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HUMAN IMMUNODEFICIENCY VIRUS: EMERGING MODALITIES IN TREATMENT

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Abstract:

Human immunodeficiency virus (HIV) continues to represent a major global health burden, with millions of individuals affected worldwide despite substantial progress in antiretroviral therapy (ART). The advent of combination ART has effectively transformed HIV infection into a chronic, manageable disease; however, therapeutic success remains constrained by challenges including suboptimal long-term adherence, the emergence of drug-resistant viral strains, and persistent inequities in access to care. Recent investigational efforts have prioritized the development of alternative therapeutic modalities, particularly long-acting injectable (LAI) antiretroviral agents and immunologically based interventions, with the dual aims of improving adherence and achieving durable virologic remission. Pharmacological innovation has facilitated a paradigm shift from conventional daily oral ART toward extended-duration formulations, exemplified by cabotegravir, rilpivirine, and lenacapavir. These LAI regimens mitigate the burden of daily pill-taking, enhance virologic suppression rates, and may reduce HIV-related stigma, especially within marginalized populations.

Concurrently, immunotherapeutic strategies are under active investigation. These include broadly neutralizing monoclonal antibodies (bNAbs), immune checkpoint blockade, and chimeric antigen receptor (CAR) T-cell therapies, each with potential to augment host immune control and, in select contexts, induce sustained viral suppression or functional cure. Despite these advances, several barriers remain. Resistance-associated mutations pose a significant threat to therapeutic durability, while issues of cost, infrastructure, and equitable distribution limit global accessibility. Furthermore, long-term safety and tolerability of novel agents require ongoing evaluation.

This review synthesizes recent clinical trial data, delineates the therapeutic advantages and limitations of emerging HIV interventions, and highlights future research priorities. Continued progress in LAI formulations and immunotherapeutic approaches holds promise for optimizing treatment outcomes, broadening access to care, and advancing toward the ultimate goal of a functional cure for HIV infection.

Keywords:

HIV; AIDS; Antiretroviral therapy (ART); Combination ART (cART); Long-acting injectable therapy (LAI); Cabotegravir; Rilpivirine; Lenacapavir; Pre-exposure prophylaxis (PrEP); Viral reservoirs; Functional cure; Broadly neutralizing antibodies (bNAbs); CAR T-cell therapy; CRISPR/Cas9 gene editing; Shock and kill; Block and lock; Drug resistance; Pharmacokinetic tail; Adherence; Global health initiatives (UNAIDS, EHE); Clinical trials (CAPELLA, PURPOSE); CD4+ T lymphocytes; Gut-associated lymphoid tissue (GALT); Central nervous system (CNS) reservoirs; Non-AIDS comorbidities; HIV prevention; HIV stigma

Introduction

Human immunodeficiency virus (HIV) infection continues to be a major global health issue, affecting millions of individuals worldwide. It is a chronic and progressive infection that, if left untreated, culminates in acquired immunodeficiency syndrome (AIDS). HIV and AIDS have claimed countless lives and imposed a substantial socioeconomic burden across societies. At present, no universally effective cure exists, making prevention the most efficient and cost-effective strategy to reduce disease impact.

Despite significant achievements in treatment and prevention, unmet needs persist and the global burden remains considerable. Each year, approximately 1.5 million people acquire HIV, with an estimated 650,000 deaths attributable to HIV-related complications. Although unprecedented investment in public health has expanded access to care, nearly one-third of individuals living with HIV remain undiagnosed, untreated, or inadequately managed. Addressing this epidemic remains a top priority for the international public health community.

In the United States, the federal government has launched the Ending the HIV Epidemic (EHE) initiative, aiming to reduce new infections by 90% by 2030. Globally, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has introduced the Fast-Track initiative, which seeks to lower annual new infections to fewer than 200,000 and eliminate HIV-related stigma. This target is considered achievable if, by 2030, 95% of individuals living with HIV are aware of their status, 95% of those diagnosed are receiving treatment, and 95% of those on therapy achieve viral suppression.

Nevertheless, many individuals face barriers to sustained therapy, including treatment interruptions that increase the risk of disease progression and onward transmission. Expanding access to long-acting antiretroviral therapies is critical, though implementation remains uncertain and progress is vulnerable to fluctuations in public health funding. Continued refinement of existing antiretroviral drugs will be beneficial, but the central challenge to achieving a cure lies in the persistence of latent viral reservoirs resistant to current therapies.

Latent HIV persists in anatomical sanctuaries such as gut-associated lymphoid tissue (GALT) and the central nervous system (CNS), where drug penetration is limited. Reservoirs within resting CD4+ T cells and myeloid cells can reignite viral replication within weeks to months of ART discontinuation. In addition, HIV infection impairs immune function, leading to inadequate humoral responses and diminished CD4+ and CD8+ T-cell activity. Effective cure strategies must therefore both eliminate latent reservoirs and restore immune competence.

Emerging approaches include immune-based therapies, therapeutic vaccines, and gene-editing technologies such as CRISPR/Cas9, which aim to disrupt viral replication and target reservoirs. Genome editing holds promise for achieving prolonged remission or functional cure. The concept of a functional cure—sustained viral control without continuous therapy—represents a major milestone in HIV research. Strategies such as “shock and kill” seek to reactivate latent virus, enabling immune clearance or pharmacologic eradication.

Animal models remain indispensable for advancing cure research, providing insights into viral pathogenesis and therapeutic efficacy. By leveraging these models, investigators can accelerate translation of promising interventions into human trials.

This review provides an overview of recent advances in HIV prevention and treatment, highlighting persistent challenges and emerging strategies. We examine the expanding repertoire of therapeutic approaches, their synergies, and their potential to enhance overall HIV management. Literature from the past decade, including clinical trials, translational studies, systematic reviews, and landmark investigations, is synthesized. Quantitative benchmarks are incorporated, such as global ART coverage reaching 30.7 million individuals in 2023, the decline in AIDS-related deaths from over 2 million annually in the mid-2000s to approximately 650,000 in 2022, and efficacy outcomes from key vaccine and immunotherapy trials. These data contextualize ongoing progress and future directions in the pursuit of a functional cure for HIV.

Human immunodeficiency virus (HIV) is a retrovirus that compromises the immune system by targeting CD4+ T lymphocytes, leading to progressive immunodeficiency. Transmission occurs when infected bodily fluids—including blood, semen, vaginal secretions, and breast milk—gain access to susceptible sites of entry. Upon invasion of CD4+ target cells, HIV integrates into the host genome, establishing a proviral state that underpins lifelong infection.

Since its identification in 1981, HIV has evolved into a major global public health challenge. In 2023, an estimated 39.9 million people were living with HIV worldwide, of whom 20.8 million resided in Africa, including 1.4 million children aged 0–14 years. Women and girls accounted for 53% of all people living with HIV, with 86% aware of their status. Since the onset of the epidemic, AIDS-related illnesses have claimed approximately 42.3 million lives, including 630,000 deaths in 2023 alone. In the same year, 1.3 million new infections were reported globally, with Africa contributing nearly 450,000 cases. Notably, in certain regions of Africa, 10–20% of individuals living with HIV harbor multiple viral variants, complicating treatment strategies.

Combination antiretroviral therapy (cART), comprising agents from diverse drug classes—including reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitors, capsid inhibitors, entry inhibitors, attachment inhibitors, and CD4-directed postattachment monoclonal antibodies—remains the cornerstone of HIV management. These therapies target distinct stages of the viral replication cycle and are highly effective in suppressing viral replication. However, cART does not eradicate HIV, nor does it cure infection.

Despite the success of cART in reducing plasma viral loads to undetectable levels, viral reservoirs persist, precluding eradication. Long-term therapy is associated with non-AIDS comorbidities such as hepatic disease, malignancies, cardiovascular disorders, central and peripheral nervous system complications, renal and metabolic abnormalities, and osteoporosis. Furthermore, the high mutation and recombination rates of HIV pose formidable barriers to vaccine development. For this reason, early diagnosis and prompt initiation of ART remain essential, irrespective of clinical stage, infection duration, or CD4+ cell count. Advances in pharmacology have simplified treatment to once-daily single-pill regimens, transforming HIV into a clinically manageable chronic illness. Nonetheless, lifelong therapy, adherence challenges, and cumulative toxicities underscore the urgent need for innovative strategies capable of achieving durable viral suppression without continuous medication.

Therapeutic research has increasingly focused on neutralizing latent reservoirs and restoring immune competence. Investigational approaches include chimeric antigen receptor (CAR) T-cell therapy, CRISPR-based gene editing, vectored delivery of broadly neutralizing antibodies (bNAbs), antibody-dependent cellular cytotoxicity (ADCC)-mediated bNAbs, and latency-targeting strategies such as “shock and kill” (reactivation and clearance) and “block and lock” (transcriptional silencing). Parallel efforts have expanded long-acting ART (LA-ART) formulations, offering more patient-friendly alternatives, while vaccine trials continue to

highlight both promise and limitations of immunological interventions.

Persistent gaps in vaccine development and the challenges of lifelong ART necessitate exploration of emerging therapeutic modalities. Gene-editing technologies, particularly CRISPR, represent a promising frontier for functional cures by directly targeting viral reservoirs and disrupting replication pathways. The concept of a functional cure—sustained viral control without ongoing therapy—marks a critical milestone in HIV research.

This narrative review synthesizes recent advances in HIV prevention, treatment, and cure research. It highlights novel therapeutic and preventive strategies, evaluates their potential to achieve long-term viral control, and considers how global collaboration and technological innovation may accelerate progress toward HIV eradication.

Results

Our review highlights a rapidly evolving pipeline of HIV therapeutics, with agents categorized by mechanism of action.

Capsid Inhibition: Lenacapavir

Lenacapavir (LEN) is the first-in-class HIV-1 capsid inhibitor, targeting multiple stages of the viral lifecycle. By binding to a conserved site on the capsid protein, LEN disrupts both viral core assembly and disassembly, conferring potent activity across all major HIV-1 subtypes without cross-resistance to existing antiretroviral classes.

Evidence from the CAPELLA trial demonstrated LEN's efficacy in heavily treatment-experienced individuals with multidrug-resistant HIV. During the initial functional monotherapy phase, oral LEN achieved significant viral load reductions compared to placebo. When combined with an optimized background regimen and administered subcutaneously every 26 weeks, LEN maintained high rates of virologic suppression at both 52 and 104 weeks, accompanied by meaningful CD4+ T-cell recovery.

LEN's pharmacokinetic profile, characterized by an exceptionally long half-life, enables semi-annual dosing. Oral bridging therapy has been shown effective if injections are delayed, and intramuscular formulations under investigation may allow for once-yearly administration. Resistance to LEN is primarily associated with mutations in the Gag protein near the capsid binding site. Its relatively low genetic barrier means that single mutations can reduce drug activity, underscoring the importance of combining LEN with other active agents. The long pharmacokinetic tail, while offering flexibility for delayed dosing, also increases the risk of resistance if doses are missed. Importantly, LEN shows no cross-resistance with other antiretroviral classes, reinforcing its role in salvage therapy.

Beyond treatment, LEN has demonstrated strong potential in HIV prevention. The PURPOSE 1 and 2 trials confirmed superior efficacy of semi-annual subcutaneous LEN compared to daily oral emtricitabine/tenofovir alafenamide, leading to its designation as a Breakthrough Therapy for pre-exposure prophylaxis (PrEP).Discussion

In summary, our results suggest that variation in genes related to immune function and regulation of the insulin receptor and PI3K activity may modify the association between diabetes and colorectal cancer risk. These results provide novel insights into the biology underlying diabetes and colorectal cancer relationship. Further experimental studies are warranted to understand the mechanisms by which these genes play a role in linking diabetes and colorectal cancer development.

Discussion

This review highlights a promising trajectory for the future of HIV therapy, marked by diversification of mechanisms of action and significant reductions in dosing frequency. The approval and implementation of long-acting cabotegravir–rilpivirine (CAB-RPV LA) has

provided proof-of-concept for injectable therapy, while the development of agents such as lenacapavir represents a major advance bridging treatment and prevention. These innovations are reshaping the management of multidrug-resistant HIV.

However, their introduction brings important implementation challenges. Long-acting therapies require a shift from patient-managed, pharmacy-based care to clinician-administered, system-dependent models. This transition necessitates improvements in supply chain logistics, patient scheduling, electronic health record integration, and strategies to re-engage individuals who miss appointments. Resistance management is particularly complex due to the long pharmacokinetic tail of these agents. Prolonged sub-therapeutic drug levels following missed doses increase the risk of resistance, making adherence to injection schedules more critical than with daily oral therapy. Standardized protocols for resistance testing, oral bridging, and patient re-engagement are essential to ensure safe and effective use.

Resistance management itself involves several layers of complexity. First, the long pharmacokinetic tail of injectable agents such as cabotegravir, rilpivirine, and lenacapavir means plasma concentrations can persist for months after discontinuation, creating extended periods of functional monotherapy or dual therapy at suboptimal levels. This environment strongly favors the selection of resistant variants. Robust strategies for oral lead-in or bridging therapy are therefore required to mitigate interruptions.

Second, access to resistance testing remains limited, particularly in low- and middle-income countries. Genotypic testing requires advanced laboratory infrastructure, trained personnel, and financial resources that are often unavailable in high-burden settings. Without baseline resistance testing, clinicians may inadvertently prescribe ineffective therapy to individuals with pre-existing resistance, leading to treatment failure and further transmission of resistant HIV strains.

Third, archived resistance poses an insidious challenge. HIV integrates into host DNA, creating latent reservoirs that preserve resistance mutations acquired years earlier. Standard resistance assays only detect circulating plasma virus, meaning archived mutations may remain undetected until re-emergence under selective pressure from new therapies. This is especially relevant for heavily treatment-experienced patients, whose reservoirs often contain complex resistance profiles. New agents must therefore demonstrate activity against circulating virus while maintaining a high barrier to resistance to prevent rapid selection of archived variants.

Overall, while long-acting and novel therapies represent transformative advances, their successful implementation will depend on robust systems for adherence support, resistance monitoring, and equitable access to diagnostic infrastructure.

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