Scientific Research Publishing

Advances in Bioscience and Biotechnology, 2026, 17(8), 324-350
https://www.scirp.org/journal/abb
ISSN Online: 2156-8502
ISSN Print: 2156-8456

HIV Vaccines in Sub-Saharan Africa: Linking Correlates of Protection, Early Immune Pathways, and ART Gaps to Advance Prophylactic and Therapeutic Strategies: A Systematic Review

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How to cite this paper: Sangany, C.M. and Kabuya, K.E. (2026) HIV Vaccines in Sub-Saharan Africa: Linking Correlates of Protection, Early Immune Pathways, and ART Gaps to Advance Prophylactic and Therapeutic Strategies: A Systematic Review. *Advances in Bioscience and Biotechnology*, **17**, 324-350.
https://doi.org/10.4236/abb.2026.178021

Received: May 18, 2026
Accepted: August 10, 2026
Published: August 13, 2026

Abstract

Background: Sub-Saharan Africa (SSA) remains the epicenter of the global HIV epidemic, accounting for nearly two-thirds of people living with HIV worldwide. While antiretroviral therapy (ART) has transformed HIV into a manageable chronic condition by substantially reducing morbidity, mortality, and transmission, major challenges persist, including latent viral reservoirs, chronic immune activation, incomplete immune restoration, treatment access gaps, and structural barriers. Consequently, effective prophylactic and therapeutic HIV vaccines remain essential components of long-term HIV prevention and remission strategies. **Objective:** This systematic review synthesizes the current landscape of HIV vaccine research in SSA, focusing on immune correlates of protection, early immunological events following primary HIV infection, persistent challenges associated with ART, and emerging prophylactic and therapeutic vaccine strategies. **Methods:** This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A comprehensive search of electronic databases identified 300 records using predefined search terms related to HIV vaccines, immune correlates of protection, ART-associated immune dysfunction, and vaccine efficacy. After removal of duplicates (n = 35), 265 records underwent title and abstract screening, with 165 articles assessed for full-text eligibility. Following application of predefined inclusion and exclusion criteria, 125 studies were included in the final qualitative synthesis. Data were extracted and narratively synthesized across four thematic domains:

(i) correlates of HIV protection, (ii) immune responses during primary HIV infection, (iii) ART-related immunological and virological limitations, and (iv) advances in prophylactic and therapeutic HIV vaccine development. A formal risk-of-bias assessment was not performed due to substantial heterogeneity in study designs, populations, methodologies, and outcome measures, which limited comparability across studies. **Results:** Evidence from SSA cohorts indicates that effective HIV control is associated with a multifaceted immune profile involving broadly neutralizing antibodies, Fc-mediated antibody functions, HIV-specific T-cell responses, favorable cytokine signatures, mucosal immunity, and host genetic factors. Following primary infection, rapid innate immune activation, type I interferon signaling, depletion of $CCR5^+$ $CD4^+$ T cells in gut-associated lymphoid tissue, microbial translocation, immune exhaustion, and early establishment of viral reservoirs contribute to persistent infection. Despite effective viral suppression with ART, challenges remain, including delayed diagnosis, treatment interruptions, residual inflammation, incomplete immune reconstitution, and persistence of viral reservoirs in anatomical and cellular compartments. Recent advances in HIV vaccine development include germline-targeting immunogens, broadly neutralizing antibody-based strategies, mRNA vaccine platforms, mosaic immunogens, conserved-region T-cell vaccines, dendritic cell-based approaches, and combination strategies integrating therapeutic vaccination with latency-targeting and immune-modulating interventions. **Conclusions:** HIV vaccine research in SSA is entering a new era characterized by precision immunogen design, systems immunology, and integrated prevention-to-remission (P2R) approaches. Although the absence of a formal methodological quality assessment and heterogeneity among included studies warrant cautious interpretation, decades of vaccine research have generated critical biological insights that are informing next-generation strategies. Future progress will require integration of advanced immune engineering approaches with context-specific implementation frameworks, strengthened health systems, and expanded African-led research, manufacturing, and clinical trial capacity. The convergence of prophylactic and therapeutic vaccine approaches provides a promising pathway toward durable immune-mediated viral control, reduced reliance on lifelong ART, and the possibility of functional HIV remission in SSA.

Keywords

HIV Vaccine, SSA, Broadly Neutralizing Antibodies,
Germline-Targeting Immunogens, Immune Correlates of Protection,
Viral Reservoirs, Mucosal Immunity, Systems Immunology,
mRNA Vaccine Platforms, HIV Remission

1. Introduction

By the end of 2024, an estimated 40.8 million people were living with HIV worldwide, including 1.4 million children aged 0 - 14 years and 39.4 million adults aged

≥15 years [1]. Despite remarkable progress in HIV prevention and treatment, HIV remains a major global public health challenge. In 2024 alone, approximately 630,000 deaths were attributed to HIV-related causes, including 75,000 deaths among children aged 0 - 14 years and 550,000 deaths among adults aged ≥ 15 years. Although HIV-related mortality has declined by 54% since 2010 and by nearly 70% compared with the epidemic peak in 2004, the pandemic has claimed an estimated 44.1 million lives worldwide since its emergence [2].

Sub-Saharan Africa (SSA) continues to bear a disproportionate share of the epidemic, accounting for nearly two-thirds of the global HIV burden. Approximately 25.6 million individuals are living with HIV in the region, with the majority residing in Eastern and Southern Africa (20.8 million), while Western and Central Africa account for 4.8 million cases. In 2022, the region recorded an estimated 760,000 new HIV infections and 380,000 AIDS-related deaths, highlighting the persistent public health and socioeconomic impact of HIV despite decades of progress [3]. These figures underscore the urgent need for innovative, sustainable, and regionally relevant prevention and treatment strategies, including the development of next-generation HIV vaccines.

The advent of antiretroviral therapy (ART) has fundamentally transformed the natural history of HIV infection, converting a once-fatal disease into a manageable chronic condition and markedly reducing HIV-related morbidity and mortality [3] [4]. Nevertheless, several unresolved challenges continue to hinder efforts toward sustained viral remission and eradication. These include the persistence of latent viral reservoirs, chronic immune activation and systemic inflammation, incomplete immune reconstitution, and the emergence of drug-resistant viral variants [5]. Collectively, these biological constraints underscore the need for complementary immunotherapeutic strategies capable of achieving durable viral control and ultimately facilitating functional cure or sterilizing immunity [6]. Beyond these biological barriers, progress toward HIV control is further complicated by persistent structural, behavioral, and socioeconomic determinants [7]. In many settings, particularly in SSA, limited healthcare infrastructure, disparities in access to care, stigma and discrimination, poverty, gender inequities, and high-risk behavioral patterns continue to impede the uptake of preventive interventions, participation in vaccine trials, and equitable access to emerging therapeutic innovations [8] [9].

HIV vaccines, encompassing both prophylactic and therapeutic approaches, represent a crucial addition to current HIV prevention and treatment paradigms [10]. Prophylactic vaccines aim to prevent viral acquisition by inducing protective immune responses prior to exposure, whereas therapeutic vaccines are designed to enhance immune-mediated control in individuals with established infection, with the long-term goals of reducing viral reservoirs, decreasing reliance on lifelong ART, and achieving sustained remission [11]. Recent advances in HIV vaccine research have been exemplified by the African-led Pre-Exposure Prophylaxis Vaccine (PrEPVacc) trial, which evaluated novel vaccine regimens alongside oral

pre-exposure prophylaxis (PrEP) in Uganda, Tanzania, Mozambique, and South Africa [12]. Although the vaccine component of the trial was discontinued in late 2023 following interim analyses indicating a low probability of demonstrating efficacy against HIV acquisition [12] [13], effective PrEP modalities, including long-acting injectable formulations such as lenacapavir and established oral PrEP regimens, have emerged as essential pillars of HIV prevention, demonstrating remarkable efficacy in reducing HIV transmission and contributing substantially to efforts aimed at alleviating the region's disproportionate HIV burden [14].

Another recent development is the trial of the Gorilla Adenovirus Vectored HIV Networked Epitopes Vaccine candidate (GRAdHIVNE1), a novel CD8+ T-cell-inducing vector vaccine being evaluated in Phase 1 studies in Zimbabwe to assess safety and immunogenicity of networked HIV-epitope constructs [15]. The GRAdHIVNE1 vaccine faces challenges, including its early-phase focus on safety rather than efficacy, limited effectiveness of T-cell-based responses in preventing HIV infection, potential interference from pre-existing immunity, restricted population representativeness due to exclusion criteria, and lack of protection against early infection [16].

Studies of the unique immune landscape in SSA have identified key considerations for HIV vaccine development, including the induction of tissue-resident memory (TRM) cells, preservation of germinal center and T follicular helper (Tfh) cell function to promote broadly neutralizing antibody (bNAbs) responses, and enhancement of follicular cytotoxic (fCTLs) activity to limit viral reservoir formation [17] [18]. Moreover, vaccine efficacy must be evaluated in the presence of endemic co-infections, such as tuberculosis, malaria, and helminthiasis, underscoring the need for integrated prevention strategies tailored to the epidemiological and immunological context of the region [19].

This systematic review critically evaluates the current landscape of HIV vaccine research in SSA, with particular emphasis on immunological correlates of protection, early host immune responses following HIV acquisition, strategies aimed at overcoming the limitations of ART, and the structural, socioeconomic and behavioural determinants that influence vaccine uptake and implementation. This review further examines emerging vaccine candidates and next-generation technologies, including epitope-network immunogens, germline-targeting approaches, and mRNA-based platforms, which collectively represent promising avenues for advancing HIV prevention, supporting remission-oriented interventions, and strengthening the continuum of HIV care in the region. Collectively, these developments underscore the transition toward increasingly precise and integrated approaches to HIV control in SSA.

2. Methodology

2.1. Search Strategy

The present systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A comprehensive

search of multiple electronic databases identified 300 records. Search terms included: "HIV vaccine," "prophylactic vaccine," "therapeutic vaccine," "correlates of protection," "immune response," "broadly neutralising antibodies," "T-cell response," "immune activation," "ART coverage," "SSA," and "vaccine efficacy."

After the removal of duplicate entries (n = 35), 265 unique records underwent title and abstract screening. Of these, 165 articles were considered potentially relevant and were subsequently subjected to full-text assessment for eligibility according to the predefined inclusion and exclusion criteria.

2.2. Inclusion and Exclusion Criteria

To ensure scientific rigor, transparency, and minimize selection bias, predefined inclusion and exclusion criteria were systematically applied. Following full-text review, 40 records were excluded because they comprised animal-only or preclinical studies lacking direct translational relevance to humans, commentaries, review articles, editorials, or publications without primary data, studies unrelated to HIV vaccine immunogenicity, immune correlates of protection, or ART-associated immune dysfunction, and articles published in languages other than English.

A total of 125 studies met the eligibility criteria and were included in the review. Eligible studies were peer-reviewed articles published in English only, conducted in populations or cohorts from SSA, and focused on HIV vaccines, correlates of protection, or immunological gaps associated with ART. Both experimental studies, including clinical trials, and observational studies reporting immunological, virological, or clinically relevant outcomes were considered for inclusion.

2.3. Screening Process

All retrieved records were imported into EndNote software for reference management and the identification and removal of duplicate entries. The screening process was conducted in accordance with the PRISMA 2020 guidelines and comprised two sequential stages.

Title and Abstract Screening: Following duplicate removal, two independent reviewers screened the titles and abstracts of all identified records against the predefined eligibility criteria. Studies deemed irrelevant were excluded at this stage. Any discrepancies between reviewers were resolved through discussion and, when necessary, consultation with a third reviewer to achieve consensus.

Full-Text Review: Articles considered potentially eligible underwent full-text assessment by two independent reviewers. Each study was evaluated for compliance with the inclusion and exclusion criteria. Differences in study selection were resolved through consensus discussions, with arbitration by a third reviewer when required.

2.4. Data Extraction and Analysis

Data from the 125 eligible articles were systematically extracted using a standardized data extraction form. Information collected included study population char-

acteristics (age, sex, geographic location, and cohort demographics), HIV clade distribution and its relevance to regional vaccine design, vaccine platform and regimen (e.g., viral vector-based, mRNA, or protein subunit vaccines), immunological parameters assessed (humoral, cellular, and innate immune responses), and clinical outcomes, including vaccine efficacy, safety, and viral load reduction.

Following data extraction, the findings were synthesized narratively and organized thematically to address four key areas of interest.

Correlates of Protection: Studies were evaluated to identify humoral, cellular, and innate immune markers associated with protection against HIV acquisition, vaccine-induced immunity, and viral control.

Immune Pathways Following Primary HIV Infection: Particular attention was given to the mechanisms underlying innate immune sensing, adaptive immune priming, and immune activation and exhaustion during early HIV infection, as well as their implications for vaccine-induced responses.

Unmet Needs of ART: The review examined persistent viral replication within anatomical sanctuary sites, establishment and maintenance of viral reservoirs, chronic immune activation, and incomplete immune reconstitution despite effective ART, all of which may limit vaccine responsiveness and therapeutic efficacy.

Recent Advances in HIV Vaccine Development: Current progress in prophylactic and therapeutic HIV vaccine strategies was reviewed, with emphasis on viral vector-based platforms, mRNA technologies, protein subunit vaccines, and broadly neutralizing antibody (bNAb)-based approaches with demonstrated or potential applicability in SSA populations.

2.5. Methodological Quality Assessment

A formal risk-of-bias assessment was not performed because this review incorporated evidence from diverse study designs, including randomized controlled trials, early-phase clinical studies, immunological investigations, narrative reviews, and systematic reviews. The substantial heterogeneity in study populations, interventions, methodologies, and outcome measures prevented the application of a single validated appraisal tool across the entire evidence base. Although design-specific tools could have been applied, this approach would have reduced comparability across studies. Instead, key study characteristics, including study design, population characteristics, HIV/ART status, vaccine platforms, immune correlates, and principal findings, were systematically extracted and narratively synthesized to enhance transparency. However, the absence of a formal risk-of-bias assessment limits the ability to quantitatively evaluate the certainty and strength of the synthesized evidence, and findings should therefore be interpreted within the context of the methodological diversity of the included studies.

2.6. PRISMA Flow Diagram

The study selection process was documented using a PRISMA 2020 flow diagram, which illustrates the number of records identified through database searches,

screened for eligibility, excluded at each stage, and included in the final qualitative synthesis. The corresponding flow diagram is presented in the Results section.

2.7. Limitations and Future Research

This review identified several ongoing challenges in HIV vaccine research, including limited representation of diverse African populations in clinical trials, variability in immunological methodologies, and the incomplete definition of correlates of protection across SSA cohorts. Future studies should focus on integrated vaccine ART approaches, the application of systems immunology and multi-omics technologies to identify predictive biomarkers, and the conduct of region-specific clinical trials that reflect local viral subtype distribution and host genetic diversity. Addressing these gaps will be critical for advancing the development and implementation of effective HIV vaccine strategies tailored to SSA populations.

3. Results

3.1. Study Selection

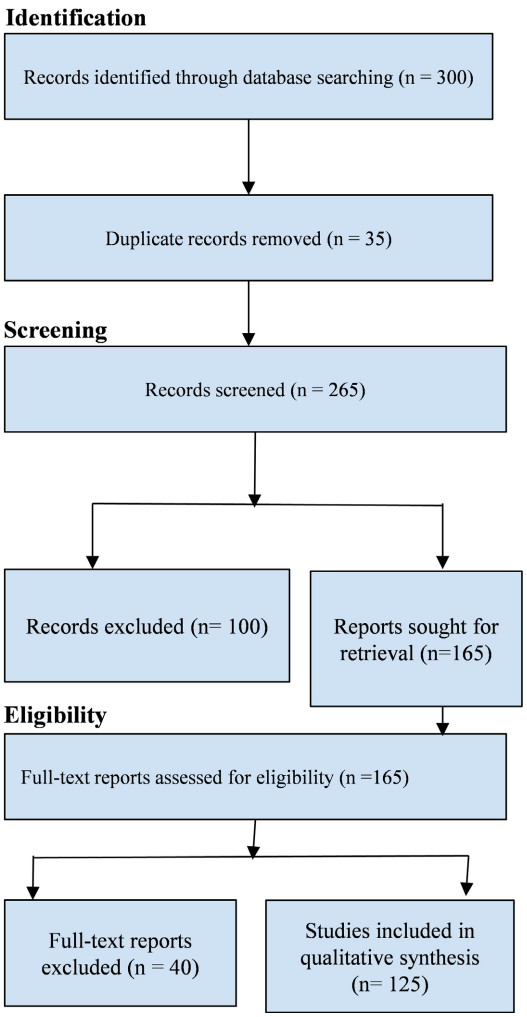

Figure 1. PRISMA 2020 flow diagram of study selection process.

A total of 300 records were identified through systematic database searching. After the removal of duplicate records (n = 35), 265 unique articles underwent title and abstract screening. Of these, 100 records were excluded, and 165 potentially relevant articles were subjected to full-text eligibility assessment. Following full-text review, 40 articles were excluded based on predefined exclusion criteria. Consequently, 125 studies were deemed eligible and included in the final qualitative synthesis. A detailed overview of the study selection process is presented in the PRISMA 2020 flow diagram (**Figure 1**).

3.2. Characteristics of Included Studies (Table 1)

A total of 125 studies were included in this systematic review. The studies were conducted across multiple countries in SSA, including multicountry investigations spanning Eastern, Southern, Western, and Central Africa. The included studies employed diverse methodological designs, including randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, exploratory immunological investigations, narrative reviews, and systematic reviews. Sample sizes varied considerably, ranging from small early-phase vaccine trials to large population-based cohorts.

Study populations included HIV-negative adults enrolled in vaccine efficacy trials, individuals living with HIV, women at high risk of HIV acquisition, adolescents, and other priority populations. The studies investigated HIV vaccine candidates, immune correlates of protection, viral reservoir dynamics, ART—related outcomes, and emerging prophylactic and therapeutic vaccine approaches.

Table 1. Characteristics of studies included in the systematic review of HIV vaccines in SSA.

Author (Year)	Country/Region	Study Design	Study Population	Articles Included (n)	Vaccine Candidate /Intervention	Immune Correlates Investigated	ART Status/Gap Assessed	Key Findings
Chanda C *et al.* (2025)—HIV-CORE 006	Eastern and Southern Africa	Phase 1 Randomized Placebo-Controlled Trial	Healthy HIV-negative adults	20	HIVconsvX conserved mosaic T-cell vaccine (ChAdOx1/MVA vectored)	HIV-specific T-cell responses, breadth and magnitude of cellular immunity	Partial	Demonstrated safety and broad T-cell immunogenicity supporting next-stage efficacy testing.
Gray G *et al.* (2025)	Africa-wide	Narrative Review/Research Synthesis	HIV vaccine development programs	10	Multiple candidate HIV vaccines	bnAb induction, cellular immunity, correlates of protection	Yes	Highlighted Africa's central role in HIV vaccine development and future efficacy trials.

Continued

Gray GE *et al.* (2024)—Imbokodo /HVTN 705	Southern Africa (South Africa, Zimbabwe, Zambia, Malawi, Mozambique)	Phase 2b Randomized Controlled Trial	HIV-negative women aged 18–35 years	25	Ad26.Mos4.HIV + gp140 mosaic vaccine regimen	Binding antibodies, neutralizing antibodies, cellular immune responses	No	Robust humoral and cellular immunity generated but insufficient protection against HIV acquisition.
Mgodi NM *et al.* (2021)	Sub-Saharan Africa	Phase 2b Prevention Trial	Women at high risk of HIV infection	15	VRC01 broadly neutralizing monoclonal antibody	Neutralizing antibody activity, antibody-mediated protection	No	Provided evidence that bnAb-mediated protection is feasible against sensitive HIV strains.
Moodie Z *et al.* (2022)—HVTN 702	South Africa	Phase 2b/3 Randomized Trial	HIV-negative adults	30	ALVAC-HIV + subtype C gp120/MF59	V1V2 IgG antibodies, Env-specific binding antibodies, polyfunctional CD4+ T-cell responses	No	Vaccine failed to demonstrate efficacy but identified important immune correlates associated with HIV acquisition risk.
Msafiri F *et al.* (2022)	Mozambique and Sub-Saharan Africa	Exploratory Vaccine Immunology Study	Vaccine trial participants	10	Experimental HIV vaccine platforms	Vaccine-induced seroreactivity, antibody responses affecting HIV diagnostics	No	Demonstrated that vaccine-induced antibodies may interfere with HIV testing algorithms.
Scott GY & Worku D (2024)	Global with Sub-Saharan Africa focus	Systematic Review	HIV vaccine trials and cohorts	15	Multiple HIV vaccine candidates	Broadly neutralizing antibodies, T-cell responses, immune memory markers	Yes	Summarized advances in HIV vaccine development and identified remaining immunological challenges.
Total				125				

3.3. Study Findings

3.3.1. Correlates of HIV Protection in SSA Cohorts

Across the included studies, protection against HIV acquisition and improved vi-

ral control were associated with a complex interplay of immunological, behavioral, structural, and socioeconomic determinants.

At the immunological level, several correlates of protection were consistently identified, including the induction of broadly neutralizing antibodies (bnAbs), enhanced Fc-mediated antibody effector functions, robust HIV-specific $CD4^+$ and $CD8^+$ T-cell responses, favorable cytokine and chemokine profiles, and lower levels of systemic immune activation and inflammation [20]. Emerging evidence further highlighted the importance of mucosal immunity, particularly at genital and gastrointestinal sites of viral entry, as well as host genetic factors that influence susceptibility, viral control, and vaccine responsiveness [21] [22].

Behavioral factors associated with reduced HIV transmission risk included consistent condom use, high adherence to ART and PrEP, uptake of voluntary medical male circumcision, regular HIV testing, and active engagement in combination prevention programs [23]. In contrast, behavioral patterns such as multiple or concurrent sexual partnerships, age-disparate relationships, and inconsistent condom use were repeatedly associated with increased vulnerability to HIV acquisition [24].

Structural determinants also played a critical role in shaping HIV outcomes. Key factors identified across studies included access to healthcare services, ART availability and coverage, HIV-related stigma and discrimination, gender inequality, population mobility and migration, and broader socioeconomic disparities. Communities characterized by high ART coverage and lower community viral loads generally experienced substantially lower HIV incidence, underscoring the importance of treatment as prevention strategies [25].

Socioeconomic conditions further influenced both HIV risk and access to prevention and treatment interventions. Higher educational attainment, income stability, employment, food security, secure housing, and strong social support networks were consistently associated with improved uptake of HIV services, better treatment adherence, and more favorable health outcomes [26]. Collectively, these findings emphasize that effective HIV prevention and vaccine strategies in SSA must address not only biological mechanisms of protection but also the behavioral, structural, and socioeconomic contexts that shape HIV vulnerability and resilience.

3.3.2. Immune Pathways Following Primary HIV Infection

The included studies characterized primary HIV infection as a highly dynamic phase marked by rapid and extensive activation of both innate and adaptive immune responses. Acute infection was associated with the early engagement of innate immune sensing pathways and a pronounced increase in type I interferon production, which contributed to initial viral containment and antiviral defense [27]. However, sustained immune activation beyond this early phase was consistently linked to immune dysregulation, accelerated disease progression, and impaired immune recovery [28].

Several studies reported profound depletion of activated $CCR5^+$ $CD4^+$ T cells

within gut-associated lymphoid tissue (GALT) during the earliest stages of infection. This loss of mucosal immune integrity was accompanied by disruption of epithelial barriers, microbial translocation, and the establishment of chronic systemic inflammation, all of which are recognized drivers of HIV pathogenesis [29]. HIV-specific $CD8^+$ T-cell responses emerged rapidly following infection and played a critical role in the initial reduction of plasma viremia [30]. Nevertheless, persistent antigenic stimulation resulted in progressive T-cell exhaustion, characterized by increased expression of inhibitory receptors such as PD-1, TIM-3, and LAG-3, ultimately compromising antiviral function and immune control.

In parallel, studies documented impaired germinal center formation, dysfunctional T follicular helper (Tfh) cell responses, delayed antibody maturation, and the early establishment of long-lived latent viral reservoirs, which together pose major obstacles to durable immune control and viral eradication [31] [32]. Importantly, residual immune activation and inflammation frequently persisted despite partial viral suppression, indicating that virological control alone does not fully restore immune homeostasis.

Within SSA populations, coinfections such as Tuberculosis, Malaria, and helminth infections were frequently reported to further modulate immune activation, alter host immune responses, and accelerate HIV disease progression, highlighting the need for vaccine and therapeutic strategies that account for the complex infectious landscape of the region [33].

3.3.3. ART-Related Challenges in Sub-Saharan Africa (SSA)

The reviewed studies identified several persistent challenges that continue to limit the long-term effectiveness and population-level impact of ART programs across SSA. Retention in care and sustained treatment adherence remained inconsistent across many settings, with treatment interruptions frequently linked to population mobility, HIV-related stigma, socioeconomic hardship, and healthcare system limitations, including medication stockouts, long travel distances to clinics, and workforce shortages [34].

Late HIV diagnosis was particularly common among men, adolescents, and highly mobile populations, leading to delayed ART initiation, advanced disease presentation, and increased opportunities for onward transmission before viral suppression could be achieved [35]. Although ART has proven highly effective in suppressing plasma viremia and reducing HIV-related morbidity and mortality, multiple studies highlighted the persistence of latent viral reservoirs within lymphoid tissues, the gastrointestinal tract, and other anatomical sanctuaries that remain inaccessible to conventional therapy [36]. The long-term persistence of these reservoirs was consistently identified as a major obstacle to sustained HIV remission and cure strategies.

Furthermore, several studies reported evidence of ongoing immune activation and chronic inflammation among individuals receiving suppressive ART despite successful virological control [37]. This residual inflammatory state was attributed to factors including microbial translocation resulting from persistent mucosal

barrier dysfunction, chronic coinfections, and incomplete restoration of immune homeostasis. Persistent immune activation has important clinical implications, as it contributes to immune aging, non-AIDS comorbidities, and suboptimal immune recovery.

At the population level, undiagnosed infections, incomplete viral suppression, suboptimal adherence, and recurrent treatment interruptions were identified as major contributors to continued HIV transmission despite substantial expansion of ART coverage across the region [38]. Collectively, these findings underscore the limitations of ART as a standalone intervention and reinforce the need for complementary strategies, including effective prophylactic and therapeutic vaccines, to achieve durable epidemic control in SSA.

3.3.4. Emerging Prophylactic and Therapeutic HIV Vaccine Strategies

The included studies highlighted substantial progress in HIV vaccine research, with major advances occurring in the development of germline-targeting immunogens, bnAb-based approaches, mRNA vaccine technologies, and therapeutic vaccination strategies. Collectively, these innovations reflect a shift from conventional vaccine design toward precision immunology and rational immune engineering aimed at overcoming the extraordinary genetic diversity and immune evasion mechanisms of HIV.

Among prophylactic vaccine approaches, germline-targeting immunogens designed to activate rare precursor B cells capable of generating bnAb lineages demonstrated promising immunogenicity and favorable safety profiles in early-phase clinical trials [39] [40]. Several studies further described sequential immunization strategies intended to guide the progressive maturation of B cells toward the production of potent and broadly neutralizing antibodies, thereby mimicking the natural evolutionary pathways observed in a subset of individuals with chronic HIV infection.

mRNA-based vaccine platforms emerged as a particularly important area of investigation, building on the success of mRNA technologies in other infectious diseases [41]. Experimental mRNA HIV vaccine candidates were reported to induce robust humoral and cellular immune responses while maintaining favorable safety and tolerability profiles in early clinical studies [42] [43]. The flexibility, rapid manufacturability, and capacity for iterative antigen optimization offered by mRNA technology position this platform as a promising avenue for future HIV vaccine development.

Additional innovative strategies included DNA origami-based antigen presentation systems, mosaic immunogens designed to improve coverage against globally diverse HIV strains, and viral vector platforms engineered to enhance the breadth, magnitude, and durability of vaccine-induced immune responses [44] [45]. These approaches seek to address one of the central challenges in HIV vaccinology: the extensive genetic variability of circulating viral strains, particularly within SSA (**Table 2**).

Therapeutic vaccine development focused primarily on strengthening HIV-specific cellular immunity and improving immune-mediated viral control among

individuals receiving ART [46]. Investigated strategies included T-cell—directed vaccines targeting highly conserved HIV epitopes, mRNA-based therapeutic vaccines, dendritic cell vaccines, and combination approaches integrating bnAbs with latency-reversing or latency-targeting interventions aimed at reducing viral reservoirs [47]. Such strategies are intended not only to enhance immune control of residual viral replication but also to contribute to long-term remission and functional cure efforts.

Overall, the emerging HIV vaccine landscape is increasingly characterized by integrated, multi-component strategies that combine advanced immunogen design, antibody induction, cellular immune enhancement, and reservoir-targeting interventions, offering renewed optimism for both prophylactic and therapeutic HIV vaccine development in SSA and globally.

Table 2. Major HIV Vaccine Trials in SSA.

Trial Name	Period	Location(s)	Vaccine Strategy	Trial Phase	Outcome	Key Contribution
HVTN 702 (Uhambo)	2020 (analysis/termination phase)	South Africa	RV144-derived clade C ALVAC + gp120	Phase 2b/3	No efficacy (futility stopped)	Confirmed lack of protection of RV144-adapted regimen in African subtype C epidemic
HVTN 705 (Imbokodo)	2020 - 2021	South Africa, Zimbabwe, Zambia, Malawi, Mozambique	Ad26.Mos4.HIV + gp140 boost (mosaic vaccine)	Phase 2b	No efficacy	Demonstrated failure of mosaic-based prophylactic vaccine in women
HVTN 706 (Mosaico)	2020 - 2023	South Africa (plus global sites)	Ad26.Mos4.HIV + gp140	Phase 3	Stopped for futility (no efficacy)	Ended major mosaic vaccine program; confirmed lack of protective effect
HVTN 703/704 (AMP Study)	2020 - 2021	South Africa & global	VRC01 broadly neutralizing antibody infusion	Phase 2b	No overall efficacy (strain-dependent protection only)	First large-scale test of bnAb prevention strategy in Africa
PrEPVacc Trial	2020 - 2023	South Africa, Uganda, Tanzania	Dual vaccine regimens + oral PrEP comparison	Phase 2b	Vaccines ineffective (stopped early)	Showed no protective effect; reinforced PrEP superiority in prevention
IAVI G001	2020 - 2021	Rwanda (Africa cohort) + USA	Germline-targeting (eOD-GT8 nanoparticle)	Phase 1	Successful bnAb precursor activation	First proof that vaccination can initiate bnAb lineages

Continued

IAVI G002	2021 - 2023	Africa & USA	Sequential immunogen boosting	Phase 1	Enhanced bnAb precursor maturation	Validated stepwise immune "guidance" strategy
IAVI G003	2022 - 2024	Kenya, Rwanda, South Africa	mRNA-delivered germline-targeting immunogens	Phase 1	Strong immunogenicity	First African-led mRNA HIV vaccine immunogenicity study
mRNA HIV vaccine programs (IAVI-Moderna)	2021 - 2023	South Africa & global	mRNA-based Env immunogens	Phase 1	Safe; strong immune response	First application of mRNA platform to HIV vaccine development
CAPRISA 012/Tat-based therapeutic studies	2020 - 2024	South Africa (Durban)	Tat antigen therapeutic immunization	Phase 1/2	Immunogenic; limited virologic impact	Explored therapeutic vaccine as ART adjunct
HIV remission/ post-treatment control studies	2020 - 2025	South Africa (Durban cohorts)	Immune modulation ± therapeutic vaccination ± bnAbs	Early-phase	Partial ART-free viral control in minority cases	Supports feasibility of functional cure research but not durable remission

4. Discussion

This systematic review synthesized evidence from 125 studies investigating HIV vaccine development in SSA, with particular emphasis on immune correlates of protection, early immunological events following HIV acquisition, persistent ART gaps, and emerging prophylactic and therapeutic vaccine strategies. The findings highlight both the substantial scientific progress achieved in HIV vaccinology and the persistent biological, epidemiological, and implementation challenges that continue to impede the development of an effective vaccine. Despite more than four decades of research, HIV remains among the most challenging vaccine targets due to extensive viral diversity, rapid mutation rate, sophisticated immune escape mechanisms, and the early establishment of latent reservoirs. Consequently, successful vaccine development requires not only advances in immunogen design but also a comprehensive understanding of host immunity, epidemic heterogeneity, and health-system realities within SSA, which remains disproportionately affected by the global HIV epidemic [48].

A central finding emerging from this review is that protection against HIV is unlikely to be mediated by a single immune mechanism. Instead, effective immunity requires coordinated interactions between humoral, cellular, innate, and mucosal immune responses. Broadly neutralizing antibodies (bnAbs), Fc-mediated antibody functions, antibody-dependent cellular cytotoxicity, HIV-specific

$CD4^+$ and $CD8^+$ T-cell responses, tissue-resident immunity, and durable immune memory have all been identified as important components associated with reduced susceptibility or improved viral control [49] [50]. Unlike many vaccine-preventable infections where a single immune correlate can predict protection, HIV appears to require a multifaceted immune response capable of recognizing diverse viral variants, preventing early viral establishment at mucosal entry sites, and limiting systemic dissemination. This complexity highlights the need for vaccine approaches that generate coordinated immune networks rather than targeting isolated immune pathways.

The limitations of ART further emphasize the need for complementary vaccine-based strategies. Although ART, particularly dolutegravir-based regimens, has transformed HIV management by improving survival, reducing viral transmission, and increasing life expectancy across SSA, treatment alone has not achieved epidemic elimination [51]-[54]. Persistent challenges, including delayed diagnosis, treatment interruptions, loss to follow-up, incomplete viral suppression, and inequitable access to healthcare services, continue to compromise long-term epidemic control [55]. Progress toward the UNAIDS 95-95-95 targets remains highly variable across and within countries, reflecting persistent disparities in healthcare delivery and programme implementation [56]-[58]. These challenges disproportionately affect adolescents, young women, migrants, and key populations, who continue to experience elevated HIV acquisition risks due to overlapping biological, behavioural, and structural vulnerabilities. Furthermore, uptake of preventive interventions such as pre-exposure prophylaxis (PrEP) remains suboptimal among many African populations, demonstrating that biomedical availability alone is insufficient without addressing social barriers, stigma, gender inequality, poverty, and healthcare accessibility [59]-[61].

Beyond limitations in prevention and treatment delivery, ART does not eliminate HIV infection. Latent viral reservoirs established during the earliest stages of infection remain largely inaccessible to current therapies and represent the major barrier to achieving a cure [62] [63]. In addition, persistent immune activation and chronic inflammation continue despite long-term viral suppression, contributing to increased risks of cardiovascular disease, neurocognitive impairment, malignancies, and accelerated ageing. These observations suggest that future HIV interventions must extend beyond viral suppression toward strategies capable of restoring immune function and achieving durable remission. Consequently, vaccines should not be viewed as alternatives to ART but as complementary components within an integrated prevention-to-remission (P2R) framework that combines prevention, optimized treatment, immune restoration, and reservoir-targeting strategies.

Understanding the earliest stages of HIV infection remains fundamental for designing effective vaccines. Following exposure, HIV rapidly disseminates, depletes CCR5-expressing $CD4^+$ T cells, induces widespread immune activation, and establishes reservoirs within days, thereby narrowing the window for vaccine-me-

diated intervention. Early immune responses therefore represent both a challenge and an opportunity for vaccine development. Type I interferon responses illustrate this complexity, as early activation contributes to antiviral defence and viral containment, whereas prolonged activation promotes inflammation, immune exhaustion, and impaired adaptive immunity [64] [65]. Future vaccines must therefore achieve a balance between inducing rapid and potent antiviral immunity while avoiding excessive immune activation that may enhance susceptibility or compromise immune regulation.

The immunological environment of SSA introduces additional considerations that may influence vaccine responsiveness. High exposure to endemic infections such as tuberculosis, malaria, helminth infections, and recurrent viral pathogens contributes to chronic immune stimulation and immune modulation, potentially altering vaccine-induced responses [66]. Furthermore, overlapping epidemics, including the COVID-19 pandemic, have demonstrated the vulnerability of HIV-affected populations to disruptions in healthcare delivery and competing health priorities [67]. Therefore, vaccine development strategies should incorporate region-specific factors, including co-infection burden, inflammatory profiles, microbiome composition, nutritional status, and environmental exposures, to better define determinants of vaccine responsiveness among African populations [68]. Immune correlates identified in one epidemiological setting may not necessarily translate directly to populations with different infectious exposures and immunological backgrounds.

Although several HIV vaccine efficacy trials have failed to demonstrate sufficient protection for widespread implementation, these studies have generated critical knowledge that continues to guide the field. Trials including RV144, HVTN 702 (Uhambo), HVTN 705 (Imbokodo), HVTN 706 (Mosaico), and PrEPVacc revealed important limitations of conventional vaccine approaches and demonstrated that immune responses must possess greater breadth, durability, and functional quality to overcome HIV diversity [69] [70]. Rather than representing failures, these outcomes have refined understanding of protective immunity and accelerated the development of more rational vaccine strategies. For example, conserved-region approaches such as HIVconsvX have demonstrated the potential of targeted T-cell immunogens to generate broad cellular responses adapted to regional epidemiological characteristics [71].

Recent advances in vaccine science provide renewed optimism that these challenges may be overcome. HIV vaccine development has increasingly shifted from empirical approaches toward precision immune engineering informed by structural biology, computational modelling, artificial intelligence, and systems immunology. Germline-targeting strategies represent a major conceptual advance by attempting to guide naïve B-cell populations toward maturation pathways capable of producing bnAbs. Similarly, mRNA technologies provide new opportunities for delivering complex immunogens, enabling sequential immunization strategies, and accelerating vaccine development through flexible and scalable plat-

forms [72]. Additional approaches, including mosaic vaccines, nanoparticle-based delivery systems, conserved-region immunogens, and structure-guided envelope designs, aim to overcome the limitations imposed by HIV genetic diversity [73] [74]. Together, these innovations represent a transition toward vaccine strategies designed to deliberately shape protective immunity rather than relying on naturally occurring immune responses.

Parallel progress in therapeutic vaccines and remission-focused interventions has expanded the objectives of HIV vaccine research beyond prevention alone. Therapeutic vaccines aim to enhance immune-mediated control of HIV replication, reduce dependence on lifelong ART, and contribute to durable remission. Current strategies include dendritic cell vaccines, T-cell-directed immunotherapies, bnAb combinations, and latency-reversing approaches designed to expose reservoir cells for immune clearance. Evidence from bnAb studies in African populations suggests that antibody-based interventions may contribute to prolonged viral suppression and post-treatment control [75]. However, complete eradication remains unlikely through a single intervention. Future remission strategies will probably require combination approaches targeting viral reservoirs, residual replication, chronic inflammation, and immune dysfunction simultaneously [76].

However, scientific innovation alone will not guarantee public health impact. Lessons from previous vaccination programmes in SSA demonstrate that vaccine effectiveness depends not only on biological efficacy but also on health-system preparedness, community acceptance, and equitable access [77] [78]. Successful introduction of future HIV vaccines will require investment in supply chains, healthcare workforce capacity, surveillance systems, sustainable financing, community engagement, and integration within existing HIV and primary healthcare programmes [79]-[81]. Implementation science should therefore be incorporated throughout vaccine development rather than considered only after regulatory approval.

Sustainable HIV vaccine deployment will also depend on addressing financial and structural challenges. Although international funding has driven major HIV control achievements over recent decades, dependence on external resources creates vulnerability to changing global priorities and funding reductions [82] [83]. Strengthening domestic investment, regional vaccine manufacturing capacity, and sustainable healthcare infrastructure will be essential for maintaining long-term HIV control and ensuring equitable access to future innovations [84] [85]. Furthermore, biomedical advances must be accompanied by interventions addressing social determinants of HIV vulnerability, including gender inequality, stigma, poverty, educational disparities, and social marginalization. Community trust and vaccine confidence will also be critical determinants of future vaccine uptake, requiring culturally appropriate communication strategies and meaningful community engagement [86]-[88].

This review provides a comprehensive multidisciplinary synthesis of HIV vaccine development in SSA by integrating evidence from immunology, vaccinology,

epidemiology, implementation science, and HIV cure research. The inclusion of recent advances in germline-targeting immunogens, mRNA platforms, bnAbs, and therapeutic vaccine strategies provides an updated perspective on a rapidly evolving field. Nevertheless, substantial heterogeneity among included studies, differences in study populations and methodologies, limited availability of late-stage clinical data, and the dynamic nature of HIV vaccine research restrict definitive comparisons between approaches. These limitations highlight the need for continued longitudinal research and region-specific clinical evaluation.

Overall, HIV vaccine research in SSA is entering a transformative phase characterized by precision vaccine design, immune engineering, and remission-oriented strategies. Although previous efficacy trials have not produced a licensed vaccine, they have generated essential insights that now guide next-generation approaches. The evidence supports a shift away from a prevention-versus-treatment framework toward an integrated P2R continuum combining vaccination, long-acting prevention technologies, optimized ART delivery, immune restoration, reservoir-targeting interventions, and strengthened health systems. Achieving sustained HIV control and eventual functional cure will require not only scientific innovation but also equitable investment, political commitment, community partnership, and strengthened regional capacity to ensure that future breakthroughs benefit the populations most affected by the epidemic.

A limitation of this review relates to the substantial methodological heterogeneity among included studies, encompassing differences in study design, populations, vaccine platforms, immunological assays and outcome definitions. These variations limited the applicability of a single standardized risk-of-bias assessment tool across all studies and constrained direct comparisons of findings. Although a structured methodological quality appraisal was undertaken, the certainty and strength of the synthesized evidence could not be quantitatively graded using a uniform framework. Therefore, the findings should be interpreted within the context of the diversity and evolving nature of HIV vaccine research, particularly in SSA settings.

5. Conclusions

Despite major progress in ART scale-up across SSA, HIV remains incompletely controlled at both population and immunological levels. ART has substantially reduced HIV-associated morbidity, mortality, and transmission; however, it does not eliminate latent viral reservoirs, fully restore immune homeostasis, or resolve chronic immune activation. These persistent biological limitations, together with structural and health-system barriers, highlight the need for complementary prophylactic and therapeutic vaccine strategies.

To date, no HIV vaccine has achieved licensure, and previous efficacy trials have not demonstrated sufficient protection for population-level implementation. Although long-acting PrEP agents, including lenacapavir, have shown exceptional efficacy in preventing HIV acquisition, they provide pharmacological protection

without generating durable immune memory, requiring continued access and administration. This underscores the need for vaccines capable of inducing sustained, broadly protective immune responses.

HIV vaccine development is now advancing through precision immunogen design, systems immunology, and immune engineering approaches. Emerging strategies include mRNA platforms, germline-targeting immunogens, stabilized SOSIP envelope constructs, viral vectors, and nanoparticle-based delivery systems designed to guide bnAb development, enhance cellular immunity, and overcome previous barriers to vaccine efficacy. However, most candidates remain in early clinical development, and their ability to generate durable protection across diverse populations remains to be determined.

Sub Saharan Africa presents unique challenges for HIV vaccine development, including HIV-1 subtype C diversity, complex mucosal transmission dynamics, and immune modulation driven by endemic co-infections such as tuberculosis, malaria, and helminths. These biological factors, combined with delayed diagnosis, ART access challenges, socioeconomic inequalities, and health-system constraints, influence immune responses and vaccine implementation outcomes.

This systematic review synthesizes evidence across four key domains: (i) immune correlates of HIV protection; (ii) early immune pathways following primary infection and their role in viral set point and reservoir establishment; (iii) persistent ART limitations, including reservoir persistence and incomplete immune restoration; and (iv) emerging prophylactic and therapeutic vaccine platforms relevant to SSA.

Collectively, the evidence supports a shift from a prevention-versus-treatment paradigm toward an integrated P2R framework. Within this model, prophylactic vaccines aim to prevent infection through rapid immune protection at viral entry sites, while therapeutic vaccines seek to enhance immune control and reduce reservoir persistence among individuals receiving ART. The convergence of vaccine innovation, systems immunology, and African-led research capacity offers a promising pathway toward durable HIV control and potential functional remission.

A limitation of this review is the considerable methodological heterogeneity among included studies, including differences in populations, vaccine platforms, immunological assays, and outcome measures. This variability limited application of a uniform risk-of-bias assessment framework and constrained direct comparisons across studies. Therefore, findings should be interpreted within the context of an evolving HIV vaccine research landscape.

Acknowledgements

The authors sincerely acknowledge the invaluable contributions of researchers, healthcare professionals, and scientific communities whose dedication to HIV research and vaccine development has advanced the field and made this review possible. We also extend our appreciation to our colleagues, mentors, and affiliated

institutions for their guidance, support, and encouragement throughout the development of this manuscript.

Author Contributions

Charline Mukasa Sangany developed the study concept and design, undertook the full literature review, and prepared the initial manuscript draft. She led all aspects of project management, ensuring coordination and integration of the research, analysis, and writing activities.

Kalala Elisée Kabuya contributed to the development of the study framework, conducted the data analysis, and participated in the review and revision of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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Abbreviation

ART	Antiretroviral therapy
SSA	Subsaharan africa
PrEPVacc	Pre-exposure prophylaxis vaccine
GRAdHIVNE1	Gorilla Adenovirus Vectored HIV Networked Epitopes Vaccine
IFN	Interferon
SOSIPs	Soluble, stabilized trimeric HIV envelope proteins
PrEP	Pre-exposure prophylaxis
P2R	Prevention-to-Remission
TRM	Tissue-resident memory cells
Tfh	T follicular helper
fCTLs	Follicular cytotoxic
bNAbs	Broadly neutralizing antibody