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Therapeutic HIV Vaccines with Toll-Like Receptor Agonists: Immune Responses and Viral Reservoir Reduction

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ABSTRACT

The advent of antiretroviral therapy has transformed Human Immunodeficiency Virus infection from a fatal diagnosis into a manageable chronic condition, yet the virus persisted in latent reservoirs that remained untouched by current treatment strategies. Despite decades of viral suppression, patients cannot safely discontinue therapy without experiencing rapid viral rebound, underscoring the urgent need for curative interventions. This review examined the emerging role of toll-like receptor agonists as adjuvants in therapeutic HIV vaccines designed to reduce or eliminate viral reservoirs. This article synthesized current literature on TLR agonist based therapeutic vaccines, examining preclinical studies, clinical trial data, and immunological mechanisms underlying their potential efficacy. The findings revealed that TLR agonists, particularly those targeting TLR7, TLR8, and TLR9, demonstrated significant capacity to reverse viral latency, enhance HIV specific cytotoxic T lymphocyte responses, and promoted innate immune activation that collectively contributed to measurable reductions in reservoir size. Clinical trials had shown promising but variable results, with some patients achieving prolonged periods of viral control following analytical treatment interruption. The integration of TLR agonists into therapeutic vaccine platforms represented a scientifically rational approach to achieving functional HIV cure, though significant challenges regarding safety, efficacy, and patient selection remained. Future research should prioritize combination immunotherapeutic strategies that synergistically target multiple aspects of viral persistence.

Keywords: Therapeutic HIV vaccines, Toll like receptor agonists, Viral reservoir, Latency reversal, Functional cure.

INTRODUCTION

The landscape of Human Immunodeficiency Virus management has undergone remarkable transformation since the introduction of combination antiretroviral therapy in the mid-1990s [1, 2]. Contemporary antiretroviral regimens achieve sustained viral suppression in adherent patients, extending life expectancy to near normal levels and reducing transmission risk to negligible rates. However, this therapeutic success remains fundamentally incomplete. The virus establishes latent infection in long lived memory CD4 positive T cells and other cellular compartments early during acute infection, creating stable reservoirs that persist indefinitely despite years of effective viral suppression [3]. These latently infected cells harbor replication competent provirus that remains transcriptionally silent, effectively invisible to both immune surveillance and antiretroviral drugs. Upon treatment interruption, viral rebound occurs with remarkable consistency, typically within two to four weeks, necessitating lifelong therapy with its attendant challenges of cost, adherence, toxicity, and stigma.

The persistence of latent viral reservoirs represents the principal barrier to HIV cure [4]. These reservoirs are established within days of initial infection and are maintained through multiple mechanisms including homeostatic proliferation of infected cells, clonal expansion, and anatomical sequestration in sanctuary sites with suboptimal drug penetration. The reservoir is both small, comprising approximately one latently infected cell per million resting CD4 positive T cells, and extraordinarily stable, with an estimated half-life exceeding four years under suppressive

therapy [5]. This biological reality has catalyzed intensive research into cure strategies, with therapeutic vaccines emerging as a promising approach. Unlike preventive vaccines that aim to block infection, therapeutic vaccines are administered to individuals already infected, with the goal of enhancing immune responses sufficiently to control or eliminate the virus without continued antiretroviral therapy. The integration of toll-like receptor agonists into therapeutic vaccine platforms represents a mechanistically sound strategy that addresses two critical requirements for reservoir clearance: latency reversal to expose hidden virus and immune enhancement to eliminate cells harboring reactivated provirus.

This article explores the scientific foundation and clinical progress of TLR agonist adjuvanted therapeutic HIV vaccines. The discussion begins with detailed examination of viral reservoir biology and the mechanisms underlying HIV latency. Subsequent sections characterize toll-like receptors and their signaling pathways, analyze specific TLR agonists under investigation as vaccine adjuvants, and describe current therapeutic vaccine strategies incorporating these agents. The article then evaluates immune responses generated by TLR agonist-based vaccines, reviews clinical evidence for viral reservoir reduction, and critically assesses challenges limiting current approaches. The purpose of this review is to provide a comprehensive analysis of TLR agonists in therapeutic HIV vaccination, integrating molecular immunology with clinical outcomes to inform future research directions and accelerate progress toward functional cure.

THE HIV VIRAL RESERVOIR CHALLENGE

The establishment and persistence of latent HIV reservoirs constitute the fundamental obstacle to viral eradication. During acute infection, HIV preferentially targets activated CD4-positive T cells, which support robust viral replication [6]. However, as these cells transition to a resting memory state through normal immune regulation, a subset harbors an integrated provirus that becomes transcriptionally silent. This latent infection is remarkably stable because the provirus is integrated into host chromosomal DNA and maintained through normal cellular processes. The infected cell appears phenotypically normal, expresses no viral proteins, and thus evades immune recognition while remaining capable of producing infectious virus upon cellular activation.

The anatomical distribution of latent reservoirs adds substantial complexity to eradication efforts. While circulating memory CD4-positive T cells represent the most extensively studied reservoir, latently infected cells also reside in lymphoid tissues, including lymph nodes, gut-associated lymphoid tissue, and potentially the central nervous system [7, 8]. These anatomical sanctuaries may experience suboptimal antiretroviral drug concentrations and limited immune surveillance, providing additional protection for persistent virus. Furthermore, recent research has identified tissue-resident memory T cells as an important reservoir component, and these cells exhibit distinct biological characteristics compared to their circulating counterparts.

Multiple molecular mechanisms contribute to the establishment and maintenance of HIV latency. Transcriptional interference represents a primary mechanism, wherein the integrated provirus occupies regions of condensed chromatin characterized by repressive histone modifications and DNA methylation that physically restricts access of transcriptional machinery [9, 10]. Additionally, the absence of critical transcription factors in resting cells, particularly nuclear factor kappa B and positive transcription elongation factor b, prevents efficient proviral transcription even when the promoter region is accessible. Post-transcriptional blocks, including inefficient RNA splicing and nuclear export, further contribute to latency in some cellular contexts. The virus has essentially evolved to exploit normal cellular quiescence mechanisms to ensure its own persistence.

The clinical implications of reservoir persistence are profound. Despite achieving undetectable plasma viremia for years or even decades, patients who interrupt antiretroviral therapy experience viral rebound with only rare exceptions. This rebound originates from reactivation of latently infected cells and subsequent spread to new target cells. The speed and consistency of rebound following treatment interruption underscore both the size of the latent reservoir and the inadequacy of natural immune responses to control reactivated virus. Mathematical modeling suggests that without intervention to either eliminate latently infected cells or enhance immune control, spontaneous viral clearance would require multiple human lifetimes [11, 12]. This biological reality has focused cure research on strategies that actively reduce reservoir size or enhance immune function, with therapeutic vaccines representing a rational approach to achieving both objectives.

UNDERSTANDING TOLL-LIKE RECEPTORS IN IMMUNITY

Toll-like receptors occupy a critical position at the interface between innate and adaptive immunity, functioning as pattern recognition receptors that detect conserved molecular structures associated with pathogens. The human genome encodes ten functional TLRs, each recognizing distinct pathogen-associated molecular patterns. TLR1, TLR2, TLR4, TLR5, and TLR6 localize to cell surface membranes and primarily detect bacterial components, while TLR3, TLR7, TLR8, and TLR9 reside in endosomal compartments and recognize nucleic acid structures [13, 14]. This subcellular localization serves important biological functions, as endosomal TLRs can detect viral nucleic acids

following endocytosis and degradation of viral particles while remaining physically separated from host nucleic acids in the cytoplasm and nucleus.

The signaling cascades initiated by TLR engagement are both rapid and profound. Upon ligand binding, TLRs undergo conformational changes that facilitate recruitment of adaptor proteins, primarily myeloid differentiation primary response 88 or TIR domain containing adapter inducing interferon beta [15, 16]. These adaptors initiate downstream signaling through multiple pathways, including nuclear factor kappa B, mitogen-activated protein kinases, and interferon regulatory factors. The result is swift transcriptional upregulation of inflammatory cytokines, type I interferons, and costimulatory molecules that collectively establish an antiviral state. This immediate innate response serves as a critical bridge to adaptive immunity by enhancing antigen presentation, promoting dendritic cell maturation, and providing inflammatory signals that augment T cell and B cell activation.

TLR7, TLR8, and TLR9 have garnered particular attention in therapeutic HIV vaccine development due to their recognition of nucleic acid structures and preferential expression in immune cell subsets critical for antiviral immunity. TLR7 and TLR8 recognize single-stranded RNA and are expressed primarily in plasmacytoid dendritic cells and myeloid cells, respectively, though notable species differences exist in cellular expression patterns. Upon engagement, these receptors trigger robust type I interferon production and inflammatory cytokine secretion. TLR9 recognizes unmethylated CpG DNA motifs characteristic of bacterial and viral genomes and is expressed in plasmacytoid dendritic cells and B cells [17]. Activation of these endosomal TLRs induces phenotypic and functional maturation of antigen-presenting cells, characterized by upregulation of major histocompatibility complex molecules and costimulatory receptors, including CD80 and CD86, thereby enhancing their capacity to prime and activate T cells.

The rationale for incorporating TLR agonists into vaccine formulations extends beyond simple adjuvant effects. These molecules fundamentally reprogram the immune microenvironment at vaccination sites and in draining lymph nodes, creating conditions favorable for generating robust and durable adaptive responses. The inflammatory milieu established by TLR activation promotes differentiation of memory T cells with enhanced functional capacity and longevity. Furthermore, TLR agonists can overcome certain immunosuppressive mechanisms that limit vaccine efficacy in chronic viral infections, including regulatory T cell activity and expression of inhibitory checkpoint molecules [18]. In the specific context of HIV, TLR agonists offer the additional theoretical benefit of reversing viral latency through activation of signaling pathways that promote proviral transcription, potentially exposing latently infected cells to immune clearance mechanisms enhanced by the vaccine itself.

TLR AGONISTS AS THERAPEUTIC VACCINE ADJUVANTS

The translation of TLR biology into practical vaccine development has focused on several synthetic agonists with favorable pharmaceutical properties and manageable safety profiles. Among these, the imidazoquinoline compounds resiquimod and its analogs have received substantial attention as TLR7 and TLR8 agonists [19]. These small molecules activate both receptors, though with species-specific differences in potency and selectivity that complicate translation from preclinical models to human trials. In humans, these compounds preferentially activate TLR8 in myeloid dendritic cells and monocytes, driving production of interleukin 12 and tumor necrosis factor alpha, cytokines critical for promoting type 1 T helper cell differentiation and cytotoxic T lymphocyte function. Vesatolimod represents a particularly well-characterized TLR7 agonist that has progressed through clinical evaluation, demonstrating the capacity to induce transient increases in plasma HIV RNA in suppressed patients, consistent with latency reversal activity [20].

Synthetic oligonucleotides containing unmethylated CpG motifs function as potent TLR9 agonists and have been incorporated into various vaccine platforms [21]. These molecules can be chemically modified to enhance stability and reduce off-target effects while retaining immunostimulatory properties. CpG oligonucleotides are classified into distinct categories based on sequence characteristics and backbone modifications, with type A CpG inducing high levels of interferon alpha from plasmacytoid dendritic cells and type B CpG promoting B cell activation and antibody production. The choice of CpG type can be strategically matched to desired immunological outcomes, with type A potentially favored for generating cellular immunity and type B for humoral responses. Several HIV vaccine trials have incorporated CpG oligonucleotides as adjuvants, generally demonstrating acceptable safety and enhanced immunogenicity compared to unadjuvanted formulations.

The mechanisms by which TLR agonists enhance vaccine immunogenicity operate at multiple levels. At the cellular level, these agents induce maturation of dendritic cells, the professional antigen-presenting cells that initiate adaptive immune responses. Mature dendritic cells exhibit enhanced capacity for antigen uptake, processing, and presentation, coupled with expression of costimulatory molecules essential for T cell activation. The inflammatory cytokines produced following TLR engagement establish a microenvironment that favors differentiation of CD4-positive T cells toward effector phenotypes rather than regulatory phenotypes, and promotes the generation of highly functional CD8-positive cytotoxic T lymphocytes [22, 23]. At the tissue level, TLR agonists recruit

additional immune cells to vaccination sites and draining lymph nodes, amplifying the magnitude of the response. Furthermore, certain TLR agonists can directly activate B cells, enhancing antibody production and affinity maturation.

Safety considerations represent a critical dimension of TLR agonist development. The same inflammatory pathways that make these molecules effective adjuvants can also produce systemic symptoms, including fever, malaise, and flu-like symptoms when administered systemically. This has necessitated careful optimization of dose, route, and formulation. Local administration at vaccination sites can concentrate immune activation while limiting systemic exposure. Formulation strategies, including encapsulation in lipid nanoparticles or conjugation to vaccine antigens, can further enhance local retention and reduce systemic distribution [24, 25]. Clinical experience with TLR agonists in HIV trials has generally demonstrated acceptable tolerability, though dose-limiting toxicities have been observed with higher doses of certain compounds, particularly the TLR7 agonists. Ongoing research aims to identify optimal dosing regimens that maximize immunological benefit while maintaining acceptable safety profiles, recognizing that the benefit-to-risk calculation differs substantially for therapeutic interventions in people already infected compared to preventive vaccines in healthy individuals.

THERAPEUTIC VACCINE STRATEGIES FOR HIV

The conceptual framework for therapeutic HIV vaccination centers on two complementary objectives: reversing viral latency to expose hidden reservoir cells and enhancing immune responses to eliminate those cells once exposed. This "shock and kill" paradigm has guided much of the field, though recent thinking has evolved toward more nuanced "reduce and control" strategies that acknowledge the difficulty of complete eradication while pursuing the more achievable goal of sufficient reservoir reduction to enable natural immune control. TLR agonists theoretically address both components of this approach through their dual capacity for latency reversal and immune enhancement, making them attractive candidates for inclusion in therapeutic vaccine platforms [26, 27].

Latency reversal strategies aim to induce transcription and translation of latent provirus without promoting viral spread or cellular proliferation that could paradoxically expand the reservoir. TLR agonists, particularly those targeting TLR7 and TLR8, can activate signaling pathways including nuclear factor kappa B that drive HIV transcription from the integrated provirus. Clinical studies with TLR7 agonists have demonstrated transient increases in cell associated HIV RNA and occasionally plasma viremia in patients on suppressive antiretroviral therapy, providing proof of concept for latency reversal activity [28]. However, the magnitude and duration of this effect have been modest in most studies, and latency reversal alone has not produced measurable reservoir reduction, underscoring the critical importance of concurrent immune enhancement to eliminate reactivated cells.

The immune enhancement component of therapeutic vaccines seeks to generate or restore HIV specific immune responses with sufficient magnitude and quality to recognize and eliminate infected cells. In natural HIV infection, virus specific CD8 positive T cell responses are rapidly generated but prove unable to control infection due to multiple factors including viral immune evasion through mutation, T cell exhaustion characterized by upregulation of inhibitory receptors, and numerical and functional deficits induced by chronic antigen stimulation [29]. Therapeutic vaccines aim to overcome these limitations by providing strong immunogenic stimuli in the context of viral suppression, when antigen load is minimal and immune dysfunction potentially reversible. The inclusion of TLR agonists as adjuvants provides inflammatory signals that can partially reverse T cell exhaustion phenotypes and promote differentiation of highly functional effector cells.

Several therapeutic vaccine platforms incorporating TLR agonists have advanced to clinical testing. Dendritic cell based vaccines represent one approach, wherein autologous dendritic cells are loaded with HIV antigens ex vivo in the presence of TLR agonists and maturation factors, then reinfused to prime or boost T cell responses [30, 31-37]. This personalized approach allows precise control over antigen presentation and costimulation but requires complex manufacturing and individualized production. Peptide based vaccines utilize defined HIV epitopes formulated with TLR agonists to directly prime T cell responses in vivo, offering simpler manufacturing and standardized dosing but potentially limited by human leukocyte antigen restriction and incomplete epitope coverage. Viral vector based vaccines employ replication incompetent viruses to deliver HIV genes, generating robust cellular immunity through natural antigen processing pathways, with TLR agonists added to further enhance responses. DNA and mRNA vaccines represent newer platforms that combine efficient antigen expression with intrinsic immunostimulatory properties, potentially synergizing with added TLR agonists.

The integration of therapeutic vaccination with other cure strategies represents an evolving area of investigation. Combination approaches might include broadly neutralizing antibodies to limit viral spread during latency reversal, immune checkpoint inhibitors to enhance T cell function, or therapeutic gene editing to disable proviral DNA [32, 38-45]. The timing and sequencing of these interventions require careful consideration, as immune enhancement might be most effective after maximal reservoir reduction, or alternatively, immune priming might optimally

precede latency reversal to ensure activated cells are rapidly eliminated. Clinical trials are beginning to explore these combinations systematically, guided by mechanistic studies in animal models and ex vivo human systems.

IMMUNE RESPONSES GENERATED BY TLR AGONIST VACCINES

The immunological outcomes of TLR agonist adjuvanted therapeutic HIV vaccines have been assessed through detailed characterization of cellular and humoral responses in clinical trials and preclinical models. CD8-positive cytotoxic T lymphocytes represent the primary effector population of interest, given their capacity to recognize and eliminate infected cells through recognition of viral peptides presented by major histocompatibility complex class I molecules [46-50]. Therapeutic vaccines incorporating TLR agonists have demonstrated the capacity to expand HIV specific CD8 positive T cell populations, with increased frequencies detectable by interferon gamma enzyme-linked immunosorbent spot assays and multiparameter flow cytometry. Importantly, these expanded populations often exhibit enhanced functional quality characterized by polyfunctionality, meaning simultaneous production of multiple effector cytokines, including interferon gamma, tumor necrosis factor alpha, and interleukin 2, a phenotype associated with superior viral control in natural infection.

Beyond simple expansion and cytokine production, the differentiation state and tissue distribution of vaccine-induced T cells critically influence their efficacy against viral reservoirs. Effector memory T cells possess immediate cytotoxic capacity and home to peripheral tissues where reservoirs reside, while central memory T cells provide long-term maintenance of the response [51-57]. Optimal therapeutic vaccines should ideally generate both populations, and some TLR agonist adjuvanted vaccines have demonstrated the capacity to induce balanced memory differentiation. Tissue resident memory T cells represent a particularly important population for reservoir clearance, given the anatomical distribution of latently infected cells, and recent studies have begun assessing whether systemic vaccination can generate or expand these tissue-localized populations. The incorporation of specific TLR agonists may influence tissue distribution through effects on chemokine receptor expression and homing molecule upregulation.

CD4-positive T helper cells fulfill critical functions beyond direct antiviral activity, providing help for CD8-positive T cell responses and B cell antibody production. However, as the primary target of HIV infection, enhancing CD4-positive T cell responses must be balanced against the theoretical risk of expanding the pool of susceptible target cells [36, 58-64]. TLR agonist adjuvanted vaccines have generally induced HIV specific CD4 positive T cell responses that skew toward type 1 helper phenotypes, characterized by interferon gamma production and support for cellular immunity, rather than type 2 phenotypes associated with antibody responses. This polarization is consistent with the preferential activation of interleukin 12 production by certain TLR agonists and may be advantageous for promoting CD8-positive T cell function.

Humoral immune responses, while not traditionally emphasized in therapeutic vaccine design, may contribute to viral control through multiple mechanisms. Antibodies can neutralize cell-free virus during latency reversal episodes, potentially limiting reservoir reseeding [38, 65-69]. Furthermore, antibodies can mediate antibody-dependent cellular cytotoxicity, wherein antibody-coated infected cells are recognized and eliminated by natural killer cells and other effector populations. Some therapeutic vaccine trials have reported enhanced HIV specific antibody responses following TLR agonist adjuvanted vaccination, including occasional induction of antibodies with neutralizing activity. The functional quality of these antibodies, particularly their capacity for Fc-mediated effector functions, may prove as important as their quantity or neutralization breadth.

Innate immune activation represents an immediate and transient response to TLR agonist administration that both supports adaptive immunity and may directly impact viral reservoirs [39]. Natural killer cells, activated by inflammatory cytokines produced following TLR engagement, can eliminate stressed or infected cells through multiple mechanisms. Type I interferons induced by TLR7, TLR8, and TLR9 activation establish antiviral states in surrounding cells and enhance adaptive immune cell function. However, the relationship between innate activation and clinical outcomes remains incompletely defined, with some studies suggesting that the magnitude of innate responses correlates with subsequent adaptive immunity, while others report dissociation between these parameters.

EVIDENCE FOR VIRAL RESERVOIR REDUCTION

Clinical assessment of viral reservoir reduction following therapeutic vaccination presents substantial methodological challenges, as the reservoir is both small and heterogeneous, requiring sensitive and specific measurement techniques. The most direct measure involves quantifying replication-competent virus through viral outgrowth assays, wherein resting CD4-positive T cells are maximally stimulated ex vivo to reactivate latent provirus, with replication-competent units quantified through culture supernatant viral RNA or p24 antigen measurements [40]. These assays, while considered the gold standard, are resource-intensive, require large blood volumes, and demonstrate significant variability between replicates. Surrogate markers, including total and integrated HIV DNA, cell-associated HIV RNA, and induced RNA following ex vivo stimulation, provide more practical alternatives but imperfectly correlate with the replication-competent reservoir.

Several clinical trials of TLR agonist adjuvanted therapeutic vaccines have reported reductions in reservoir markers, though results have been variable and often modest in magnitude. The AGS 004 dendritic cell vaccine trial, which combined autologous dendritic cells loaded with autologous HIV RNA and matured with a TLR7 and TLR8 agonist cocktail, demonstrated significant reductions in viral DNA in some participants and prolonged time to viral rebound following analytical treatment interruption in a subset of individuals [41]. Similarly, trials combining TLR9 agonist CpG oligonucleotides with HIV peptides or proteins have reported enhanced immune responses and, in some cases, measurable decreases in reservoir markers, though not all participants responded uniformly.

The analytical treatment interruption represents the most clinically relevant measure of therapeutic vaccine efficacy, as it directly assesses whether interventions have sufficiently reduced the reservoir or enhanced immune control to delay or prevent viral rebound. Multiple trials have incorporated carefully monitored treatment interruptions with predefined criteria for antiretroviral therapy reinitiation. Results have demonstrated that while most participants experience viral rebound with kinetics similar to historical controls, a subset exhibits delayed rebound or lower viral set points during interruption [42, 43]. These partial responders provide valuable insights into factors associated with success and highlight the potential achievability of a functional cure in select individuals. However, the proportion of participants achieving clinically meaningful benefit has remained disappointingly small in most studies to date.

Important insights have emerged from correlative analyses examining relationships between vaccine-induced immune responses and reservoir outcomes. Some studies have identified associations between the magnitude or quality of CD8-positive T cell responses and the degree of reservoir reduction or time to rebound. Polyfunctional T cells and cells exhibiting high cytotoxic potential have shown stronger correlations with favorable outcomes than total response magnitude [44]. Additionally, the breadth of T cell recognition across multiple HIV epitopes may provide redundancy that prevents viral escape and correlates with better control. These findings are guiding the development of next-generation vaccines designed to optimize these response characteristics.

The biological heterogeneity of study participants likely contributes substantially to variable outcomes [45]. Individuals differ in reservoir size at baseline, immune function despite viral suppression, human leukocyte antigen types that influence epitope presentation, and viral sequence variations that affect antigen recognition. Some individuals may have been treated during acute infection and possess smaller reservoirs more amenable to clearance, while others initiated therapy during chronic infection with larger, more stable reservoirs. Future studies increasingly incorporate stratification by these factors and utilize analytical approaches that account for individual variability rather than simply assessing group mean effects.

CHALLENGES AND FUTURE DIRECTIONS

Despite scientific rationale and encouraging preliminary data, therapeutic HIV vaccines incorporating TLR agonists face substantial challenges that must be addressed to achieve clinically meaningful efficacy. The magnitude of immune responses generated to date, while enhanced compared to unadjuvanted vaccines, may remain insufficient to eliminate the extremely low frequency of latently infected cells [46, 47]. Mathematical modeling suggests that cytotoxic T lymphocyte killing rates must be extraordinarily high to significantly impact reservoir half-life, potentially requiring response magnitudes orders of magnitude greater than currently achieved. This reality motivates exploration of more potent adjuvants, optimized antigen formulations, and prime boost strategies that sequentially utilize different vaccine platforms to maximize and broaden responses.

The quality of vaccine-induced immune responses represents an equally important consideration. Exhausted T cells expressing multiple inhibitory receptors, including programmed cell death protein 1, cytotoxic T lymphocyte-associated protein 4, and T cell immunoglobulin and mucin domain containing protein 3, exhibit impaired effector function despite normal or even elevated frequencies [48, 49]. Current therapeutic vaccines have shown limited success in reversing T cell exhaustion, prompting investigation of combination approaches with immune checkpoint inhibitors. Early phase trials combining therapeutic vaccination with programmed cell death protein 1 blockade have demonstrated safety and preliminary evidence of enhanced immune responses, though whether this translates to reservoir reduction requires further study.

The anatomical sanctuary hypothesis presents another significant challenge. Even if circulating reservoirs are reduced through therapeutic vaccination, residual virus in tissue sanctuaries with limited immune surveillance may persist and ultimately reseed infection [50, 51]. Strategies to enhance T cell trafficking to these sites or locally deliver immunotherapeutic agents are under investigation. Furthermore, recent recognition that tissue resident memory T cells may constitute a distinct and substantial reservoir component necessitates the development of approaches specifically targeting these cells, potentially through mucosal vaccination or systemically administered agents that preferentially accumulate in tissues.

Safety considerations become increasingly important as therapeutic vaccine research moves toward combination regimens incorporating multiple immunostimulatory agents. The inflammatory responses beneficial for reservoir

clearance could theoretically increase the risk of immune-mediated pathology, particularly in tissues already affected by chronic HIV associated inflammation [52]. Long-term safety data from the extended follow-up of trial participants will be essential for understanding the full benefit-to-risk profile. Additionally, the theoretical concern that immune activation could expand the target cell pool available for infection necessitates careful monitoring for any evidence of reservoir expansion in response to vaccination.

The path forward likely requires integration of therapeutic vaccination with other cure modalities into comprehensive treatment regimens. Latency-reversing agents administered shortly before or concurrent with vaccination could maximize exposure of infected cells to enhanced immune responses [53]. Broadly neutralizing antibodies could prevent viral spread during latency reversal and provide passive immunity while active vaccine responses develop. Therapeutic gene editing to inactivate coreceptors or proviral DNA could complement immunological approaches. Clinical trial designs must evolve to efficiently test these complex combinations while identifying optimal sequencing and timing of components.

Importantly, the definition of success in HIV cure research continues to evolve. While complete viral eradication remains the ultimate goal, intermediate endpoints including sustained virological remission without antiretroviral therapy, reduced reservoir size permitting treatment simplification, or delayed disease progression without therapy represent meaningful clinical benefits. Therapeutic vaccines incorporating TLR agonists may prove most valuable not as monotherapies but as components of combination cure regimens, contributing incremental benefits that collectively achieve functional cure in substantial proportions of patients [54].

CONCLUSION

Therapeutic HIV vaccines adjuvanted with toll-like receptor agonists represent a scientifically grounded approach to addressing the fundamental challenge of viral persistence in latent reservoirs. The integration of these innate immune activators into vaccine platforms provides dual benefits of latency reversal to expose hidden virus and immune enhancement to eliminate reactivated infected cells. Clinical experience to date has demonstrated proof of concept for both activities, with TLR agonists inducing measurable latency reversal and augmenting HIV specific immune responses compared to unadjuvanted controls. Several trials have reported encouraging signals, including reservoir marker reductions in subsets of participants and delayed viral rebound following treatment interruption in select individuals, validating the potential of this approach. However, translation of scientific promise into consistent clinical benefit has proven challenging. The small magnitude of responses relative to the theoretical threshold required for reservoir elimination, the persistence of T cell exhaustion despite vaccination, the anatomical sequestration of reservoirs in immune sanctuaries, and substantial interindividual variability in outcomes all constrain current efficacy. These limitations should not be interpreted as a failure of the fundamental concept but rather as indicators of the biological complexity of HIV persistence and the need for more sophisticated intervention strategies. The field is appropriately moving toward combination approaches that integrate therapeutic vaccination with complementary modalities, including latency-reversing agents, immune checkpoint blockade, broadly neutralizing antibodies, and potentially therapeutic gene editing. Future research priorities include optimization of vaccine antigen selection and formulation to maximize epitope coverage and response quality, identification of biomarkers that predict vaccine responsiveness to enable personalized approaches, development of strategies to enhance immune responses in tissue sanctuaries where reservoirs persist, and rigorous testing of combination regimens with mechanistically complementary agents. Equally important are continued efforts to understand the biological determinants of the small subset of participants who demonstrate favorable responses, as these individuals provide critical insights into achievable outcomes and factors enabling success. Long-term safety monitoring remains essential as more potent immunostimulatory regimens are tested, ensuring that the pursuit of a cure does not compromise the excellent outcomes already achievable with antiretroviral therapy.

The ultimate measure of success will be the proportion of HIV infected individuals who achieve sustained virological remission without antiretroviral therapy, the durability of that remission, and the quality of life during remission periods. While a complete cure remains elusive, incremental progress toward a functional cure would represent a transformative advancement for millions living with HIV globally. Therapeutic vaccines incorporating TLR agonists constitute an important component of the scientific toolkit being assembled to achieve this goal, contributing critical immunological enhancement to comprehensive cure strategies. The path forward requires sustained commitment to rigorous clinical investigation, mechanistic research to understand successes and failures, and collaborative efforts to integrate promising approaches into optimized combination regimens.

Future therapeutic HIV vaccine development should prioritize rational combination strategies that synergistically integrate TLR agonist adjuvants with complementary immunotherapeutic modalities, including immune checkpoint inhibitors and broadly neutralizing antibodies, guided by biomarker-driven patient selection, to maximize the probability of achieving durable virological remission without antiretroviral therapy in substantial proportions of infected individuals.

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