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A Review of the Development and Drug Resistance Mechanisms of HIV Antiviral Drugs

Hanyu Liu*

Friendship Christian School, Raleigh, United States

**Corresponding author: Hanyu Liu.*

Abstract

Human immunodeficiency virus (HIV) infection remains a major global public health challenge. The widespread adoption of antiretroviral therapy (ART) has transformed AIDS from a fatal disease into a chronically manageable condition. Early reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) laid the theoretical and clinical foundation for highly active antiretroviral therapy (HAART), effectively reducing AIDS related mortality. With iterative drug development, integrase strand transfer inhibitors (INSTIs), with their high genetic barrier to resistance, favorable safety profile, and good tolerability, have largely replaced traditional regimens and become the backbone of contemporary first line HIV treatment. Despite continuous optimization of treatment paradigms, HIV drug resistance cannot be completely avoided. Its emergence is not driven by a single factor but rather by a multidimensional interplay of viral genetic characteristics, drug pharmacologic properties, individual pharmacokinetic variability, and public health service deficiencies. The inherently high mutation rate of HIV provides the genetic substrate for resistance; sustained drug selection pressure enriches mutant strains; irregular adherence and drug drug interactions leading to suboptimal exposure further amplify resistance risk; and differences in genetic barriers across drug classes combined with limited treatment accessibility in resource limited settings collectively drive the emergence and spread of drug resistant strains. Against this background, this review addresses four key questions: (1) How have major antiviral drug classes such as RTIs, PIs, and INSTIs evolved? (2) What are the similarities and differences in the molecular pathways of drug resistance across different targets? (3) How should HIV drug resistance be tested and the results interpreted? (4) What novel resistance risks do long acting antiviral regimens pose? By integrating current research evidence, this review aims to clarify the evolutionary patterns of HIV drugs, multilevel resistance mechanisms, and existing bottlenecks of long acting therapies, providing a theoretical reference for optimizing clinical antiviral treatment strategies.

Keywords

HIV, reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitor resistance, genotypic resistance monitoring, capsid inhibitors, long acting combination antiretroviral drugs

1. Introduction

The iterative development and widespread adoption of antiretroviral therapy (ART) have fundamentally changed the disease prognosis of HIV infection. Standardized combination therapy can effectively and sustainably suppress viral replication, restore patient immune function, significantly prolong survival, and

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greatly reduce the risk of HIV interpersonal transmission, transforming AIDS from a fatal disease into a chronically manageable condition [1-2]. As the most pivotal medical breakthrough in AIDS prevention and control over the past four decades, ART has substantially alleviated the global burden of AIDS-related mortality.

Although modern treatment systems are increasingly mature, current ART still faces several unavoidable clinical shortcomings. Existing drugs cannot eradicate the viral latent reservoir, requiring patients to undergo lifelong continuous treatment without achieving a complete cure [3]. Long-term medication is accompanied by chronic drug toxicity and metabolic adverse effects that persistently impact patient quality of life. Meanwhile, the continuous evolution of viral drug resistance mutations constantly threatens treatment stability, and global disparities in drug accessibility, along with inadequate primary-level monitoring systems, further exacerbate the spread of drug-resistant strains and the risk of treatment failure [4,5].

The emergence of HIV drug resistance has a clear viral biological basis. HIV reverse transcriptase lacks proofreading function, resulting in a high mutation frequency during replication and generating a highly diverse viral quasispecies pool in vivo, providing the innate genetic substrate for the emergence of drug-resistant variants [4]. Rapid viral replication and genetic recombination further accelerate the accumulation of mutations, constituting the fundamental internal cause of the selection and enrichment of drug-resistant strains.

At the clinical and pharmacokinetic level, the triggers of drug resistance are far more complex than simple missed doses. Different classes of antiviral drugs have significantly different half-lives; after treatment interruption, short-half-life drugs are rapidly cleared, whereas long-half-life drugs remain in the body, thereby creating functional monotherapy exposure and generating a window for the selection of resistance [6]. Meanwhile, gastrointestinal absorption abnormalities, fluctuations in liver and kidney function, and drug-drug interactions caused by concomitant medications can all lead to subtherapeutic drug exposure, reducing viral suppression efficiency. Combined with health system factors such as fluctuations in patient adherence and uneven regional medical resources, these ultimately jointly promote the emergence and spread of drug-resistant strains [3].

Based on the above background, this review defines its research scope: to systematically review the developmental evolution and functional characteristics of three major antiviral drug classes—RTIs, PIs, and INSTIs; to compare differences in resistance molecular pathways across drug targets; to elucidate resistance mechanisms and testing logic from viral, pharmacokinetic, clinical, and public health dimensions; and to analyze the application advantages and novel resistance risks of next-generation long-acting antiviral formulations, to provide references for optimizing clinical treatment regimens and new drug development.

2. Development of Classic HIV Antiviral Drugs

2.1 Reverse Transcriptase Inhibitors (RTIs)

Reverse transcriptase is responsible for reverse transcribing viral RNA into DNA and is an essential enzyme for viral replication. RTIs are divided into nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). NRTIs are nucleoside analogs that, after phosphorylation in cells, are incorporated into the growing viral DNA strand; because they lack a 3'-hydroxyl terminus, they cause DNA chain termination and block viral genome synthesis. Zidovudine (AZT), as the first approved anti-HIV drug, can improve clinical symptoms. Still, monotherapy readily and rapidly induces drug resistance and is accompanied by significant myelosuppression toxicity, limiting its clinical application [1,7]. The toxicity and low genetic barrier of first-generation drugs drove the iterative development of subsequent NRTIs, with next-generation drugs such as lamivudine, emtricitabine, and tenofovir successively emerging. Tenofovir has undergone two generations of formulation optimization: tenofovir disoproxil fumarate (TDF) has strong antiviral efficacy and low cost, but long-term use carries risks of renal impairment and bone density reduction; tenofovir alafenamide (TAF), leveraging lymphocyte-targeted enrichment technology, maintains equivalent antiviral activity while significantly improving bone and renal safety [6,8]. With their broad antiviral spectrum, good tolerability, and ease of combination use, NRTIs have long served as the foundational backbone of HAART combination regimens. Key resistance mutations in clinical practice directly guide regimen selection: M184V/I is the hallmark mutation of lamivudine and emtricitabine treatment failure,

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causing high-level resistance to both drugs but partially restoring viral sensitivity to tenofovir; K65R primarily mediates tenofovir resistance, significantly weakening TDF efficacy with relatively limited impact on TAF; accumulated TAMs can induce broad-spectrum NRTI resistance, and when such mutations appear, traditional NRTI combinations should be abandoned in favor of INSTI-based treatment regimens [2,3,5].

NNRTIs do not participate in DNA strand synthesis; instead, they bind to an allosteric site on reverse transcriptase, altering the enzyme's conformation and thereby inhibiting its catalytic activity. Representative drugs include efavirenz and rilpivirine, which have strong antiviral activity but a low genetic barrier—a single amino acid mutation can induce high-level resistance, and cross-resistance is common among drugs in this class. New-generation NNRTIs retain inhibitory activity against some drug-resistant strains while reducing the central nervous system-related adverse effects associated with efavirenz.

2.2 Protease Inhibitors (PIs)

HIV protease cleaves viral precursor polyproteins to generate mature functional viral proteins, a critical step for progeny viruses to acquire infectivity. Protease inhibitors competitively bind to the protease's active site, blocking protein cleavage and ultimately producing non-infectious viral particles.

2.2.1 Pharmacokinetic Boosting Mechanisms and Clinical Positioning

The first PI class drugs entered clinical practice in the mid-1990s. Ritonavir itself possesses antiviral activity, but therapeutic doses are rarely used in current clinical practice; low-dose ritonavir exerts a pharmacokinetic boosting effect by inhibiting hepatic CYP3A enzymes, delaying the metabolic clearance of other PIs, and increasing their plasma concentrations [7]. Cobicistat is also a CYP3A inhibitor used for pharmacokinetic boosting but has no antiviral activity. Both agents can cause numerous drug-drug interactions, requiring clinical assessment of concomitant medication risks and careful medication management [9]. Darunavir, a representative second-generation PI, has a higher genetic barrier and retains inhibitory activity against some drug-resistant strains.

Early PIs required high dosing frequency and were prone to adverse effects such as lipid metabolism disorders and gastrointestinal discomfort. During the HAART era, PIs were once important pillars of combination therapy; in the contemporary treatment landscape dominated by INSTIs, PIs are no longer first-line choices and are mostly used as salvage therapy regimens for patients with INSTI treatment failure or multi-drug-resistant HIV infection [8]

2.2.2 PI Resistance Characteristics and Genetic Barrier

PI resistance is jointly mediated by major resistance mutations and compensatory (accessory) mutations. Major mutations alter the conformation of the protease active site, reducing drug-binding capacity; compensatory mutations are located in non-active regions and do not directly confer resistance but can restore the catalytic function of the mutated enzyme, restore viral replication fitness, and enable drug-resistant strains to persist and propagate [10]. A typical evolutionary pathway is as follows: major active-site mutations, such as V82A/I, emerge first, followed by the accumulation of compensatory mutations, such as M46I and L63P, which gradually confer high-level resistance [5].

2.3 Integrase Strand Transfer Inhibitors (INSTIs)

Integrase strand transfer inhibitors are the core drug class of contemporary first-line ART and the hallmark drugs of HIV treatment iteration over the past decade [6]. HIV integrase catalyzes the integration of reverse-transcribed viral DNA into the host genome, involving two key steps—3' end processing and strand transfer—and is an essential step for the virus to establish persistent infection and complete progeny replication [4]. INSTIs specifically bind to the catalytic core of the viral integrase-DNA complex, chelating the magnesium cofactor at the active site and precisely blocking the strand-transfer reaction, thereby preventing integration of the viral genome into host-cell chromosomes and suppressing sustained viral replication at its source [3,8].

Based on differences in developmental generation and genetic barrier, INSTIs can be divided into first- and second-generation formulations. First-generation representative drugs include raltegravir and elvitegravir, which have strong antiviral activity but a limited genetic barrier; long-term use is prone to characteristic

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mutations such as Q148H, N155H, and Y143C, which induce target conformational changes, reduce drug-binding capacity, and confer a significant risk of cross-resistance [2,5]. Second-generation INSTIs, represented by dolutegravir, Bictegravir, and cabotegravir, have optimized molecular structures that bind more stably to the integrase-DNA complex and exhibit slower dissociation rates, thereby significantly increasing the genetic barrier, such that single-point mutations rarely cause treatment failure; they are currently the first-line core drugs preferentially recommended by global guidelines [1,6]. Among them, cabotegravir also has long-acting formulation properties and is a core component of long-acting injectable treatment regimens, facilitating the transition from oral first-line therapy to long-acting sustained-release treatment [8].

Compared with traditional RTIs and PIs, INSTIs have, overall, fewer adverse effects, weaker drug-drug interactions, and greater patient tolerability, fundamentally reshaping the traditional HAART medication landscape [7]. However, second-generation INSTIs still carry a risk of resistance; multiple accumulated and compensatory mutations can progressively reduce drug sensitivity, and treatment failure can still occur, particularly in populations with incomplete viral suppression or baseline carriage of mutant strains [10].

3. Mechanisms of HIV-1 Drug Resistance

3.1 Viral Genetic Variation and Drug Selection Pressure

HIV-1 reverse transcriptase lacks proofreading activity, resulting in a high replication mismatch rate. Infected individuals naturally harbor a highly heterogeneous viral quasispecies pool, and some drug-resistant mutations exist at low frequencies even before drug exposure [4]. When the effective in vivo drug concentration is insufficient to suppress the virus completely, drug selection pressure selects and amplifies drug-resistant mutant strains, making them the dominant population and causing virological failure. Viral genetic recombination can integrate multiple mutations into a single genome, significantly accelerating the evolution of multidrug-resistant strains [10].

3.2 Molecular Resistance Mechanisms of Various Drug Classes

Two primary molecular mechanisms exist: nucleoside excision, in which mutated reverse transcriptase uses ATP to remove drug molecules already incorporated into the DNA strand; and altered nucleotide selectivity, which reduces the enzyme's recognition affinity for drug analogs [3]. TAMs are the hallmark resistance mutations to zidovudine; upon accumulation, they confer high-level resistance and induce NRTI cross-resistance. M184V/I and K65R confer resistance to lamivudine/emtricitabine and tenofovir, respectively, and other mutations also alter the viral drug-susceptibility phenotype to other nucleoside drugs [2].

Resistance arises from amino acid substitutions in the allosteric binding pocket of reverse transcriptase, disrupting drug-target binding. Drugs in this class have a low genetic barrier—a single-point mutation can cause complete loss of drug efficacy, and cross-resistance among mutations is common [6].

PI resistance is driven by amino acid substitutions in the protease coding region. Major mutations are located in the drug-binding pocket and directly hinder drug binding; distal conformational changes indirectly reduce drug affinity. Typical major mutations include V82A/I, and compensatory mutations include M46I and L63P. Compensatory mutations themselves do not cause resistance but repair protease function and restore viral replication fitness [5]. Clinical genotypic resistance algorithms convert sequencing results into drug susceptibility classifications based on mutation types and weights, guiding clinical regimen-switching decisions [9].

3.2.1 INSTI Resistance

Resistance mutations are concentrated in the integrase gene. First-generation INSTIs typically involve Y143C, N155H, and Q148H/R/K, with Q148-related mutations conferring broad cross-resistance; second-generation INSTIs rarely cause treatment failure due to single-point mutations, and resistance is mostly conferred by multi-site mutations combined with compensatory mutations that restore enzyme function and maintain replication capacity [11].

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3.3 Cross-Resistance and Viral Replication Fitness

Cross-resistance refers to a set of mutations simultaneously reducing viral sensitivity to multiple drugs of the same class and is an important limitation in regimen adjustment. Most major resistance mutations impair the catalytic activity of viral proteins, thereby reducing replication fitness; compensatory mutations can restore protein function, offset fitness loss, and enable drug-resistant strains to acquire replication and transmission capacity approaching that of wild-type strains [10]. Even after removal of drug pressure, drug-resistant mutant strains can remain latent in the viral quasispecies pool and rapidly rebound upon re-exposure to the corresponding drug.

3.4 Clinical and Health System Driving Factors

The viral genetic basis is the internal cause of resistance. Still, the actual emergence of resistance largely stems from factors that reduce the intensity of effective drug suppression, thereby creating a window for the selection of resistance.

Adherence and treatment interruption: Different drug classes have varying half-lives, and after treatment cessation, functional monotherapy exposure forms, inducing mutation selection [6];

Pharmacokinetic factors: Gastrointestinal absorption disorders, abnormal liver and kidney function, and drug-drug interactions from concomitant medications lead to subtherapeutic concentrations; insufficient drug penetration in some tissues forms local sanctuary sites;

Prior treatment history: Drug-resistant quasispecies retained from previous treatment failures can rapidly become dominant strains upon re-exposure to drugs of the same class;

Health system deficiencies: Delayed viral load monitoring makes it difficult to identify incomplete suppression promptly; an unstable drug supply in some regions and intermittent treatment further amplify the risk of resistance [3].

3.5 Drug Resistance Testing and Clinical Interpretation of Results

Clinically, testing is divided into genotypic testing and phenotypic testing. Genotypic testing sequences the reverse transcriptase, protease, and integrase genes to identify resistance mutations, offering rapid turnaround and broad applicability; phenotypic testing directly measures in vitro drug-susceptibility fold changes but is costly and has a long turnaround time [9]. Sampling should be performed when viral load is >1000 copies/mL; sampling during viral suppression is prone to false negatives. Test results cannot be interpreted in isolation and must be evaluated alongside viral load, adherence, drug-drug interactions, and the complete treatment history. Archived mutation databases have limitations—the clinical significance of some rare mutations remains unclear, and relying solely on algorithmic interpretation carries the risk of misclassification [12].

3.6 HIV-1 Drug Resistance Epidemiology

Drug resistance is classified into three categories: acquired drug resistance, pre-treatment drug resistance (PDR), and transmitted drug resistance (TDR).

Acquired drug resistance: Induced by drug pressure after ART initiation. Before the widespread use of INSTIs, acquired resistance to NRTIs and NNRTIs accounted for a relatively high proportion in low- and middle-income regions; after the widespread adoption of dolutegravir, overall acquired INSTI resistance remains at a low level, but the detection rate of related mutations has locally increased in populations with persistent treatment failure [11].

Pre-treatment drug resistance: Treatment-naive patients harbor baseline drug-resistance mutations. WHO 2021-2024 monitoring shows that NNRTI pre-treatment resistance in some resource-limited regions of Asia and Africa has exceeded the 10% alert threshold, posing challenges to initial treatment regimens [4].

Transmitted drug resistance: Drug-resistant strains spread directly through interpersonal transmission. INSTI-transmitted resistance in high-income regions is currently low overall, but with the expansion of long-acting INSTIs, continuous monitoring of changes in the mutation spectrum remains necessary to guard against impacts on first-line treatment [12].

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4. Next-Generation Long-Acting Antiretroviral Drugs

Traditional daily oral ART is highly dependent on patient adherence, and missed doses and treatment interruptions readily create windows for the selection of resistance, driving the development of long-acting sustained-release formulations. Based on intended use, they can be divided into long-acting treatment and long-acting pre-exposure prophylaxis (PrEP). Marketed drugs and investigational candidates differ significantly in targets, indications, dosing intervals, and resistance risks, and should not be discussed interchangeably.

4.1 Approved Long-Acting Formulations

The cabotegravir-rilpivirine combination injectable is the first complete long-acting treatment regimen, consisting of the second-generation INSTI cabotegravir and the NNRTI rilpivirine, administered intramuscularly every 4-8 weeks. Phase III clinical trials confirmed that its antiviral efficacy is non-inferior to oral regimens, with the most common adverse effect being injection site pain [7]. This regimen is indicated only for infected individuals who have already achieved complete viral suppression and cannot be used in treatment-naive populations; the risk of resistance remains, and integrase or reverse transcriptase target mutations can directly trigger virological failure.

Lenacapavir is a capsid inhibitor that interferes with capsid assembly, nuclear import, and viral genome release [13]. In the treatment setting, it is indicated for treatment-experienced adults with multidrug-resistant HIV-1 and must never be used as monotherapy—it must be combined with at least one other effective antiviral drug. A separate formulation is available for long-acting pre-exposure prophylaxis in high-risk populations, administered subcutaneously every 6 months. Mutations at capsid protein sites can mediate resistance, and related mutations have been reported in both treatment and PrEP settings [12].

4.2 Investigational Long-Acting Drug Candidates

Islatravir is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) with a mechanism distinct from traditional NRTIs, administered via subcutaneous implant, and possesses inhibitory activity against some multidrug-resistant strains [11]. However, clinical trials identified safety concerns of lymphocyte decline, and dosing and regimens continue to be adjusted. It is currently still in the developmental stage with no approved indications, and its evidence level differs from that of marketed drugs.

4.3 Limitations and Clinical Considerations of Long-Acting Drugs

Long-acting formulations have not eliminated resistance risk, and their unique pharmacokinetic properties bring new clinical challenges:

- Long-tail effect driving resistance: Drugs remain in the body for extended periods; once viral breakthrough occurs, residual drugs continuously create subtherapeutic selection pressure, accelerating the accumulation of resistance mutations;
- Follow-up execution burden: Injections must be completed on schedule, and missed injections cause declines in blood drug concentrations, placing higher demands on institutional follow-up management capacity;
- Safety issues: Local reactions such as injection site pain and induration exist; long-term real-world data in special populations such as pregnant individuals and adolescents remain insufficient, and some patients have limited acceptance of injectable administration;
- Drug-drug interactions and accessibility: Metabolic interactions exist with anti-tuberculosis drugs; high formulation costs and supply chain limitations result in uneven global accessibility.

5. Conclusion

Over the past four decades, HIV antiviral drugs have completed iterations from monotherapy, HAART combination regimens, to long-acting sustained-release formulations. RTIs and PIs laid the foundation for early treatment; INSTIs, with their high genetic barrier, have become the core of contemporary first-line

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therapy; and long-acting formulations have freed patients from daily dosing constraints, improving patient prognosis and reducing transmission risk.

However, the current system still has significant shortcomings. The virus's inherently high mutation rate, combined with pharmacokinetic abnormalities, adherence fluctuations, and health system deficiencies, makes it difficult to completely eradicate resistance. Cross-resistance, acquired resistance, and transmitted resistance continuously threaten treatment efficacy; with the widespread application of INSTIs and long-acting drugs, novel resistance mutations warrant vigilance. In addition, long-term safety data in special populations are limited, innovative drugs are costly, and resistance testing capacity is insufficient in resource-limited regions, restricting global rollout.

Future research has several priority directions: developing drugs with novel targets such as capsid inhibitors and optimizing molecular structures to enhance the genetic barrier; improving global resistance monitoring networks and accumulating real-world data in the era of long-acting drugs; advancing rapid and low-cost resistance testing technologies to translate molecular evidence into individualized treatment plans; and improving the global accessibility of innovative drugs to narrow regional healthcare gaps. Through multidimensional collaborative advancement, ART strategies can be continuously optimized, helping to achieve the public health goal of HIV viral suppression.

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Conflicts of Interest

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