVgp120duoCAR-T cells	NCT04648046	Steven Deeks, University of California, San Francisco	Phase I/IIa	December 2027
Cal-1: Dual anti-HIV gene transfer construct	NCT02390297	Calimmune, Arizona	Phase I/II	October 2031
An ATI study to evaluate the impact of **AGT103-T** to suppress HIV replication in the absence of ART	NCT05540964	American Gene Technologies International Inc., Maryland	Phase I	July 2025
CD4 CAR + SB-728mR modified T cells	NCT03617198	University of Pennsylvania, Philadelphia	Phase I	December 2027
bNAb-derived Chimeric Antigen Receptor (CAR)-T cell therapy	NCT03240328	Guangzhou 8th People's Hospital, Guangdong	Phase I	December 2030
CMV-specific HIV-CAR T Cells	NCT06252402	City of Hope Medical Center, California	Phase I	March 2028
EBT-101 (long-term follow-up study)	NCT05143307	Excision BioTherapeutics, San Francisco	Phase I	April 2037
Long-term follow-up of HIV + participants exposed to **SB-728-T** or **SB-728mR-T**	NCT04201782	Sangamo Therapeutics, California	Phase I	June 2035
Long-term follow-up of study participants treated with **AGT103-T**	NCT05529342	American Gene Technologies International Inc., Maryland	Phase I	September 2038
SB-728mR-HSPC (autologous hematopoietic stem/progenitor cells modified at the CCR5 gene)	NCT02500849	City of Hope Medical Center, California	Phase I	August 2024
Stem cells gene-modified with CCR5 shRNA/TRIM5alpha/TAR decoy	NCT02797470	AIDS Malignancy Consortium, California and New York	Phase I/II	June 2025
Stem cells gene-modified to encode multiple anti-HIV RNAs (rHIV7-shI-TAR-CCR5RZ)	NCT02337985	City of Hope Medical Center, California	Phase I	December 2024
Stem cells gene-modified to encode multiple anti-HIV RNAs (rHIV7-shI-TAR-CCR5RZ) + busulfan	NCT01961063	City of Hope Medical Center, California	Phase I	December 2024

ment controllers like highly functional T-cell responses (RIVER trial) [73]. HIVconsv T cell vaccine may enhance immune-surveillance and long-term control of residual reservoir cells after latency reversal by LRAs and rapidly eliminated by 3BNC117 [74].

- Block, Lock and Excise: This approach aims to inhibit viral transcription(block),keeping the virus blocked or silenced without ART(lock) and permanently inactivating proviral DNA using epigenomic and genomic approaches(excise). The graded transformation of residual HIV among PLHIVs from latent to silent into permanently defective proviruses is an acceleration of the natural path to endogenous retrovirues. HIV Obstruction by Programmed Epigenetics(HOPE) Collaboratory is working toward this approach for both "functional" and "classical" cure. Their objective include targeted genome engineering to disable HIV provirus by developing double strand break-free genome engineering method(Brec1,dCas9,DNA-PNA) and establishing in-vivo delivery platforms(VLP,PLGA-NP,Brec1–αhuCD7 conjugates) [75].

Concluding Remarks

This study focused on the newer concepts emerging in last few years which could shape HIV cure research. The disadvantage of the study is that it could only provide an overview of emerging concepts in HIV cure research because each sub-section has itself a vast scope to review.

The spectrum of HIV cure research has significantly evolved in the last few years. Four more patients(Düsseldorf patient, City of hope patient, New York patient and London patient) reported HIV remission and possible cure through CCR5Δ32/Δ32 stem cells transplantation in last five years after Berlin patient(2009). A Few LRAs have remarkably succeeded in reversing HIV latency in human trials. Addition of bNAbs and therapeutic vaccines to these LRAs has cured primate models enhancing hope of success in undergoing clinical trials. A bNAbs(3BNC117) changed the course of HIV disease and diminished reservoir size when administrated at start of ART. Novel interventions like epigenetic modification to block proviral activation,AAV-delivered CRISPR gene-editing to delete or permanently inactivate proviruses,AAV-delivered CD4 mimetics that bind viral envelope and neutralize all HIV subtypes,engineering autologous CD4 + cells to block viral entry,engineered B cells that express HIV specific bNAbs,drugs to sensitize reservoir cells towards apoptosis and drug-delivery platforms to viral reservoirs are promising approaches that are currently under active investigation and can change the direction of HIV cure research. Due to limitations associated with complete eradication of HIV,a durable control of viral replication without ART is a more achievable aim of HIV cure research community among in-vivo trials.

Low-income high-burden countries have genetically and biologically diverse proviral population with geographically and ethnically diversities in host immunity. Recently established HIV Cure Africa Acceleration Partnership could enable wider engagement. People from multiple academia,industries,private sector,community and government are coming together to pool common resources and coordinate complex studies with only aim of expediting research for a globally applicable,acceptable,and affordable HIV cure. There is no limitation of funds and field is highly committed to bring up an effective and scalable remission or cure.

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