

Human Immunodeficiency Virus: A Comprehensive Review of Virology, Immunopathogenesis, Antiretroviral Pharmacology, Drug Resistance, and Emerging Curative Strategies

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ABSTRACT

Human Immunodeficiency Virus type 1 (HIV-1) infection remains one of the foremost global health challenges of the modern era, with approximately 39.9 million people living with HIV worldwide as of 2023 and 1.3 million new infections occurring annually. Despite four decades of intensive biomedical research, a definitive cure remains elusive.

This narrative review comprehensively addresses the molecular virology and replication cycle of HIV-1, the immunopathogenic mechanisms underlying progressive CD4⁺ T-cell depletion and immune dysfunction, contemporary global epidemiology, antiretroviral pharmacology and preferred treatment regimens, drug resistance mechanisms and surveillance, viral latency and reservoir biology, and the current landscape of curative strategies. Evidence was synthesised from primary research articles, systematic reviews, meta-analyses, landmark clinical trials, and international guidelines published between 2000 and 2024 (with select seminal/foundational studies from the late 1990s retained for historical context), retrieved from PubMed/MEDLINE, Embase, and the Cochrane Library.

Modern integrase strand-transfer inhibitor (INSTI)-based regimens achieve virological suppression exceeding 95% in treatment-naïve adults. However, the transcriptionally silent proviral reservoir in resting CD4⁺ T cells persists lifelong, necessitating novel combinatorial interventions. Emerging curative approaches including shock-and-kill latency reversal, block-and-lock epigenetic silencing, CRISPR-Cas9-mediated proviral excision, broadly neutralising antibodies, and allogeneic stem cell transplantation represent credible scientific pathways toward functional or sterilising cure.

Equitable global access to antiretroviral therapy and sustained investment in cure research are indispensable to achieving the UNAIDS 95–95–95 targets and ending the HIV pandemic.

Keywords: *HIV-1; antiretroviral therapy; viral latency; drug resistance; cure strategies; immunopathogenesis; broadly neutralising antibodies; CRISPR-Cas9.*

1. Introduction

Human Immunodeficiency Virus type 1 (HIV-1), the aetiological agent of acquired immunodeficiency syndrome (AIDS), represents one of the most devastating pandemics in the annals of modern medicine. Since its initial clinical description in 1981 and the landmark viral isolation by Barre-Sinoussi and Montagnier in 1983 recognised by the 2008 Nobel Prize in Physiology or Medicine HIV has infected an estimated 85 million individuals and claimed more than 40 million lives globally.

As of 2023, UNAIDS estimates that 39.9 million people are living with HIV (PLHIV) globally, with approximately 1.3 million new infections and 630,000 AIDS-related deaths annually [1]. These figures, while reflecting the transformative impact of combination antiretroviral therapy (cART), underscore the persistent magnitude of the epidemic and the inequitable global distribution of its burden.

The advent of highly active antiretroviral therapy (HAART) in 1996 fundamentally transformed the natural history of HIV infection, dramatically reducing AIDS-defining illnesses and enabling near-normal life expectancy in adherent, virologically suppressed individuals [2].

Nevertheless, ART is not curative; lifelong adherence is required, drug resistance continues to emerge globally, and approximately 10 million PLHIV remain without access to treatment. This comprehensive review addresses the virology, molecular biology, immunopathogenesis, global epidemiology, pharmacological management, resistance mechanisms, and emerging curative strategies relevant to HIV-1, providing a definitive and clinically actionable reference for researchers, clinicians, and public health practitioners.

2. Virology and Molecular Biology

2.1. Classification and Genomic Architecture

HIV-1 is an enveloped, positive-sense, single-stranded RNA virus classified within the genus *Lentivirus*, family *Retroviridae* [3]. Its ~9.7 kilobase genome encodes nine genes: three structural genes (*gag*, *pol*, *env*), two regulatory genes (*tat*, *rev*), and four accessory genes (*vif*, *vpr*, *vpu*, *nef*) [4]. The virion (~120 nm diameter) comprises a cone-shaped capsid enclosing two copies of the genomic RNA and the enzymes reverse transcriptase (RT), integrase (IN), and protease (PR), enveloped within a host-derived lipid bilayer studded with trimeric gp120/gp41 glycoprotein spikes mediating cellular tropism and entry.

HIV-1 is classified into four phylogenetic groups (M, N, O, and P), with Group M subdivided into subtypes A through K and numerous circulating recombinant forms (CRFs) responsible for more than 98% of global infections [5]. This extraordinary genetic diversity has significant implications for diagnostic test sensitivity, vaccine antigen selection, and drug resistance surveillance.

2.2. The HIV Replication Cycle

The HIV replication cycle comprises six sequentially orchestrated stages, each constituting a validated pharmacological target (Figure 1).

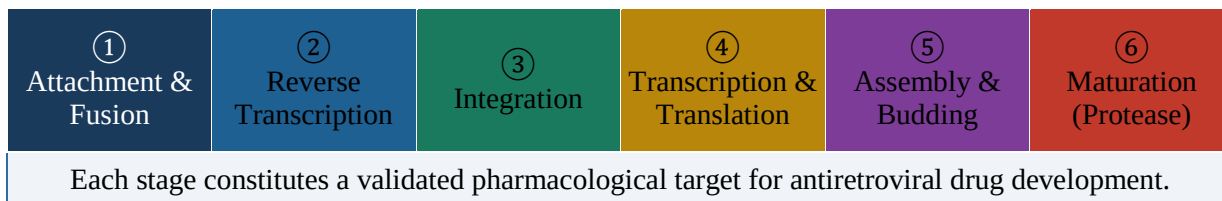


Figure 1. Schematic representation of the six principal stages of HIV-1 replication, each representing a validated pharmacological target for antiretroviral drug development.

2.2.1. Attachment and Membrane Fusion

Viral entry is initiated by high-affinity interaction of gp120 with the host CD4 receptor, inducing conformational changes that expose the co-receptor binding domain. Sequential engagement with CCR5 or CXCR4 co-receptors activates gp41-mediated membrane fusion, delivering the viral core into the cytoplasm [6]. CCR5-tropic (R5) strains predominate during primary infection; CXCR4-tropic (X4) variants emerge in ~50% of individuals with advanced disease, correlating with accelerated CD4⁺ T-cell depletion and having direct therapeutic relevance for the CCR5 antagonist maraviroc.

2.2.2. Reverse Transcription and Nuclear Import

Within the cytoplasmic reverse transcription complex (RTC), RT converts the viral RNA genome into double-stranded DNA (dsDNA). The intrinsic error rate of RT ($\sim 3 \times 10^{-5}$ substitutions/nucleotide/cycle), combined with high viral turnover (10^9 – 10^{10} virions/day in untreated infection), generates extraordinary genetic diversity and underlies rapid emergence of drug-resistant variants [7]. The resulting pre-integration complex (PIC) is actively transported into the nucleus via the nuclear pore complex.

2.2.3. Integration

Integrase catalyses the strand-transfer reaction, covalently inserting viral dsDNA into the host chromosome an irreversible process constituting the molecular foundation of viral latency [8]. Integration preferentially occurs in actively transcribed chromosomal regions; the integrated provirus is indistinguishable from host chromosomal DNA and remains refractory to immune recognition in transcriptionally silent cells.

2.2.4. Transcription, Translation, and Viral Protein Synthesis

Proviral transcription is driven by the HIV LTR promoter in conjunction with host transcription factors (NF- κ B, SP1, NFAT), dramatically amplified by the viral transactivator Tat via recruitment of P-TEFb. Rev facilitates nuclear export of incompletely spliced and unspliced viral mRNAs. Gag and Gag-Pol polyproteins are translated on cytoplasmic ribosomes; envelope glycoproteins undergo endoplasmic reticulum processing and are displayed on the cell surface.

2.2.5. Budding and Maturation

Immature virions bud from the plasma membrane via the host ESCRT machinery. The viral protease activated by dimerisation during budding subsequently cleaves Gag and Gag-Pol polyproteins in a temporally regulated cascade, driving capsid condensation and generating infectious mature virions [6]. Protease inhibitors exploit this obligatory maturation step, producing morphologically aberrant non-infectious particles.

3. Immunopathogenesis

3.1 Clinical Staging and CD4⁺ Count Dynamics

HIV infection follows a predictable clinical trajectory defined by the dynamic interplay between viral replication kinetics, cytopathicity, and host immunological responses (Table 1).

Table 1. Longitudinal relationship between CD4⁺ T-cell count and plasma viral load across the three principal stages of untreated HIV-1 infection.

Clinical Phase	CD4 ⁺ T-Cell Count	Plasma Viral Load
Acute HIV Infection (Weeks 0–12)	↓ Transient drop (may reach <200/ μ L)	Peak: 10^6 – 10^7 copies/mL
Chronic / Asymptomatic	Gradual decline 500→200	Set-point: 10^3 – 10^5 copies/mL

(Months to Years)	cells/ μ L	
AIDS (CD4 < 200 cells/ μ L)	↓↓↓ Severe depletion <200 cells/ μ L	>100,000 copies/mL

Acute HIV infection is characterised by explosive viral replication achieving peak plasma viral loads of 10^6 – 10^7 copies/mL within 2–4 weeks of transmission, accompanied by transient CD4⁺ T-cell depletion and a mononucleosis-like prodromal syndrome in 40–90% of infected individuals [9].

Robust CD8⁺ CTL responses and neutralising antibody production partially suppress viral replication, establishing an individual viral set-point that powerfully predicts the rate of subsequent disease progression.

The chronic asymptomatic phase is characterised by ongoing viral replication at the set-point, progressive depletion of CD4⁺ T cells (~50–100 cells/ μ L/year), and sustained generalised immune activation [10]. Paradoxically, this chronic immune activation driven by microbial translocation across the disrupted intestinal epithelial barrier accelerates immunosenescence, inflammaging, and the development of non-AIDS comorbidities.

AIDS is defined by a CD4⁺ T-cell count below 200 cells/ μ L and/or the occurrence of AIDS-defining conditions (ADCs) enumerated in the 1993 CDC classification. Without antiretroviral intervention, median time from primary infection to AIDS is ~10 years, and median survival after AIDS diagnosis averages 3 years [5].

3.2 Mechanisms of CD4⁺ T-Cell Depletion

Multiple non-mutually exclusive mechanisms underlie the progressive CD4⁺ T-cell loss that defines HIV immunopathogenesis:

- (i) Direct cytopathic effects of productive infection, including Nef-mediated MHC-I downregulation.
- (ii) CTL-mediated killing of infected cells.
- (iii) Pyroptotic death of abortively infected bystander CD4⁺ T cells triggered by caspase-1 activation.
- (iv) Fas/FasL-mediated apoptosis.
- (v) Chronic immune activation-driven T-cell exhaustion characterised by upregulation of inhibitory receptors PD-1, Tim-3, and LAG-3 [5,10].

3.3 Innate Immune Evasion

HIV employs multifaceted strategies to circumvent innate immune sensing. Vif mediates proteasomal degradation of APOBEC3G; Vpr targets SAMHD1 a dNTP triphosphohydrolase depleting nucleotide pools necessary for reverse transcription in non-dividing cells enabling efficient macrophage and dendritic cell infection [11]. The HIV capsid shields reverse transcription intermediates from cytosolic DNA sensors (cGAS, IFI16), delaying innate immune activation until after proviral integration is complete.

4. Global Epidemiology

The global HIV epidemic is characterised by profound geographic heterogeneity, reflecting regional differences in transmission dynamics, key population demographics, healthcare infrastructure, and ART access (Table 2). Sub-Saharan Africa bears ~65% of the global PLHIV burden, with generalised epidemics sustained primarily by heterosexual transmission and mother-to-child transmission (MTCT) [1].

Table 2. Global HIV burden by WHO region, 2023. Source: UNAIDS Global HIV & AIDS Statistics Fact Sheet 2023 [1].

WHO Region	PLHIV	Adult Prevalence	Key Notes
Sub-Saharan Africa	25.6 million	3.4%	Most affected region; heterosexual & MTCT transmission
South & SE Asia	3.9 million	0.2%	Second largest burden; concentrated epidemic
Latin America	2.2 million	0.4%	Rising incidence among key populations
E. Europe & Central Asia	1.6 million	0.9%	Fastest growing epidemic; PWID-driven
W. & C. Europe + N. America	2.3 million	0.3%	High ART coverage; declining AIDS mortality
Middle East & N. Africa	240,000	0.1%	Limited surveillance; increasing trends
Global Total (2023)	39.9 million	0.7%	~1.3 million new infections; 630,000 deaths/year

Note: Table above reflect the major UNAIDS reporting regions as published in the cited 2023 fact sheet and are not exhaustive of all UNAIDS sub-regions. The Caribbean (~330,000 PLHIV) and refinements to Asia-Pacific sub-regional estimates are aggregated separately by UNAIDS; consequently, the listed regional figures do not sum exactly to the reported Global Total, which reflects the complete UNAIDS regional dataset.

The UNAIDS 95–95–95 targets stipulating that 95% of PLHIV know their status, 95% of those diagnosed receive ART, and 95% of those on treatment achieve viral suppression constitute the operational framework for epidemic control by 2030 [12]. Global progress as of 2023 stands at 86–89–93, with the most substantial deficits in Eastern Europe, Central Asia, and the Middle East and North Africa.

5. Antiretroviral Pharmacology and Therapeutic Strategies

5.1 Preferred First-Line Regimens (WHO 2023)

Contemporary international guidelines uniformly recommend a two-drug NRTI backbone combined with an INSTI as the preferred initial regimen in treatment-naïve adults, reflecting the superior virological potency, tolerability, and genetic barrier to resistance of INSTIs particularly dolutegravir (DTG) and bictegravir (BIC) Table 3 [12,14].

Table 3. WHO-recommended antiretroviral regimens for treatment-naïve adults (2023 consolidated guidelines). Evidence graded by WHO GRADE methodology [12,14].

Regimen	Indication	Efficacy	Grade
TDF + 3TC + DTG	Adults — preferred regimen	★★★★★	A
TDF + FTC + BIC	Adults — preferred (high barrier)	★★★★★	A
ABC + 3TC + DTG	HLA-B*5701 negative; no CVD risk	★★★★☆	A
TDF + 3TC + EFV 400 mg	Resource-limited settings	★★★★☆	B
TDF + FTC + RPV	VL <100,000; CD4 >200	★★★★☆	A

	cells/ μ L		
ZDV + 3TC + NVP	Pregnancy — alternative only	★★★★☆	B

The landmark DAWNING and ADVANCE trials definitively demonstrated the superiority of DTG-based regimens over efavirenz (EFV)-based therapy across virological, immunological, and tolerability endpoints [14]. Long-acting injectable cabotegravir plus rilpivirine (CAB+RPV), administered monthly or bimonthly, demonstrated non-inferiority to daily oral ART in the pivotal ATLAS and FLAIR trials, heralding a transformative paradigm shift in ART delivery [15].

5.2 Treatment Monitoring and Virological Goals

The primary goal of ART is sustained plasma viral load suppression below the lower limit of quantification (<50 copies/mL), associated with immunological reconstitution, prevention of AIDS-defining events, elimination of onward sexual transmission (U = U), and near-normalisation of life expectancy [12,13]. Virological failure confirmed plasma HIV RNA ≥ 200 copies/mL on two consecutive measurements after ≥ 6 months of ART necessitates genotypic resistance testing and expedited regimen optimisation.

6. Antiretroviral Drug Resistance

6.1 Molecular Mechanisms and Mutation Pathways

Antiretroviral drug resistance emerges through Darwinian selection of pre-existing minority variants harbouring resistance-conferring mutations, driven by RT infidelity, absence of proofreading activity, high viral replication turnover, and selective pressure from subtherapeutic drug concentrations Table 4 [16]. Resistance mutations exert effects through distinct pathways: reduced drug binding affinity (e.g., K103N for NNRTIs), steric exclusion of chain-terminating NRTIs (e.g., M184V), or structural remodelling of the integrase active site (e.g., Q148H/R/K)

Table 4. Major antiretroviral resistance-associated mutations by drug class, affected agents, and clinical significance [16].

Class	Key Mutation(s)	Affected ARV(s)	Clinical Significance
NRTI	M184V/I	3TC, FTC	Most prevalent; reduces viral fitness; sensitises to TDF
NRTI	K65R	TDF	Reduced TDF susceptibility; thymidine analogue mutations
NNRTI	K103N	EFV, NVP	No replication cost; highly prevalent in TDR surveillance
NNRTI	E138K	ETR, RPV	Rilpivirine/etravirine resistance; associated with low-VL failure
PI	I50V	ATV/r	Atazanavir-specific primary resistance mutation
PI	D30N / L90M	NFV	Multiple PI cross-resistance; reduced susceptibility
INSTI	Q148H/R/K	RAL, EVG, CAB	Major pathway; high-level resistance to multiple INSTIs
INSTI	N155H	RAL, EVG	Secondary pathway; often with accessory mutations

6.2 Transmitted Drug Resistance

Transmitted drug resistance (TDR) acquisition of resistance mutations from the infecting strain prior to treatment initiation poses an increasingly prevalent threat to empirical first-line therapy. WHO surveillance data document NNRTI TDR prevalence exceeding 10% in multiple high-prevalence countries, providing the epidemiological basis for WHO guidance recommending transition from EFV-based to DTG-based first-line regimens [12,16]. The substantially higher genetic barrier of DTG and BIC renders INSTI-based therapy substantially more resilient to TDR in contemporary practice.

6.3 Resistance Testing and Clinical Management

Genotypic resistance testing should be performed at baseline, at confirmed virological failure, and prior to regimen modification in treatment-experienced individuals. HIV co-receptor tropism testing is obligatory prior to maraviroc prescription [14,16]. The Stanford HIV Drug Resistance Database and IAS-USA mutation panels provide validated, evidence-based frameworks for clinical resistance interpretation.

7. Viral Latency and Reservoir Biology

7.1 Establishment and Characterisation of the Latent Reservoir

The transcriptionally silent proviral reservoir in long-lived resting CD4⁺ T cells constitutes the central barrier to HIV eradication by conventional ART. This reservoir is established within days of primary infection, predominantly in central memory (TCM) and transitional memory (TTM) CD4⁺ T-cell subsets [17].

Mathematical modelling estimates a reservoir half-life of ~44 years, rendering complete eradication by pharmacological means alone biologically impossible within a human lifespan [8].

Additional reservoirs exist within CNS tissue macrophages, gut-associated lymphoid tissue (GALT), lymph node follicular dendritic cells, and haematopoietic progenitor cells.[18] The CNS reservoir is of particular clinical importance: limited drug penetration across the blood-brain barrier may permit low-level viral replication contributing to HIV-associated neurocognitive disorders (HAND), even in systemically suppressed individuals

7.2 Clonal Expansion and Reservoir Persistence

The latent reservoir is dynamically maintained through antigen-driven and homeostatic clonal proliferation of infected memory CD4⁺ T cells. Integration site analyses demonstrate the reservoir is oligoclonal, with individual proviral clones expanding to constitute substantial fractions of the total reservoir [8,17]. Critically, proviruses integrated within cancer-associated proto-oncogenes (BACH2, MKL2, STAT5B) may confer selective proliferative advantage, ensuring reservoir renewal independent of de novo infection.

8. Emerging Curative Strategies

The HIV cure research field has coalesced around two paradigmatic goals:

- (i) a sterilising curecomplete elimination of all replication-competent proviral DNA;
- (ii) (ii) a functional cure durable, ART-free virological suppression analogous to HIV elite controllers.

Table 5 summarises the principal curative strategies under investigation.

Table 5. Overview of HIV curative strategies: mechanisms, development stages, and key examples (2024).

Strategy	Mechanism	Stage	Examples
Shock-and-Kill	LRAs reactivate silent provirus; immune system clears infected cells	Phase I/II	Vorinostat, Panobinostat
Block-and-Lock	Permanent epigenetic silencing of proviral transcription	Preclinical–I	dCA, CDK9 inhibitors
CRISPR-Cas9 Editing	Excise integrated proviral DNA from host genome	Phase I	EBT-101 (AAV9-CRISPR)
CCR5-Δ32 HSCT	CCR5-null donor cells confer natural HIV-1 resistance	Case Series	Berlin, London, City of Hope, Düsseldorf
Broadly Neutralising Abs	Target conserved env epitopes; durable virological control	Phase II	VRC01, PGT121, N6LS
Therapeutic Vaccines	Boost HIV-specific CTL; reduce reservoir size	Phase I/II	mRNA-HIV, HVTN 702
Long-Acting ART/PrEP	Extended dosing intervals; overcome adherence barriers	Approved/III	CAB+RPV, Lenacapavir

8.1 Shock-and-Kill Strategy

The shock-and-kill paradigm employs latency-reversing agents (LRAs) to reactivate transcriptionally silent provirus, rendering infected cells visible to cytotoxic immune effectors, followed by immune-mediated clearance. Clinical trials of HDAC inhibitors including vorinostat, panobinostat, and romidepsin have demonstrated reproducible perturbation of the latent reservoir as evidenced by increases in cell-associated HIV RNA [19].

However, no trial to date has achieved a clinically meaningful reduction in reservoir size, as CTL-mediated killing of reactivated cells is manifestly insufficient in ART-suppressed individuals.

8.2 Block-and-Lock Strategy

The block-and-lock strategy seeks to permanently reinforce epigenetic silencing of the integrated provirus. Didehydro-cortistatin A (dCA) and related compounds inhibit the Tat-SEC complex, promoting deposition of repressive histone modifications (H3K27me3) that transition the provirus into a state of deep, potentially permanent latency [18]. Preclinical modelling suggests this approach could reduce stochastic viral reactivation events below levels required to sustain a measurable reservoir.

8.3 Gene Editing Approaches

CRISPR-Cas9-mediated excision of integrated proviral DNA has achieved proof-of-concept in humanised mouse models and non-human primates. The first-in-human trial of EBT-101 employing a recombinant AAV9 vector delivering CRISPR components targeting conserved HIV-1 LTR and Gag sequences has entered Phase I evaluation [20]. Alternative platforms including ZFNs, TALENs, and

autologous CD34⁺ HSCT gene therapies incorporating CCR5 disruption are in parallel development.

8.4 Broadly Neutralising Antibodies

Broadly neutralising antibodies (bNAbs) target conformationally conserved epitopes on HIV-1 envelope glycoprotein, including the CD4-binding site (VRC01), V3-glycan supersite (PGT121, 10-1074), and MPER (10E8). In clinical trials, bNAbs have achieved transient virological suppression in ART-naïve individuals and prolonged time-to-viral-rebound following analytical treatment interruption [21]. Combinations of bNAbs with complementary epitope specificities dramatically reduce probability of viral escape and are now being evaluated in Phase II trials as both therapeutic and prophylactic agents.

8.5 Allogeneic Stem Cell Transplantation and CCR5 Ablation

The most compelling proof-of-concept for HIV cure derives from the Berlin, London, City of Hope, and Düsseldorf patients, who achieved sustained HIV remission following allogeneic HSCT from donors homozygous for the CCR5-Δ32 mutation, conferring natural resistance to CCR5-tropic HIV-1 [20]. Although broadly inapplicable due to transplant-related morbidity, these cases provide irrefutable evidence that HIV eradication is achievable in humans and directly inform scalable autologous gene therapy approaches.

9. Prevention Strategies

9.1 Treatment as Prevention (TasP)

The HPTN 052 trial provided landmark randomised evidence that early ART initiation in serodiscordant couples reduced the risk of linked HIV transmission by 96% [22]. The subsequent PARTNER 1 and 2 and Opposites Attract cohort studies documented zero phylogenetically linked transmissions among virologically suppressed individuals across a combined 126,000 condomless sex acts, cementing the scientific consensus encapsulated in the U = U paradigm.

9.2 Pre-Exposure Prophylaxis (PrEP)

Daily oral TDF/FTC PrEP reduces HIV acquisition risk by 86–99% in adherent individuals across all key populations at elevated risk, as demonstrated in multiple pivotal randomised trials [23,24]. Event-driven (2-1-1) PrEP demonstrated equivalent efficacy in MSM in the IPERGAY trial [25]. The HPTN 083 trial established long-acting injectable cabotegravir (CAB-LA, 600 mg every 8 weeks) as superior to daily oral TDF/FTC PrEP in cisgender MSM and transgender women, reducing incident HIV by 66% relative to TDF/FTC (hazard ratio 0.34, 95% CI 0.18–0.62) [15].

9.3 Biomedical and Vaccine Prevention

Medical male circumcision reduces female-to-male HIV transmission by ~60% and is recommended by WHO in high-prevalence settings [26]. Despite decades of intensive research, an efficacious HIV vaccine remains an unrealised scientific goal. The RV144 Thai trial remains the sole study demonstrating partial efficacy (31.2%); the subsequent HVTN 702 trial failed to demonstrate efficacy in South Africa. The emergence of mRNA vaccine platforms and structure-guided immunogen design have reinvigorated the field, with multiple Phase I/II trials underway as of 2024.

10. HIV-Associated Comorbidities and the Chronic Disease Paradigm

As PLHIV on effective ART now achieve near-normal life expectancy, non-AIDS-defining comorbidities have emerged as dominant determinants of morbidity and premature mortality [27]. Persons living with HIV experience substantially elevated age-adjusted rates of cardiovascular disease

(~2-fold), non-AIDS-defining malignancies, chronic kidney disease, osteoporosis, type 2 diabetes, and neurocognitive impairment relative to HIV-uninfected age-matched controls.

The overarching pathophysiological framework linking these comorbid conditions is chronic immune activation and inflammaging a state of premature immunosenescence characterised by persistent elevation of inflammatory biomarkers (IL-6, hs-CRP, D-dimer, sCD163), telomere shortening, and exhaustion of naive T-cell compartments [10]. This inflammatory milieu is driven by residual low-level viral replication, ongoing microbial translocation from the damaged gut epithelium, CMV co-infection, and ART immunotoxicity. HIV-associated neurocognitive disorder (HAND) constitutes a clinically heterogeneous spectrum from asymptomatic neurocognitive impairment (ANI) to HIV-associated dementia (HAD) affecting up to 50% of PLHIV [28]. HAND is not fully mitigated by systemic viral suppression, implicating CNS reservoir-driven neuroinflammation and blood-brain barrier disruption as primary pathological substrates. Management necessitates CNS-penetrating ART combinations, neuropsychiatric evaluation, and targeted cognitive rehabilitation.

11. Discussion

The trajectory of HIV medicine over four decades constitutes one of the most remarkable success stories in biomedical science transforming an invariably fatal infection into a manageable chronic disease with near-normal life expectancy in adherent, virologically suppressed individuals [2]. The molecular dissection of the HIV replication cycle has yielded more than 30 approved antiretroviral agents, while elucidation of transmission dynamics has validated treatment-as-prevention and pre-exposure prophylaxis as potent biomedical prevention tools [22]. Yet the very success of ART has revealed the depth of remaining challenges. The latent viral reservoir, maintained for decades through clonal proliferation of long-lived memory T cells, remains fundamentally impervious to current pharmacological approaches [8]. No LRA evaluated in clinical trials to date has achieved a clinically meaningful reduction in reservoir size [19].

Novel combinatorial strategies integrating reservoir reactivation or silencing with immune enhancement represent the most promising framework for future cure research. Drug resistance surveillance remains a non-negotiable public health imperative, particularly in low- and middle-income countries where genotypic resistance testing infrastructure remains underdeveloped [16]. The global expansion of INSTI-based first-line therapy necessitates concurrent investment in INSTI resistance surveillance to prevent the population-level emergence of INSTI-resistant strains.

Long-acting injectable ART formulations including CAB+RPV and investigational lenacapavir-containing regimens promise to overcome adherence limitations of daily oral regimens, enabling sustained virological suppression in populations for whom daily pill-taking remains an unrealistic expectation [15]. Achieving the UNAIDS 95–95–95 targets demand not merely biomedical innovation, but structural transformation addressing poverty, gender inequality, stigma and discrimination, criminalisation of key populations, and systematic underfunding of community-led health services [1,29].

11.1 Limitations of This Review

As a narrative rather than systematic review, this work does not follow a PRISMA-style protocol with predefined search strings, dual independent screening, or formal quality appraisal (e.g., GRADE) of the underlying evidence; source selection instead reflects the authors' judgment of relevance and authority, which carries an inherent risk of selection bias.

HIV therapeutics and cure research are evolving rapidly, and several findings discussed here — particularly around long-acting antiretroviral formulations, gene-editing approaches, and allogeneic cure strategies — are drawn from early-phase or single-arm studies that may not generalise, and could be

superseded by newer data before or shortly after publication. Cited literature is predominantly sourced from PubMed/MEDLINE, Embase, and the Cochrane Library, with an emphasis on English-language publications; evidence from non-indexed regional journals or non-English sources, particularly from high-burden settings in sub-Saharan Africa and South & South-East Asia, may therefore be underrepresented. Finally, this review synthesises epidemiological, virological, and clinical data from heterogeneous sources with differing geographic scope and reporting years; where feasible the most recent figures were used, but readers should consult primary sources for jurisdiction-specific or time-sensitive decision-making.

12. Conclusions

HIV infection remains a global public health emergency demanding sustained, multidisciplinary, and equitably resourced scientific and programmatic responses. This review has systematically delineated the molecular virology of HIV-1, immunopathological mechanisms driving CD4⁺ T-cell depletion, the global epidemiological burden, and the substantial advances in antiretroviral pharmacology that have irrevocably altered patient outcomes. The frontiers of HIV cure research encompassing shock-and-kill LRA strategies, block-and-lock epigenetic silencing, CRISPR-Cas9-mediated proviral excision, broadly neutralising antibodies, and allogeneic cellular therapies represent scientifically credible pathways toward functional or sterilising cure, although significant translational hurdles must be surmounted. Long-acting ART and bNAb-based PrEP strategies are poised to redefine prevention and treatment delivery paradigms in the coming decade.

The attainment of epidemic control requires convergence of biomedical excellence, equitable global health financing, elimination of structural barriers to care, and sustained political commitment articulated in the 2021 Political Declaration on HIV and AIDS. Only through integration of scientific innovation and social justice can the international community fulfil its obligation to the 39.9 million people living with HIV worldwide.

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References

1. UNAIDS. Global HIV & AIDS statistics Fact sheet 2023. Geneva: UNAIDS; 2023. <https://www.unaids.org/en/resources/fact-sheet>
2. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med*. 1998;338(13):853-60. <https://doi.org/10.1056/NEJM199803263381301>
3. Coffin JM, Hughes SH, Varmus HE. Retroviruses. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 1997.
4. Frankel AD, Young JA. HIV-1: fifteen proteins and an RNA. *Annu Rev Biochem*. 1998;67:1-25. <https://doi.org/10.1146/annurev.biochem.67.1.1>
5. Deeks SG, Overbaugh J, Phillips A, Buchbinder S. HIV infection. *Nat Rev Dis Primers*. 2015;1:15035. <https://doi.org/10.1038/nrdp.2015.35>
6. Sundquist WI, Krausslich HG. HIV-1 assembly, budding, and maturation. *Cold Spring Harb Perspect Med*. 2012;2(7):a006924. <https://doi.org/10.1101/cshperspect.a006924>
7. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. *Cold Spring Harb Perspect Med*. 2012;2(4):a007161. <https://doi.org/10.1101/cshperspect.a007161>
8. Siliciano JM, Siliciano RF. Recent developments in the search for a cure for HIV-1 infection. *J Allergy Clin Immunol*. 2014;134(1):12-9. <https://doi.org/10.1016/j.jaci.2014.05.026>
9. Barre-Sinoussi F, Ross AL, Delfraissy JF. Past, present and future: 30 years of HIV research. *Nat Rev Microbiol*. 2013;11(12):877-83. <https://doi.org/10.1038/nrmicro3132>
10. Klatt NR, Chomont N, Douek DC, Deeks SG. Immune activation and HIV persistence: implications for curative approaches. *Immunol Rev*. 2013;254(1):326-42. <https://doi.org/10.1111/imr.12065>
11. Altfeld M, Gale M Jr. Innate immunity against HIV-1 infection. *Nat Immunol*. 2015;16(6):554-62. <https://doi.org/10.1038/ni.3157>
12. World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021. ISBN 978-92-4-003159-3.
13. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults. *JAMA*. 2016;316(2):191-210. <https://doi.org/10.1001/jama.2016.8900>
14. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Washington DC: DHHS; 2023.
15. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med*. 2021;385(7):595-608. <https://doi.org/10.1056/NEJMoa2101016>
16. Gunthard HF, Calvez V, Paredes R, et al. European recommendations for the clinical use of HIV drug resistance testing: 2019 Update. *HIV Med*. 2019;20(2):73-8. <https://doi.org/10.1111/hiv.12614>
17. Chun TW, Davey RT, Ostrowski M, Justement JS, Engel D, Mullins JI, et al. Relationship between pre-existing viral reservoirs and the re-emergence of plasma viremia after discontinuation of HAART. *Nat Med*. 2000;6(7):757-61. <https://doi.org/10.1038/77481>
18. Lewin SR, Rouzioux C. HIV cure and eradication: how will we get from the laboratory to effective clinical trials? *AIDS*. 2011;25(7):885-97. <https://doi.org/10.1097/QAD.0b013e3283467041>

19. Archin NM, Liberty AL, Kashuba AD, et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. *Nature*. 2012;487(7408):482-5. <https://doi.org/10.1038/nature11286>
20. Gupta RK, Abdul-Jawad S, McCoy LE, et al. HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. *Nature*. 2019;568(7751):244-8. <https://doi.org/10.1038/s41586-019-1027-4>
21. Caskey M, Klein F, Nussenzweig MC. Broadly neutralizing anti-HIV-1 antibodies: new insights and opportunities. *Nat Med*. 2019;25(10):1468-78. <https://doi.org/10.1038/s41591-019-0601-5>
22. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830-9. <https://doi.org/10.1056/NEJMoa1600693>
23. Buchbinder SP, Liu A. Pre-exposure prophylaxis and the promise of combination prevention approaches. *AIDS Behav*. 2011;15(Suppl 1):S72-9. <https://doi.org/10.1007/s10461-011-9894-1>
24. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2012;367(5):411-22. <https://doi.org/10.1056/NEJMoa1202614>
25. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med*. 2015;373(23):2237-46. <https://doi.org/10.1056/NEJMoa1506273>
26. Volberding PA, Deeks SG. Antiretroviral therapy and management of HIV infection. *Lancet*. 2010;376(9734):49-62. [https://doi.org/10.1016/S0140-6736\(10\)60676-9](https://doi.org/10.1016/S0140-6736(10)60676-9)
27. Havlir DV, Currier JS. Complications of HIV infection and antiretroviral therapy. *Top Antivir Med*. 2009;17(2):63-7.
28. Dalmau J, Vidal N, Clotet B, et al. HIV-1 tropism and neurocognitive disorders: a review. *Rev Med Virol*. 2011;21(5):282-93. <https://doi.org/10.1002/rmv.695>
29. Fauci AS, Redfield RR, Sigounas G, Weahkee MD, Giroir BP. Ending the HIV epidemic: a plan for the United States. *JAMA*. 2019;321(9):844-5. <https://doi.org/10.1001/jama.2019.1343>

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