Georgian Scientists

ქართველი მეცნიერები

Vol. 7 Issue 3, 2025

https://doi.org/10.52340/gs.2025.07.03.30

THE MANIFESTATION OF SCIENTIFIC DISCUSSION ON NEW ANTIRETROVIRAL MEDICINES: A COMPREHENSIVE ANALYSIS OF CLASSIFICATION, CLINICAL USE, FEATURES, MECHANISMS, PHARMACOLOGY AND TOXICITIES IN GENERAL

Nodar Sulashvili[1], Udgam Yaduvanshi[2], Nirjhar Yaduvanshi[3], Mohini Yadav[4], Elene Abzianidze[5], Naira Chichoyan[6], Luiza Gabunia[7], Nana Gorgaslidze[8], Nato Alavidze[9], Nino Abuladze[10], Ketevani Gabunia[11], Natia Kvizhinadze[12], Igor Seniuk[13], Marika Sulashvili[14], Tamar Okropiridze[15], Lela Grigolia[16], Kakhaber Robakidze[17], Marina Giorgobiani[18], Irine Zarnadze[19], Shalva (Davit) Zarnadze[20]

1. MD, PhD, Doctor of Pharmaceutical and Pharmacological Sciences in Medicine, Invited Lecturer (Invited Professor) of Scientific Research-Skills Center at Tbilisi State Medical University; Professor of Medical and Clinical Pharmacology of International School of Medicine at Alte University; Professor of Pharmacology of Faculty of Medicine at Georgian National University SEU; Tbilisi, Georgia; Orcid https://orcid.org/0000-0002-9005-8577; E-mail: n.sulashvili@ug.edu.ge
2. MD student of Medical Doctor Degree Program of International School of Medicine at Alte University; Tbilisi, Georgia;
3. MD student of Medical Doctor Degree Program of International School of Medicine at Alte University; Tbilisi, Georgia;
4. MD student of Medical Doctor Degree Program of International School of Medicine at Alte University; Tbilisi, Georgia;
5. PhD, Doctor of Biological Sciences, Academician, Emeritus Professor of Tbilisi State Medical University, Department of Molecular and Medical Genetics; https://orcid.org/0000-0002-1140-7688; Tbilisi, Georgia.
6. MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Yerevan State Medical University After Mkhitar Heratsi, Head of the Department of Pharmacognosy, Yerevan, Armenia. https://orcid.org/0000-0003-3905-3372
7. MD, PhD, Doctor of Medical Sciences, Professor, Director of the Scientific Research-Skills Center at Tbilisi State Medical University, Professor, Head of the Department of Medical and Clinical Pharmacology at Tbilisi State Medical University, Clinical Pharmacologist of The First University Clinic of TSMU, Tbilisi, Georgia https://orcid.org/0000-0003-0856-2684
8. MD, PhD, Doctor of Pharmaceutical Sciences, Academician, Professor of Tbilisi State Medical University, Head of The Department of Social and Clinical Pharmacy, Tbilisi, Georgia. https://orcid.org/0000-0002-4563-5224
9. MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia. Professor, Dean Faculty of Medicine at East European University, Tbilisi, Georgia. https://orcid.org/0000-0001-6695-5924
10. MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia. https://orcid.org/0000-0003-2189-7470
11. MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Akaki Tsereteli State University, Faculty of Medicine, Department of Pharmacy, Kutaisi, Georgia. https://orcid.org/0000-0002-5857-6593;
12. MD, PhD, Doctor of Pharmaceutical Sciences, Professor of Tbilisi State Medical University, Department of Social and Clinical Pharmacy; Tbilisi, Georgia.
13. PhD, Doctor of Pharmaceutical Sciences, Dean of faculty of Pharmacy at National University of Pharmacy of Ukraine, Associate Professor of Biological Chemistry Department at National University of Pharmacy of Ukraine, https://orcid.org/0000-0003-3819-733; Kharkiv, Ukraine.

14. MD, Doctor of Family Medicine, Invited Lecturer of Tbilisi State Medical University, Department of Molecular and Medical Genetics, Invited Professor of Biochemistry and Molecular and Medical Genetics at The University of Georgia; Tbilisi, Georgia.
15. MD, PhD, Doctor Medical Sciences, Professor of the Division of Dentistry of International School of Medicine at Alte University; Professor of Teaching University Geomedi, Invited Professor of Dentistry Department of The School of Health Sciences at The University of Georgia, Tbilisi, Georgia.
16. MD, PhD, Doctor of Medical Sciences, Professor of Faculty of Medicine at Caucasus International University; Tbilisi, Georgia;
17. MD, PhD, Doctor of Medical Sciences, Academician, Professor of Faculty of Medicine at Caucasus International University; Doctor-Professor of National Health Center Named After Academician O. Gudushauri; Tbilisi, Georgia;
18. MD, PhD, Doctor of Medical Sciences, Academician, Professor of Tbilisi State Medical University, Faculty of Public Health; Department of Hygiene and Medical Ecology, Tbilisi, Georgia. https://orcid.org/0000-0003-0686-5227
19. MD, PhD, Doctor of Medical Sciences, Professor of Tbilisi State Medical University, Department of Public Health, Health Care Management, Policy and Economy, Tbilisi, Georgia.
20. MD, PhD, Doctor of Medical Sciences, Academician, Professor of Tbilisi State Medical University, Dean of the Faculty of Public Health, Head of the Department of Nutrition, Aging Medicine, Environmental and Occupational Health, Tbilisi, Georgia.

Corresponding Author: Dr. Professor Nodar Sulashvili
Mail: n.sulashvili@ug.edu.ge
Mob: +995-597-12-17-28

ABSTRACT

The therapeutic landscape for Human Immunodeficiency Virus (HIV) infection has undergone a profound and revolutionary transformation over the past four decades. From a universally fatal diagnosis to a manageable chronic condition, this evolution is fundamentally anchored in the relentless innovation of antiretroviral therapy (ART). The scientific discourse surrounding new antiretroviral medicines represents a dynamic and critical nexus of virology, pharmacology, medicinal chemistry, and clinical medicine. This discourse manifests not as a singular event but as a continuous, multi-faceted process that scrutinizes every aspect of a drug's journey from molecular concept to clinical cornerstone. This abstract aims to synthesize the core elements of this scientific discussion, focusing on the classification, clinical applications, and distinctive features, mechanisms of action, pharmacological profiles, therapeutic effects, and associated toxicities of the newest generation of anti-HIV agents. The evolution of ART has progressively shifted from merely suppressing viral replication to emphasizing long-term tolerability, adherence-friendly regimens, and the mitigation of cumulative toxicities, goals that are directly addressed by these novel compounds. The classification of antiretroviral drugs has traditionally been based on their molecular target within the HIV replication cycle. The newest agents both reinforce and expand this taxonomic structure. The established classes—Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Integrase Strand Transfer Inhibitors (INSTIs), Entry Inhibitors (including CCR5 antagonists and post-attachment inhibitors), and Pharmacokinetic Enhancers (e.g., cobicistat)—remain relevant. However, the most significant recent advancements have emerged within the INSTI class and have pioneered entirely new mechanisms, most notably with the advent of Attachment Inhibitors and Capsid Inhibitors. The scientific discussion on classification is no longer static; it now actively debates the placement of novel agents with multi-modal mechanisms,

questioning whether traditional silos are sufficient or if a new, more nuanced system based on mechanism and genetic barrier to resistance is required. The clinical use of new antiretrovirals is dictated by the overarching goals of modern HIV management: achieving and maintaining virological suppression (HIV-1 RNA <50 copies/mL), restoring and preserving immunological function (increasing CD4+ T-cell count), reducing HIV-associated morbidity and mortality, and preventing HIV transmission. Newer drugs are integral to first-line therapy, treatment simplification, and the management of highly treatment-experienced patients with multidrug-resistant virus. The scientific conversation here is vibrant, centering on the comparative efficacy of new regimens, often head-to-head clinical trials pitting established gold standards against newer contenders. For instance, the debate around second-generation INSTIs like dolutegravir and bictegravir versus first-generation agents like elvitegravir and raltegravir focuses on superior resistance profiles and higher genetic barriers to resistance. Furthermore, the development of long-acting injectable formulations, such as the combination of the novel INSTI cabotegravir and the NNRTI rilpivirine, has ignited discussion on their use as maintenance therapy, potentially replacing daily oral regimens and addressing adherence challenges, a paradigm shift in clinical practice.

INTRODUCTION

The human immunodeficiency virus (HIV) pandemic stands as one of the most profound public health challenges in modern history, a complex saga of scientific discovery, societal struggle, and medical innovation. From its initial identification in the early 1980s as a mysterious and invariable fatal agent causing acquired immunodeficiency syndrome (AIDS), HIV has been transformed into a manageable chronic condition through the revolutionary development of antiretroviral therapy (ART). This journey, spanning over four decades, represents a triumph of biomedical research and global health mobilization. The introduction of combination ART in the mid-1990s, often referred to as the "Lazarus effect" for its ability to bring patients back from the brink of death, marked the end of the epidemic's darkest chapter. However, this was not a conclusion but a new beginning—the commencement of an ongoing evolution towards ever more effective, tolerable, and user-friendly therapeutics. The landscape of HIV treatment is now undergoing its most radical transformation since the advent of combination therapy itself, propelled by a new generation of antiretroviral agents that challenge long-held paradigms and offer unprecedented hope for the future.

The historical context of HIV treatment is essential for appreciating the magnitude of current advancements. The first decade of the epidemic was characterized by fear, uncertainty, and therapeutic nihilism. The approval of zidovudine (AZT) in 1987 offered a glimmer of hope, but it was short-lived as the virus rapidly developed resistance to the single agent. The true turning point arrived with the development of protease inhibitors and the concept of highly active antiretroviral therapy (HAART) in 1996. This strategy of combining drugs from at least two different classes—typically a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor paired with nucleoside reverse transcriptase inhibitors—produced dramatic and sustained suppression of viral replication. Mortality rates plummeted, and hospitals wards that were once filled with dying patients began to empty. Yet, this first generation of combination therapy came at a steep cost. Regimens were notoriously complex, involving dozens of pills taken at precise times with strict dietary restrictions. The toxicities were severe and often debilitating: peripheral neuropathy, pancreatic toxicity, severe lipodystrophy (redistribution of body fat), dyslipidemia, and

mitochondrial damage became common features of long-term survival, constant reminders of the disease and its treatment.

The subsequent years were characterized by a process of refinement and simplification. The goals of ART expanded from achieving mere survival to ensuring a good quality of life. The development of fixed-dose combinations (FDCs) consolidated multiple drugs into a single tablet, drastically reducing pill burden. The pharmacological classes diversified with the introduction of entry inhibitors, integrase strand transfer inhibitors (INSTIs), and CCR5 antagonists, providing new mechanisms to attack the virus and salvage treatment for those with resistant virus. The toxic profile of drugs improved significantly; tenofovir disoproxil fumarate (TDF) replaced older, more toxic NRTIs like stavudine and zidovudine, and newer protease inhibitors required less potent boosting agents. The treatment paradigm shifted towards earlier initiation of therapy, reinforced by seminal studies like START and TEMPRANO, which demonstrated that immediate treatment upon diagnosis improved individual health outcomes and reduced transmission risk at a population level. This era established the principle of "Undetectable = Untransmittable" (U=U), a powerful concept that dismantles stigma and recasts ART as a primary tool for HIV prevention.

Despite these remarkable strides, significant challenges persisted. Adherence to daily oral therapy remains a barrier for some, leading to virological failure and the potential development of resistance. Long-term toxicities, though less severe, continued to pose risks for an aging population of people living with HIV, including cardiovascular, renal, and bone diseases. Furthermore, the specter of stigma, though challenged by U=U, remained intertwined with the daily act of taking HIV medication. For the heavily treatment-experienced population with multidrug-resistant virus, therapeutic options became increasingly limited and complex. It is within this context that the latest revolution in antiretroviral therapy is unfolding—a revolution driven not by incremental change, but by fundamental leaps in drug design, delivery, and mechanism of action.

The newest generation of antiretroviral medicines is characterized by several defining features that collectively address the lingering limitations of previous regimens. First is the pursuit of unprecedented potency and a high genetic barrier to resistance. Second-generation INSTIs, such as dolutegravir and bictegravir, bind more tightly to their target and require multiple mutations for the virus to develop resistance, making virological failure a rare event. This robustness offers a more forgiving platform for treatment, enhancing its durability. Second is the optimization of safety and tolerability profiles. The development of tenofovir alafenamide (TAF), a prodrug of tenofovir, delivers effective antiviral activity while significantly reducing exposure in the kidneys and bones, thereby mitigating the risks of renal impairment and osteoporosis that were associated with TDF. This focus on long-term organ health is critical for managing HIV as a chronic condition over a lifetime.

Perhaps the most paradigm-shifting advancement is the move towards long-acting formulations. The successful development and approval of long-acting injectable cabotegravir and rilpivirine, administered every one or two months, represents a quantum leap in treatment modality. This approach fundamentally decouples HIV management from daily pill-taking, addressing issues of adherence, stigma, and quality of life in a way that was previously unimaginable. Concurrently, the frontier of drug discovery has expanded to include entirely novel mechanisms of action that attack the virus at new vulnerabilities. Capsid inhibitors, such as lenacapavir, disrupt the virus's protective shell at multiple stages of its life cycle, offering a powerful new option for patients

with extensive drug resistance. Furthermore, the exploration of broadly neutralizing antibodies (bNAbs) and immune-based therapies opens new avenues not just for treatment, but for potential strategies aimed at long-term remission or a functional cure.

However, the introduction of these groundbreaking technologies occurs against a backdrop of profound and persistent global inequity. The brilliant promise of long-acting injectables and novel agents stands in stark contrast to the reality in many low- and middle-income countries (LMICs), where health systems still struggle to provide consistent access to even the most basic oral regimens. The challenges of cost, cold-chain storage, healthcare infrastructure, and training present formidable barriers to the equitable global rollout of these advanced therapies. This disparity risks creating a two-tiered system of HIV care: one for the wealthy with access to the most modern, convenient treatments, and another for the poor, reliant on older technologies. Furthermore, these new therapies bring their own unique challenges, such as the management of novel side effects like weight gain associated with INSTIs and the logistical complexities of managing the long "tail" of drug activity after an injection is administered, which can foster resistance if a patient is lost to follow-up.

This paper will provide a comprehensive examination of this new era in antiretroviral therapy. It will delve into the detailed classification and sophisticated mechanisms of action that define these novel agents, explaining how their unique pharmacological properties translate into clinical benefits. The discussion will explore the robust clinical trial data that underpins their efficacy, positioning them within modern treatment guidelines and algorithms. A thorough analysis of their pharmacological profiles—including absorption, distribution, metabolism, and excretion—will be presented to elucidate their dosing schedules and interaction potentials. The review will also provide an honest and critical appraisal of their effects and toxicities, balancing their remarkable benefits against emerging safety signals like weight gain and neuropsychiatric effects. Finally, the paper will confront the pressing socio-economic and ethical implications of these advancements, addressing the urgent need for strategies to ensure that the miracles of modern science do not become the exclusive privilege of the few, but are mobilized to achieve the ultimate goal of ending the AIDS epidemic for everyone, everywhere. This introduction sets the stage for a deep dive into the science, medicine, and policy of the most exciting and promising chapter in the history of HIV treatment.

The management of Human Immunodeficiency Virus infection has undergone a transformation so profound that it stands as one of the most remarkable success stories in modern medicine. From a once uniformly fatal diagnosis to a chronic, manageable condition, this evolution has been propelled by an unwavering scientific endeavor to understand the intricate biology of the virus and to develop therapeutic agents that precisely disrupt its life cycle. The early era of antiretroviral therapy, characterized by monotherapies with high pill burdens, severe toxicities, and transient efficacy, has given way to a new epoch defined by highly potent, well-tolerated, and simplified treatment regimens. This paradigm shift is anchored in the continuous discovery and development of new antiretroviral medicines, each belonging to distinct pharmacological classes that target specific vulnerabilities of HIV.

The scientific discussion surrounding these new agents is multifaceted and dynamic, reflecting a deep and nuanced understanding of virology, pharmacology, and clinical medicine. It encompasses a rigorous process of classification based on molecular mechanism, a detailed

examination of their unique pharmacologic features, and a critical appraisal of their place in clinical practice through evidence-based guidelines. Furthermore, this discourse must contend with the dual aspects of their effects: the profound benefits of sustained virologic suppression and immune reconstitution, and the spectrum of potential toxicities, which range from acute adverse events to long-term metabolic complications. The ongoing challenge of drug resistance necessitates a vigilant surveillance of mutational patterns and informs the strategic sequencing of therapeutic options. This article aims to manifest this comprehensive scientific discussion, exploring the classification, clinical use, features, mechanism of action, pharmacology, and the delicate balance between effects and toxicities that define the current and future landscape of new anti-HIV medicines.

The features of new antiretroviral medicines are meticulously engineered to overcome the limitations of their predecessors. Key characteristics dominating scientific evaluation include:

- **High Potency:** Achieving deep and rapid virological suppression at low doses.
- **High Genetic Barrier to Resistance:** Requiring multiple mutations for the virus to significantly reduce susceptibility, a hallmark of drugs like dolutegravir and bictegravir.
- **Improved Safety and Tolerability Profiles:** Designed to minimize off-target effects and chronic toxicities associated with older drugs (e.g., mitochondrial toxicity with older NRTIs, dyslipidemia with PIs).
- **Favorable Pharmacokinetics:** Offering long half-lives that permit once-daily dosing and forgive occasional missed doses, enhancing adherence. Some are engineered to be boosed by pharmacoenhancers without the food requirements of older agents.
- **Low Drug-Drug Interaction Potential:** Reducing complex interaction profiles, especially with comedications for common comorbidities, a critical feature in an aging HIV-positive population.
- **Formulation Advancements:** Including fixed-dose combinations (FDCs) that consolidate entire regimens into a single tablet (e.g., Biktarvy®: bictegravir/emtricitabine/tenofovir alafenamide) and long-acting injectables that provide months of coverage.

The mechanism of action is the foundational pillar upon which each drug is built, and for new agents, it often involves refined inhibition or entirely novel targets. The INSTI class exemplifies refinement. While all INSTIs block the integration of viral DNA into the host genome, second-generation INSTIs like dolutegravir bind more tightly to the integrase enzyme and demonstrate slower dissociation kinetics, contributing to their superior resistance profile. In stark contrast, the newest classes of drugs unveil novel viral vulnerabilities. Fostemsavir, an attachment inhibitor, binds to the envelope glycoprotein gp120 on the virus surface, preventing its initial interaction with the CD4 receptor on the host cell—the very first step of infection. Lenacapavir, the first-in-class capsid inhibitor, represents a monumental leap. It exhibits a multi-stage mechanism: it disrupts the capsid core, interfering with both the nuclear import of viral DNA and the assembly and maturation of new virions. This novel target makes it a powerful option for heavily treatment-experienced patients and is being studied in long-acting formulations. The scientific discussion around mechanism is deeply intertwined with resistance profiling, using structural biology and virological assays to understand how mutations confer resistance and to inform the development of next-generation inhibitors.

The pharmacological profile—encompassing pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body)—is a critical area of intense research and

debate. For new antiretrovirals, the focus is on optimizing absorption, distribution, metabolism, and excretion (ADME) properties. A prime example is the development of tenofovir alafenamide (TAF), a prodrug of tenofovir. Compared to its predecessor, tenofovir disoproxil fumarate (TDF), TAF is more stable in plasma, leading to more efficient intracellular delivery of the active metabolite, significantly higher lymphatic and tissue concentrations, and markedly lower systemic exposure. This translates into a vastly improved renal and bone safety profile. The discussion also extensively covers drug-drug interactions (DDIs), particularly for agents metabolized by cytochrome P450 enzymes or acting as inducers/inhibitors of these enzymes. Newer drugs like dolutegravir and bictegravir have a lower DDI potential than older PIs and NNRTIs, simplifying co-administration with drugs for tuberculosis, hypertension, or mental health conditions. Therapeutic drug monitoring (TDM) and studies in special populations (hepatic/renal impairment, pregnant women) are essential components of this pharmacological discourse, ensuring safe and effective use across diverse patient demographics.

The effects of new antiretrovirals are demonstrably positive, driving the success of modern ART. The primary effect is potent and durable virological suppression, which is the direct catalyst for the secondary effects: immune reconstitution (recovery of CD4+ T-cell counts) and a dramatic reduction in AIDS-defining illnesses and mortality. Beyond these fundamental outcomes, newer agents contribute to significant qualitative improvements in patient lives. Simplified, well-tolerated regimens reduce pill burden and treatment fatigue. The improved metabolic profiles lessen the risk of non-AIDS-defining comorbidities such as cardiovascular, renal, and bone diseases, which now represent a major focus of long-term care. Perhaps one of the most profound public health effects facilitated by effective ART, including modern regimens, is the concept of Undetectable = Untransmittable (U=U). A person with a durably undetectable viral load cannot sexually transmit HIV to their partners, a fact that is powerful in dismantling stigma and revolutionizing HIV prevention strategies.

Despite their advanced design, new antiretrovirals are not devoid of toxicities, and the characterization of these adverse effects is a crucial and evolving part of their scientific narrative. While generally safer, each class and individual drug carries a unique toxicity profile that must be meticulously characterized in large, diverse clinical trials and post-marketing surveillance. For the widely used INSTI class, weight gain has emerged as a significant and unexpected class-effect concern. Patients, particularly women of African descent, initiating dolutegravir or bictegravir-based regimens have shown a greater propensity for weight gain and associated metabolic changes compared to those on older regimens. The mechanisms are under intense investigation, possibly involving effects on melanocortin-4 receptors or mitochondrial function. Neuropsychiatric effects, including insomnia, anxiety, and depression, were initially noted with dolutegravir, though longer-term data suggest they are often transient and less common than initially feared. Other toxicities include hypersensitivity reactions (e.g., to abacavir, though not a new drug, its pharmacogenetic screening remains a model for safety), gastrointestinal disturbances, and potential renal effects (though significantly reduced with TAF). The discussion around toxicities is a testament to the rigor of pharmacovigilance, balancing overwhelming efficacy with the management of often manageable side effects to ensure long-term health and quality of life.

The scientific discussion surrounding new antiretroviral medicines is a comprehensive, iterative, and indispensable process. It is a multidisciplinary dialogue that systematically evaluates

every facet of these compounds, from their molecular classification and novel mechanisms to their real-world clinical utility and long-term safety. This discourse has propelled the field from toxic, cumbersome regimens to highly effective, well-tolerated, and user-friendly therapies. The manifestation of this discussion is evident in treatment guidelines that are frequently updated based on emerging evidence, ensuring that clinical practice remains at the cutting edge of scientific progress. As research continues to push boundaries with long-acting agents, broadly neutralizing antibodies, and pursuit of a cure, the rigorous framework for scientific discussion—encompassing classification, clinical use, features, mechanism, pharmacology, effects, and toxicities—will remain the bedrock upon which future breakthroughs are evaluated and integrated, ultimately improving the lives of millions living with HIV worldwide.

BACKGROUND

The narrative of the Human Immunodeficiency Virus (HIV) and the subsequent global Acquired Immunodeficiency Syndrome (AIDS) pandemic is a profound saga of scientific discovery, medical innovation, societal struggle, and human resilience. To fully appreciate the revolutionary impact of the newest antiretroviral agents, one must first understand the deep and complex historical, virological, and therapeutic context from which they emerged. This background traces the arduous journey from the initial terrifying emergence of a mysterious fatal illness to the current era where HIV is a manageable chronic condition, setting the stage for the paradigm-shifting advancements that define the contemporary therapeutic landscape. It is a story of incremental progress, punctuated by moments of breathtaking breakthrough, each building upon the last in the relentless pursuit of overcoming one of history's most formidable pathogens.

The modern history of HIV begins in the early 1980s, when clusters of previously rare opportunistic infections—such as *Pneumocystis jirovecii* pneumonia and Kaposi's sarcoma—began appearing in previously healthy gay men in urban centers in the United States. The medical community was initially baffled by this new syndrome, which seemed to completely dismantle the human immune system. It was initially termed GRID (Gay-Related Immune Deficiency) before being renamed AIDS in 1982 as it became clear it affected other populations, including hemophiliacs, recipients of blood transfusions, and injection drug users. The fear and stigma were immediate and pervasive, fueled by misinformation and a lack of understanding about the disease's transmission. The identification of the causative agent, a retrovirus first named HTLV-III and LAV by competing research teams, was a pivotal first step. The eventual resolution of the scientific dispute and its re-designation as Human Immunodeficiency Virus in 1986 allowed the global scientific community to unite around a common target.

Understanding the virus's structure and replication cycle was the next critical hurdle. HIV is a lentivirus, a subgroup of retroviruses characterized by a long incubation period. Its structure is complex: its outer envelope, studded with glycoprotein spikes (gp120 and gp41), facilitates entry into host cells, primarily CD4+ T-lymphocytes, the master conductors of the adaptive immune response. Inside the viral particle, two copies of single-stranded RNA genome and essential enzymes—reverse transcriptase, integrase, and protease—are housed within a conical capsid. The replication cycle is a masterpiece of biological hijacking. It begins with attachment and fusion, where gp120 binds to the CD4 receptor and a coreceptor (CCR5 or CXCR4) on the host cell surface, allowing the viral envelope to fuse with the cell membrane. The viral core is released into the

cytoplasm, where reverse transcriptase converts the viral RNA into DNA. This viral DNA is then transported into the nucleus and integrated into the host's chromosomal DNA by the integrase enzyme, creating a permanent provirus. This integrated provirus can lie dormant for years, establishing the latent reservoir that remains the fundamental barrier to a cure. Upon activation, the host cell's machinery is co-opted to transcribe the viral DNA into new RNA strands, which are translated into viral proteins. The protease enzyme then cleaves these long polyproteins into functional units. Finally, new viral particles are assembled and bud from the host cell, maturing into infectious virions ready to infect new cells. Each of these steps—attachment, fusion, reverse transcription, integration, and proteolytic cleavage—would eventually become a target for therapeutic intervention.

The first therapeutic breakthrough came in 1987 with the approval of zidovudine (AZT), a nucleoside analog that inhibits reverse transcriptase. The initial euphoria was short-lived. Monotherapy with AZT led to only transient benefits, as the high mutation rate of HIV—a consequence of the error-prone reverse transcriptase enzyme—swiftly selected for resistant viral strains. The virus could evolve under drug pressure with devastating efficiency. The late 1980s and early 1990s were a period of therapeutic despair, marked by the successive introduction of other nucleoside reverse transcriptase inhibitors (NRTIs) like didanosine and zalcitabine, used sequentially or in combination with AZT, but with marginal improvements in outcomes. Mortality rates remained staggeringly high, and clinics were filled with patients dying from horrific opportunistic infections. This period underscored a fundamental virological truth that would define all future HIV treatment: to corner a virus with such immense replicative and mutational capacity, it must be hit hard and hit simultaneously with multiple drugs.

The true turning point, often called the "Lazarus era," arrived in 1996 with the advent of protease inhibitors (PIs) and the formalization of combination therapy. The introduction of saquinavir, ritonavir, and indinavir represented a completely new class of drugs that targeted a different, essential viral enzyme. When combined with two NRTIs, these regimens—dubbed Highly Active Antiretroviral Therapy (HAART)—produced dramatic and sustained suppression of viral replication. Patients on the brink of death experienced miraculous recoveries, rising from their sickbeds. Hospitals wards dedicated to AIDS-related illnesses began to empty. The effect on mortality and morbidity in countries with access to these drugs was nothing short of revolutionary. HAART established the foundational principle of modern HIV therapy: combination ART (cART) aimed at achieving and maintaining an undetectable plasma viral load, typically defined as less than 50 copies/mL.

However, this first generation of HAART came with a heavy price. The regimens were notoriously complex and burdensome. Patients had to take dozens of pills a day on strict, often inconvenient schedules, some with large high-fat meals and others on an empty stomach. The side effects were severe and could be disfiguring and debilitating. Protease inhibitors were associated with lipodystrophy—a pervasive redistribution of body fat characterized by peripheral fat wasting (in the face, arms, and legs) and central fat accumulation (in the abdomen and as a "buffalo hump" on the back)—as well as severe dyslipidemia and insulin resistance. NRTIs like stavudine and zidovudine caused mitochondrial toxicity, leading to peripheral neuropathy, pancreatitis, and lactic acidosis. The psychological toll of these toxicities was immense, as the very treatments that saved

lives also made them physically and socially difficult, serving as constant, visible stigmas of their disease.

The next decade, from approximately 2000 to 2010, was an era of refinement and simplification, driven by the goal of improving quality of life and long-term safety. The treatment arsenal expanded with new drug classes, providing more options and strategies. The non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as efavirenz and nevirapine, offered a potent once-daily pill but brought their own challenges, including neuropsychiatric side effects and rash. The entry inhibitor enfuvirtide, requiring twice-daily subcutaneous injections, was a difficult-to-use but life-saving option for highly treatment-experienced patients. Perhaps the most significant class introduced during this period was the integrase strand transfer inhibitors (INSTIs). Raltegravir, the first in its class approved in 2007, offered potent, rapid viral suppression with a clean side effect profile, heralding a new future for HIV therapy.

A critical pharmacological advancement was the strategic use of pharmacokinetic enhancers, or boosters. The PI ritonavir, at a low dose, was found to potently inhibit the cytochrome P450 3A4 enzyme in the liver, thereby dramatically increasing ("boosting") the exposure levels of other co-administered PIs. This allowed for improved efficacy, reduced pill burden, and less frequent dosing. This principle was later extended to cobicistat, a dedicated booster without antiviral activity. The development of fixed-dose combinations (FDCs) was another leap forward, consolidating multiple drugs into a single tablet. This began with two-drug combinations and eventually culminated in the first single-tablet regimen (STR), Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate), in 2006. STRs revolutionized patient adherence and convenience, reducing a complex regimen to a single daily pill.

Concurrently, the strategic approach to *when* to start therapy evolved significantly. Initially, treatment was reserved for those with advanced immunodeficiency, due to the high toxicity and complexity of early drugs. As regimens became safer and simpler, evidence mounted from large randomized trials like START and TEMPRANO that initiating ART immediately upon diagnosis improved individual health outcomes by preserving immune function and reducing inflammation-linked comorbidities. It also provided a powerful public health benefit: individuals with an undetectable viral load cannot sexually transmit HIV. This finding, conclusively proven by the HPTN 052 and PARTNER studies, gave rise to the Undetectable = Untransmittable (U=U) campaign, a transformative concept that began to dismantle the deep-seated stigma associated with HIV.

Despite these monumental advances, significant challenges persisted as the second decade of the 21st century unfolded. While safer, drugs still had long-term toxicities. Tenofovir disoproxil fumarate (TDF), a cornerstone of most regimens, was associated with a risk of renal impairment and reduced bone mineral density. Adherence, though improved, remained a critical issue; missing doses of certain drugs could still lead to virological failure and the emergence of resistance. For a small but significant population of "treatment-experienced" patients, the virus had developed resistance to multiple drug classes, leaving them with few, complex, and often suboptimal salvage options. Furthermore, the psychological burden of a lifelong daily reminder of one's HIV status—taking a pill every day—remained a source of stigma for some.

It is within this context of both triumph and lingering challenge that the latest revolution in antiretroviral therapy is taking place. The newest generation of drugs is not merely an

incremental improvement but a fundamental re-imagining of what HIV treatment can be. They are the products of decades of accumulated virological knowledge, medicinal chemistry, and pharmacological insight, designed to address the specific shortcomings of their predecessors. This new era is defined by several key themes: the pursuit of unmatched potency and genetic barrier to resistance; the optimization of long-term safety and tolerability; the introduction of ultra-long-acting formulations that decouple treatment from daily life; and the exploration of novel mechanisms of action that attack the virus in previously untargeted ways. Furthermore, the scientific community is now, for the first time, seriously pursuing strategies aimed not just at chronic suppression, but at a functional cure. This background of struggle, innovation, and evolving challenges sets the stage for the groundbreaking developments in classification, mechanism, pharmacology, and clinical application that will be explored in the subsequent sections of this work. The journey from a certain death sentence to a manageable chronic illness is complete; the journey from chronic illness to a life completely unencumbered by HIV is now underway.

RESULTS AND DISCUSSION

The investigation into the latest generation of antiretroviral therapeutics reveals a period of remarkable innovation and refinement, fundamentally altering the clinical management of human immunodeficiency virus infection. The results from a synthesis of recent clinical trials, pharmacological studies, and real-world evidence datasets paint a picture of a field that has successfully transitioned from a focus on sheer survival to an emphasis on long-term quality of life, safety, and strategic viral suppression. This discussion will integrate these findings, exploring the tangible outcomes linked to the novel mechanisms of action, superior pharmacological profiles, and enhanced clinical efficacy of these agents, while also providing a critical appraisal of the emerging safety signals and the practical implications for global treatment paradigms.

The most profound results in recent years have emerged from the continued evolution of the integrase strand transfer inhibitor class. While first-generation INSTIs like raltegravir and elvitegravir provided potent suppression, their vulnerability to resistance mutations, particularly in scenarios of suboptimal adherence, presented a clinical limitation. The introduction and widespread adoption of second-generation INSTIs, namely dolutegravir and bictegravir, have yielded results that signify a paradigm shift. Clinical endpoint studies consistently demonstrate that regimens anchored by these agents achieve rates of virological suppression that are non-inferior, and in some high-risk populations, superior, to the previous gold standards. The defining result for dolutegravir has been its exceptionally high genetic barrier to resistance; treatment-naïve patients receiving dolutegravir-based therapy exhibit an almost negligible incidence of virological failure with emergent INSTI resistance mutations. This is a direct consequence of its unique pharmacodynamic properties, specifically its slow dissociation rate from the integrase enzyme complex, which means that even if a mutation occurs that slightly weakens the binding affinity, the drug remains bound long enough to exert its inhibitory effect. This result has monumental implications for global health, offering a more forgiving and robust platform for treatment, particularly in resource-limited settings with limited options for genotypic resistance testing.

Parallel to these advances in efficacy, the pharmacological optimization of drug formulations has yielded results with direct impacts on patient safety and adherence. The development of tenofovir alafenamide as a successor to tenofovir disoproxil fumarate stands as a

landmark achievement in prodrug chemistry. The results of large-scale, randomized controlled trials and subsequent cohort studies are unequivocal: TAF-based regimens provide equivalent antiviral efficacy to TDF-based regimens but with dramatically reduced markers of renal and bone toxicity. Serum creatinine elevations, declines in estimated glomerular filtration rate, and instances of Fanconi syndrome are significantly less frequent with TAF. Furthermore, dual-energy X-ray absorptiometry scans reveal significantly less loss of bone mineral density at the hip and spine in patients initiating TAF compared to those on TDF. These results translate to a tangible reduction in long-term morbidity, allowing clinicians to prescribe potent NRTI backbones without the attendant concerns for cumulative off-target organ damage, a critical consideration for an aging population of people living with HIV who require lifelong therapy.

Beyond refining existing classes, the most groundbreaking results come from the development of agents with entirely novel mechanisms of action. The capsid inhibitor lenacapavir represents one such leap forward. Clinical trial results in heavily treatment-experienced patients with multidrug-resistant virus have been nothing short of spectacular. In a population for whom effective therapeutic options were nearly exhausted, subcutaneous administration of lenacapavir as part of an optimized background regimen resulted in a significant majority of participants achieving virological suppression to undetectable levels. The mechanistic results elucidate why this is possible; lenacapavir targets the viral capsid, a structure previously unexploited therapeutically, and disrupts its function at multiple points in the life cycle—including nuclear import of the viral genome and the assembly of new virions. This multi-stage inhibition creates a exceptionally high barrier to resistance. Furthermore, its extraordinary pharmacokinetic profile, with a half-life extending to several months, is a result that opens the door to ultra-long-acting administration schedules, potentially reducing treatment from 365 daily doses to a mere handful of injections per year.

The successful development of long-acting injectable antiretroviral therapy is perhaps the most patient-centric result of the modern era. The pivotal trials for the intramuscular combination of cabotegravir and rilpivirine demonstrated that maintenance of virological suppression was non-inferior to continuation of daily oral three-drug therapy. This result validates a fundamental shift in the philosophy of HIV care—from a daily reminder of a chronic condition to a discreet, infrequent intervention. The discussion around these results must acknowledge the importance of adherence in a new form; while freeing patients from daily pills, it introduces the necessity of strict adherence to injection appointments. Nevertheless, patient-reported outcomes from these studies consistently show a strong preference for the injectable modality, citing benefits for mental health, stigma reduction, and overall quality of life. This represents a crucial result: that therapeutic success is no longer measured solely by virological endpoints but also by its integration into and positive impact on a patient's life.

However, this comprehensive analysis would be incomplete without a thorough discussion of the emerging and sometimes unexpected safety signals associated with these new agents. The most widely discussed and carefully monitored result pertains to the issue of weight gain associated with INSTI-based regimens. Pooled data from numerous clinical trials and observational cohorts have consistently shown that patients initiating therapy with dolutegravir or bictegravir experience a greater increase in body mass index over time compared to those on regimens based on older agents like efavirenz, darunavir, or even raltegravir. This effect is most pronounced in certain demographic groups, specifically women of African descent. The mechanistic underpinnings of this

result remain a subject of intense investigation. Hypotheses include off-target effects on melanocortin-4 receptors involved in appetite regulation, interactions with adipose tissue metabolism, or perhaps a more indirect effect related to superior metabolic health and well-being leading to increased appetite. While the clinical significance of this weight gain is still being evaluated, with some patients crossing into obesity and associated health risks, it is a critical result that necessitates ongoing surveillance, patient counseling, and research into mitigating strategies.

Another area of discussion centers on the neuropsychiatric profile of certain newer agents. Early results from dolutegravir clinical trials indicated a higher incidence of insomnia, anxiety, and in rare cases, suicidal ideation, particularly in the first few weeks of therapy. This led to initial caution and specific guidance against use in patients with pre-existing psychiatric conditions. However, longer-term follow-up and larger real-world evidence studies have provided a more nuanced result. It appears that these adverse effects are often transient and self-limiting, resolving within the first four to eight weeks of treatment for the majority of patients who experience them. The discussion here highlights the importance of distinguishing between short-term tolerability issues and long-term safety concerns. It also underscores the critical role of the clinician in pre-therapy counseling, managing patient expectations, and providing supportive management during the initiation phase to ensure persistence with an otherwise supremely effective regimen.

The discussion of results must also extend to the practical and economic implications of implementing these new therapies on a global scale. The superior efficacy, tolerability, and high genetic barrier to resistance of dolutegravir-based regimens led the World Health Organization to recommend them as the preferred first-line treatment globally. The result has been a rapid scale-up across low- and middle-income countries, a monumental achievement in global health. However, this success has been tempered by the aforementioned results concerning weight gain, which has a different risk-benefit calculus in populations with higher background rates of obesity and metabolic disease. Furthermore, the high cost of the newest agents, such as long-acting injectables and novel classes like capsid inhibitors, creates a significant access disparity. The result is a two-tiered system: robust, simple, and effective regimens for the majority in resource-rich settings, and a more limited set of options for the highly treatment-experienced and those in resource-limited settings. This inequity is a critical result of market forces and intellectual property regimes that must be addressed through aggressive negotiation, generic licensing, and international cooperation.

Looking forward, the results of current research are already pointing to the next frontiers in antiretroviral therapy. The success of long-acting cabotegravir for pre-exposure prophylaxis is a result that proves the concept of using ultra-long-acting agents for prevention, a finding that could profoundly impact incidence rates if deployed effectively in high-risk populations. Furthermore, the ability of novel agents like lenacapavir to potently suppress virus in deep tissue reservoirs is generating discussion about their potential role in cure strategies, perhaps as tools to prevent viral rebound during treatment interruptions or in combination with other latency-reversing agents. The result of these inquiries is not yet known, but they represent the logical progression of a field that continues to innovate relentlessly.

In synthesizing these myriad results, the overarching discussion concludes that the current era of antiretroviral therapy is defined by an embarrassment of riches. Clinicians and patients now have access to multiple regimens that are more potent, safer, and more convenient than at any previous time in the history of the epidemic. The results demonstrate that the historical toxicities

of HIV therapy—peripheral neuropathy, pancreatic inflammation, severe lipodystrophy, and renal tubular damage—have been largely consigned to the past. They have been replaced by a new set of considerations, such as managing weight gain and understanding the long-term implications of INSTI use over decades. The central challenge has shifted from achieving suppression to choosing the right suppression strategy from a menu of excellent options, personalized to the individual patient's needs, comorbidities, and lifestyle. These results are a testament to four decades of scientific perseverance and a promise of continued improvement in the lives of people living with HIV.

The landscape of antiretroviral therapy continues to evolve at an unprecedented pace, moving beyond the paradigm of viral suppression to a holistic focus on holistic patient wellness, long-term physiological resilience, and the eradication of stigma through revolutionary drug delivery systems. The results emanating from a comprehensive synthesis of late-phase clinical trials, advanced pharmacological modeling, and expansive real-world data analytics reveal a new era defined by ultra-long-acting formulations, novel multi-stage mechanistic targets, and a deepened understanding of host-pathogen-drug interactions. This discussion will weave together these complex findings, examining the profound outcomes associated with these next-generation therapeutics, while critically engaging with the nuanced challenges of cellular toxicity, socio-economic access inequities, and the emerging role of artificial intelligence in personalized HIV medicine. The conversation has expanded from merely controlling a virus to comprehensively managing a chronic condition with an eye towards future curative strategies.

A paramount result reshaping first-line treatment guidelines globally is the solidified superiority of second-generation integrase strand transfer inhibitors, particularly dolutegravir and bictegravir, and the emerging data on their successor, cabotegravir in oral form. Long-term extension studies spanning five years and beyond now provide a robust dataset demonstrating not just sustained virological efficacy but a remarkable preservation of physiological function. The discussion around these results must highlight the concept of "metabolic neutrality" observed with bictegravir-based regimens; unlike earlier regimens which often contributed to dyslipidemia or insulin resistance, these modern cores show minimal to no deleterious impact on lipid profiles, glycemic markers, or other metabolic parameters over extended periods. This is a critical result for long-term cardiovascular health, a leading concern in an aging HIV-positive population. Furthermore, pharmaco-economic modeling results indicate that despite higher drug acquisition costs, the superior barrier to resistance and reduced need for costly resistance testing and regimen switches make these agents cost-effective or even cost-saving from a systems perspective over a patient's lifetime. This result is fundamentally changing how governments and health insurers evaluate and fund HIV treatment programs, viewing it as a long-term investment in population health.

The most revolutionary results, however, lie in the domain of long-acting antiretroviral therapy, which has transitioned from a theoretical concept to a clinically validated reality. The outcomes from the phase III trials for long-acting cabotegravir and rilpivirine injections have been successfully replicated in diverse real-world settings, often referred to as "implementation science" studies. These results demonstrate that high levels of virological suppression can be maintained outside the rigid protocol of a clinical trial, with careful patient selection and management. A deeper discussion point emerging from this data is the psychological result of decoupling HIV management from daily oral medication. Qualitative research sub-studies report a profound reduction in

internalized stigma and an improved sense of normalcy among recipients of injectable therapy. The act of taking a daily pill, a constant reminder of one's serostatus, is eliminated, leading to measurable improvements in mental health outcomes and overall quality-of-life scores. This represents a paradigm shift in evaluating treatment success, moving beyond bio-clinical markers to encompass profound psychosocial benefits.

Concurrently, the results from pre-exposure prophylaxis studies using long-acting cabotegravir are arguably among the most significant public health advancements in HIV prevention. The efficacy results, demonstrating a superior level of protection compared to daily oral PrEP, particularly in populations where adherence to a daily pill is challenging, offer a powerful tool to curb incidence rates. The discussion must focus on the implementation results, which highlight the challenges and opportunities of rolling out such a technology. Results from pilot programs indicate the necessity of building robust infrastructure for injection delivery, managing minor but common side effects like injection site reactions, and addressing the unique issue of "tail" pharmacokinetics—the long period of time after the last injection where drug levels remain sub-therapeutic but detectable, potentially fostering resistance if infection occurs. This has spurred innovative research into real-time adherence monitoring using digital health technologies and the development of predictive algorithms to personalize injection schedules.

The frontier of antiretroviral development has been boldly advanced with the arrival of agents possessing entirely novel mechanisms, most notably the capsid inhibitors. The clinical results for lenacapavir are groundbreaking, especially for the highly treatment-experienced population. What is most remarkable is the rapidity and depth of viral load decline observed even in patients with extensive resistance to all other drug classes. This result is directly attributable to its unique mechanism, which results in multi-stage inhibition of the viral life cycle. Structural biology studies have yielded results showing how lenacapavir stabilizes and hyper-stabilizes the capsid core, preventing its uncoating and disrupting the formation of new virions. Furthermore, its pharmacokinetic profile is unprecedented; results show sustained drug concentrations far above the protein-adjusted inhibitory concentration for over six months following a single subcutaneous injection. This opens up discussions for future regimen construction, potentially involving dual- or triple-long-acting injections administered semi-annually, effectively creating a "yearly regimen" for HIV. The ongoing clinical trials exploring lenacapavir in treatment-naïve patients and as part of long-acting combinations are eagerly awaited, as they could redefine the standard of care for all people living with HIV.

Another exciting new avenue is the development of broadly neutralizing antibodies (bNAbs). While not traditional small-molecule drugs, the results from clinical trials of bNAbs like teropavimab and zinlirvimab are informing a new class of biologics for HIV treatment and prevention. The discussion here is nuanced. Results show that as monotherapy, their efficacy is limited by pre-existing or rapidly emerging resistance, as HIV can easily escape the pressure of a single antibody. However, results from combination studies using two or three bNAbs targeting non-overlapping epitopes on the viral envelope are highly promising, demonstrating prolonged virological suppression in carefully selected individuals with sensitive virus. This has led to a new field of pre-treatment sensitivity screening. The most exciting discussion point is the potential role of bNAbs in kick-and-kill cure strategies. Results from animal models and early human studies suggest that by binding to the surface of infected cells, bNAbs can flag them for destruction by the

immune system through antibody-dependent cellular cytotoxicity, potentially helping to clear the latent reservoir. This remains a nascent but explosively growth-oriented area of research.

Despite these spectacular advances, the results of widespread surveillance have brought to light more detailed and concerning safety signals that require sophisticated discussion. The issue of INSTI-associated weight gain has been extensively studied, and new results provide greater clarity on its character. It is now understood to be a class effect, but with varying magnitudes. Weight gain appears to be greatest with dolutegravir and bictegravir, intermediate with cabotegravir, and modest with the newer INSTI, islatravir. The weight gain is predominantly in the visceral adipose tissue compartment, which is metabolically unfavorable and associated with higher risks of cardiovascular disease and diabetes. The discussion has moved from simply documenting the phenomenon to understanding its mechanisms. Recent results from in vitro studies suggest a potential off-target effect on melanocortin-4 receptor signaling, a key pathway in the hypothalamus for regulating appetite and energy expenditure. Other hypotheses implicate effects on adipocyte differentiation and lipid metabolism. Crucially, results from large cohort studies like RESPOND are now showing that the weight trajectory does not plateau indefinitely but tends to slow after 18-24 months. However, the clinical management of this weight gain—whether through pharmacological intervention, switching strategies, or lifestyle programs—remains an area of active investigation and debate.

Furthermore, the neurological and psychiatric safety profile of these drugs is under continued scrutiny. While the initial fear surrounding dolutegravir and suicidal ideation has been alleviated by larger datasets showing no overall increased risk, more subtle neuropsychiatric results are being documented. Patient-reported outcomes and specific cognitive testing batteries reveal that a subset of patients on INSTIs report higher rates of insomnia, anxiety, and subjective cognitive complaints like "brain fog" compared to those on protease inhibitor-based regimens. The discussion here is complex, as it is challenging to disentangle drug effects from the background high prevalence of mental health conditions and neurocognitive impairment in the HIV-positive population. Advanced neuroimaging results are now being employed to objectively measure any potential impact of these drugs on brain metabolism and structure, adding a new layer of data to this critical discussion.

The discussion of results must also confront the stark reality of access and equity. The brilliant results of modern clinical trials stand in stark contrast to the logistical and financial results of their implementation on a global scale. The World Health Organization's recommendation of dolutegravir-based regimens was a monumental step towards equity, yet results from rollout programs in sub-Saharan Africa highlight persistent challenges. These include drug stockouts, the management of the initial weight gain concern in populations with high rates of obesity and metabolic disease, and the navigation of drug-drug interactions with common co-medications for tuberculosis and endemic diseases. The chasm between the availability of cutting-edge long-acting therapies and novel agents in high-income countries versus their complete absence in public health systems in low-income countries is perhaps the most disappointing result of the modern antiretroviral era. This inequity fuels transmission chains and risks the development and global spread of resistance, undermining progress for all. The discussion must, therefore, include results from initiatives like the Medicines Patent Pool, which negotiate voluntary licenses for generic

manufacture, and the need for sustainable international financing mechanisms to ensure that therapeutic advances do not become catalysts for deeper health disparities.

Finally, the results of basic science research are now directly influencing clinical development in real-time. The application of advanced technologies like cryo-electron microscopy has yielded atomic-level results of drug-target interactions, allowing for the rational design of next-generation inhibitors that are pre-emptively engineered to be effective against common resistance mutations. For example, the development of novel NRTTIs (nucleotide reverse transcriptase translocation inhibitors) like islatravir was informed by a deep understanding of the structural limitations of previous NRTIs. Furthermore, results from research into the viral reservoir are identifying new therapeutic targets beyond the virus itself, focusing on host factors that maintain latency. Drugs that modulate these pathways could potentially be used to "shock" the reservoir, making it visible to the immune system or susceptible to antiviral drugs, a key strategy in the pursuit of a cure. The discussion is now moving towards how to intelligently combine these novel agents with existing ones to create synergistic, resistance-proof, and potentially curative regimens.

In synthesizing this vast and rapidly expanding body of results, the discussion concludes that the field of antiretroviral therapy is in a period of revolutionary ferment. The historical goals of therapy have been not just met but exceeded. The current challenge is no longer if we can suppress the virus, but how we can do it in a way that optimizes every facet of a person's life—physical, metabolic, mental, and social—over a lifespan that now approaches that of the general population. The results point towards a future of highly personalized HIV medicine, where treatment choices are tailored based on an individual's virus, co-morbidities, genetic makeup, and lifestyle preferences, from daily pills to yearly injections. These extraordinary results are a powerful testament to scientific innovation but also serve as a urgent reminder that the ultimate result—health for all—remains an unfinished goal demanding relentless advocacy, global solidarity, and scientific perseverance.

The Evolution of HIV Therapy and the Imperative for Innovation

The management of Human Immunodeficiency Virus (HIV) infection represents one of the most remarkable success stories in modern medicine. From a certain fatal diagnosis in the 1980s, HIV has been transformed into a chronic, manageable condition, primarily due to the development and continuous refinement of Antiretroviral Therapy (ART). The foundational breakthrough came with the introduction of combination ART (cART), often colloquially known as Highly Active ART (HAART), in the mid-1990s. This strategy, which involves the simultaneous use of multiple drugs targeting different stages of the HIV lifecycle, successfully suppressed viral replication, restored immune function, and dramatically reduced HIV-related morbidity and mortality.

However, the early eras of ART were fraught with significant challenges. Regimens were characterized by a high pill burden, complex dosing schedules, severe short- and long-term toxicities, and significant drug-drug interactions. Furthermore, the high rate of viral mutation, combined with suboptimal adherence driven by these difficult regimens, led to the emergence of drug-resistant viral strains, threatening the long-term efficacy of available treatments. These limitations underscored a persistent and urgent need for innovation—the development of new antiretroviral agents that were more potent, more durable against resistance, safer, and more patient-friendly.

The scientific discussion around antiretroviral drugs is, therefore, not static; it is a dynamic and ever-evolving discourse manifested in continuous clinical trials, updated treatment guidelines, pharmacovigilance reports, and real-world evidence studies. This discourse focuses on several key pillars: the precise classification of drugs based on their molecular targets; their mechanisms of action at the biochemical level; their pharmacological properties, including pharmacokinetics and pharmacodynamics; their integration into clinical use through evidence-based guidelines; their unique features and advantages over previous generations; and a critical analysis of their toxicities and safety profiles.

This comprehensive analysis aims to synthesize this vast scientific discussion, providing a detailed overview of the current landscape of new antiretroviral medicines. It will delve into the latest drug classes, such as Integrase Strand Transfer Inhibitors (INSTIs) and novel attachment and post-attachment inhibitors, while also exploring significant advancements within older classes, such as the development of tenofovir alafenamide (TAF). Furthermore, it will analyze the paradigm shift towards long-acting injectable formulations and the ongoing pursuit of strategies for managing multidrug-resistant HIV. By examining the classification, mechanisms, pharmacology, clinical utility, and toxicities of these agents, this review encapsulates the current state of ART and the future directions of HIV therapeutics.

Classification of Antiretroviral Agents: From Foundational Pillars to Novel Mechanisms

Antiretroviral drugs are systematically classified based on their specific molecular target within the HIV replication cycle. This classification is crucial for understanding drug interactions, constructing synergistic regimens, and managing cross-resistance. The traditional backbone of ART has consisted of three core classes, now joined by newer, highly effective classes and entry inhibitors.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs): NRTIs were the first class of drugs approved to treat HIV infection. They are prodrugs that require intracellular phosphorylation to become active. The active form mimics the natural deoxynucleoside triphosphates (dNTPs) that HIV reverse transcriptase uses to synthesize viral DNA. When incorporated into the growing DNA chain, they act as chain terminators, halting DNA synthesis and aborting viral replication.

- Key Agents: Zidovudine (AZT), Didanosine (ddI), Stavudine (d4T) (largely historical due to toxicity); Abacavir (ABC); Lamivudine (3TC); Emtricitabine (FTC); Tenofovir Disoproxil Fumarate (TDF); Tenofovir Alafenamide (TAF).
- Role: NRTIs form the foundational "backbone" of most modern combination regimens, typically used in pairs (e.g., TAF/FTC or ABC/3TC).

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): NNRTIs are non-competitive inhibitors of HIV reverse transcriptase. They bind to a hydrophobic pocket distal to the enzyme's active site (the NNRTI pocket), inducing a conformational change that drastically reduces the enzyme's catalytic activity. Their mechanism is distinct from and synergistic with that of NRTIs.

- **Key Agents:** Nevirapine (NVP), Efavirenz (EFV) (first-generation); Etravirine (ETR), Rilpivirine (RPV) (second-generation); Doravirine (DOR) (newest generation).
- **Role:** Historically used as a "third agent" or cornerstone in first-line regimens. Newer agents like DOR offer improved resistance and tolerability profiles.

Protease Inhibitors (PIs): PIs target the HIV-1 protease enzyme, which is essential for the post-translational processing of viral polyproteins (Gag and Gag-Pol) into mature, functional proteins (e.g., protease, reverse transcriptase, integrase, structural proteins). Inhibition results in the production of immature, non-infectious viral particles.

- **Key Agents:** Early PIs like Indinavir (IDV); Boosted PIs like Lopinavir/ritonavir (LPV/r), Darunavir/ritonavir or /cobicistat (DRV/b).
- **Role:** Now primarily reserved for second-line therapy, treatment-experienced patients, or specific clinical scenarios (e.g., pregnancy with resistance concerns) due to the potency and tolerability of newer classes. They require pharmacokinetic "boosters" (ritonavir or cobicistat) to prolong their half-life.

Integrase Strand Transfer Inhibitors (INSTIs) - The Modern Cornerstone

INSTIs represent the most significant advancement in HIV therapeutics in the past 15 years. They inhibit the HIV integrase enzyme, which is responsible for inserting the viral DNA (produced by reverse transcriptase) into the host cell's chromosome, forming a permanent provirus. INSTIs specifically block the strand transfer step of this integration process.

- **Key Agents: Raltegravir (RAL)** (first-in-class); **Elvitegravir (EVG)** (requires pharmacoenhancement); **Dolutegravir (DTG)** (second-generation); **Bictegravir (BIC)** (next-generation).
- **Role:** INSTIs are now the preferred and recommended "third agents" in first-line regimens for most patients globally due to their superior potency, high genetic barrier to resistance, and generally favorable tolerability.

Entry and Fusion Inhibitors:This class prevents HIV from entering susceptible host cells (primarily CD4+ T-cells). They target the complex process of viral entry, which involves attachment to the CD4 receptor and CCR5 or CXCR4 coreceptors, followed by fusion of the viral and cellular membranes.

- **Key Agents:** Enfuvirtide (T-20) (fusion inhibitor, injectable, largely historical); Maraviroc (MVC) (CCR5 antagonist, requires tropism testing); **Ibalizumab (IBA)** (post-attachment inhibitor, monoclonal antibody); **Fostemsavir (FTR)** (attachment inhibitor, prodrug of temsavir).
- **Role:** Primarily used as salvage therapy for heavily treatment-experienced patients with multidrug-resistant (MDR) HIV.

Pharmacokinetic Enhancers ("Boosters"): While not antivirals themselves, these agents are critical components of many regimens. They potently inhibit the cytochrome P450 3A4 (CYP3A4) enzyme in the gut and liver, which is responsible for metabolizing several ARVs (notably PIs and EVG). By inhibiting this metabolism, they significantly increase the exposure (AUC) and half-life of the co-administered drug, allowing for less frequent dosing and improved efficacy.

- **Key Agents: Ritonavir (RTV)** (low-dose); **Cobicistat (COBI)** (developed specifically as a pharmacoenhancer with no antiviral activity itself).

Mechanisms of Action: A Molecular Perspective on Viral Inhibition

Understanding the precise mechanism of action of each drug class is fundamental to appreciating their clinical utility, synergy, and the basis for resistance.

Inhibition of Reverse Transcription (NRTIs & NNRTIs)

- **NRTIs:** The mechanism is one of **competitive inhibition and chain termination**. The intracellularly phosphorylated NRTI triphosphate competes with its natural counterpart (e.g., FTC-TP competes with dCTP) for binding to the active site of reverse transcriptase. Once incorporated, the molecule lacks a 3'-hydroxyl group, which is necessary for forming the phosphodiester bond with the next incoming nucleotide. This abruptly terminates the elongating DNA chain.
- **NNRTIs:** These agents employ **allosteric inhibition**. Their binding to the NNRTI pocket induces a conformational change that locks the enzyme into an inactive state. The substrate-binding pocket becomes distorted, preventing the proper positioning of the nucleoside triphosphates for catalysis. This mechanism is highly specific to the HIV-1 reverse transcriptase.

Inhibition of Viral Maturation (Protease Inhibitors): HIV protease is an aspartyl protease that functions as a homodimer. PIs are designed to mimic the transition state of the peptide substrate that the protease normally cleaves. They bind to the enzyme's active site with very high affinity, acting as **competitive inhibitors**. This blockade prevents the cleavage of the Gag and Gag-Pol polyproteins. Consequently, new virions bud from the infected cell but are structurally disorganized and non-infectious, as core proteins remain immature and unprocessed.

Inhibition of Integration (Integrase Strand Transfer Inhibitors): HIV integrase performs a two-step reaction: 1) 3'-processing, where it removes a dinucleotide from each 3' end of the viral DNA, and 2) **strand transfer**, where it covalently inserts these processed ends into the host genome. INSTIs are structurally analogous to the viral DNA ends and chelate the divalent metal ions (Mg^{2+} or Mn^{2+}) in the integrase active site. This binding selectively inhibits the strand transfer step, leaving the viral DNA unable to integrate and vulnerable to degradation by host cell enzymes.

Inhibition of Viral Entry (Entry Inhibitors): This class employs diverse and highly specific mechanisms:

- **Fusion Inhibitors (Enfuvirtide):** Mimics the heptad repeat region 2 (HR2) of the viral gp41 envelope glycoprotein. It binds to the HR1 region on gp41, preventing the formation of the six-helix bundle structure essential for driving the fusion of the viral and cellular membranes.
- **CCR5 Antagonists (Maraviroc):** Binds specifically to the human CCR5 coreceptor, inducing a conformational change that blocks its interaction with the viral envelope gp120 protein. This prevents the necessary engagement for entry. It is ineffective against CXCR4-tropic or dual-tropic viruses.
- **Post-Attachment Inhibitors (Ibalizumab):** A recombinant monoclonal antibody that binds to domain 2 of the CD4 receptor. This binding does not block HIV attachment but induces conformational changes in the receptor that prevent the viral envelope from undergoing the necessary rearrangements for fusion, specifically hindering the transition from a CD4-bound to a coreceptor-bound state.
- **Attachment Inhibitors (Fostemsavir):** A prodrug hydrolyzed to its active form, **temsavir**. Temsavir binds directly to the gp120 subunit of the viral envelope, stabilizing it in a conformation that prevents the initial interaction with the CD4 receptor, thereby blocking the very first step of viral entry.

Clinical Use and Guidelines: From First-Line to Salvage Therapy

The scientific discussion around ART is codified in regularly updated treatment guidelines, most notably those from the U.S. Department of Health and Human Services (DHHS) and the International Antiviral Society-USA (IAS-USA). The overarching goals of therapy are to achieve and maintain durable viral suppression (plasma HIV RNA <50 copies/mL), restore and preserve immune function, reduce HIV-associated morbidity and mortality, and prevent HIV transmission.

Initial Therapy for Antiretroviral-Naïve Patients: The current universal recommendation is to initiate ART at the time of diagnosis, regardless of CD4 count. The preferred regimens for most patients are all INSTI-based due to their rapid virologic suppression, high barrier to resistance, and tolerability.

- **Recommended Regimens:**

- **Bictegravir/TAF/FTC (Biktarvy®):** A single-tablet regimen (STR) with high efficacy, a high barrier to resistance, and no need for HLA-B*5701 testing (unlike ABC). It is a first-line choice for most.
- **Dolutegravir/TAF(or TDF)/FTC:** DTG is a potent INSTI with a high genetic barrier. It can be combined with Descovy® (TAF/FTC) or Truvada® (TDF/FTC). A popular global option, especially with the availability of generic DTG.
- **Dolutegravir/ Lamivudine (Dovato®):** A two-drug regimen (2DR) demonstrated to be non-inferior to three-drug regimens in ART-naïve patients. It simplifies therapy, reduces long-term drug exposure, and is a key option for those without baseline resistance to either component.
- **Alternative Regimens:** Include boosted PI-based regimens (e.g., DRV/COBI/TAF/FTC) or the newer NNRTI Doravirine-based regimens (Doravirine/TAF/FTC or Doravirine/TDF/3TC).

- **Management of Multidrug-Resistant (MDR) HIV**: For patients with complex treatment histories and resistance to multiple drug classes, constructing a viable regimen requires genotypic resistance testing and expert advice. Newer agents have revolutionized salvage therapy.

- **Ibalizumab:** Administered intravenously every two weeks, it is active against virus resistant to other classes due to its unique host-targeted mechanism. It is a crucial addition for constructing a new regimen for MDR HIV.
- **Fostemsavir:** Used twice daily in combination with other antiretrovirals, it provides a new mechanism of action to overcome resistance in heavily treatment-experienced adults with limited treatment options.
- **Optimized Background Regimen (OBR):** These new agents are never used alone. They must be combined with at least one, and preferably two, other fully active agents based on resistance testing to form a new suppressive regimen.

Long-Acting Injectable Therapy: A Paradigm Shift: The most significant recent advancement in clinical use is the approval of long-acting (LA) injectable cabotegravir (CAB) and rilpivirine (RPV).

- **Mechanism:** This is not a new class but a novel formulation. CAB is an INSTI and RPV is an NNRTI, but they are formulated as nanocrystals allowing for slow release from the intramuscular injection site.
- **Clinical Use:** Approved for maintenance therapy in virologically suppressed adults (HIV RNA <50 copies/mL) with no history of treatment failure or resistance to either drug. It involves an oral lead-in period to assess tolerability, followed by monthly or every-two-month injections.

- **Impact:** This regimen eliminates the need for daily oral pills, addressing pill fatigue, stigma, and adherence challenges. It represents a move towards "destination regimens" that prioritize patient preference and quality of life.

Pre-Exposure Prophylaxis (PrEP): ART is also used to prevent HIV acquisition in high-risk HIV-negative individuals. The discussion has evolved from TDF/FTC to:

- **TAF/FTC (Descovy®):** Approved for PrEP in men and transgender women, with potentially improved renal and bone safety metrics compared to TDF/FTC, though its efficacy in cisgender women is not yet established via trials.
- **Long-Acting Cabotegravir (CAB-LA):** An injectable PrEP option administered every two months, which has shown superior efficacy to daily oral TDF/FTC in clinical trials, offering a discrete and adherence-independent prevention tool.

Pharmacological Properties: Absorption, Distribution, Metabolism, and Excretion (ADME)

The pharmacological profile of a drug dictates it's dosing, potential for interactions, and safety.

Pharmacokinetics of Key Newer Agents

- **Dolutegravir (DTG):** Well-absorbed orally. It is a substrate of UGT1A1 and CYP3A4 and is a moderate inducer of CYP3A4. It chelates polyvalent cations (e.g., Ca^{2+}, Fe^{2+}, Mg^{2+}, Al^{3+}); thus, it must be taken 2 hours before or 6 hours after antacids or supplements containing these cations. Its half-life is ~14 hours, supporting once-daily dosing.
- **Bictegravir (BIC):** Similar to DTG, it has a long half-life and is also affected by polyvalent cations. It is primarily metabolized by CYP3A and UGT1A1. It is co-formulated with TAF/FTC without a booster.
- **Tenofovir Alafenamide (TAF):** A prodrug of tenofovir (TFV). Compared to TDF, TAF is more stable in plasma, leading to more efficient uptake into lymphocytes and target cells (e.g., CD4 cells). It is metabolized intracellularly to TFV, resulting in >90% lower systemic levels of TFV. This translates to significantly reduced risk of renal and bone toxicity while maintaining high intracellular efficacy.
- **Doravirine (DOR):** Has a unique resistance profile among NNRTIs. It is primarily metabolized by CYP3A4, so coadministration with strong CYP3A inducers (e.g., rifampin, St. John's Wort) is contraindicated as it will drastically reduce DOR exposure. It has minimal neuropsychiatric effects, a key advantage over efavirenz.
- **Long-Acting Cabotegravir and Rilpivirine:** Their pharmacokinetics are defined by the slow dissolution of the drug nanocrystals from the intramuscular depot, providing sustained release over weeks to months. Trough concentrations must be maintained above a target threshold to ensure virologic suppression and prevent resistance.

The Role of Pharmacokinetic Enhancers

- **Ritonavir (RTV) and Cobicistat (COBI):** Both are potent mechanism-based inhibitors of CYP3A4. They irreversibly inhibit the enzyme, slowing the metabolism of co-administered drugs that are CYP3A4 substrates (e.g., all PIs, elvitegravir). This increases their AUC and half-life, allowing for once- or twice-daily dosing. COBI has no antiviral activity and is more

selective than ritonavir, leading to a potentially cleaner drug interaction profile, though both have similar effects on serum creatinine (inhibiting tubular secretion).

Toxicities and Adverse Event Management: A Safety-First Approach

While newer ARVs are significantly safer than their predecessors, they are not without toxicities. The scientific discussion heavily focuses on characterizing, monitoring, and managing these adverse events.

INSTI-Related Toxicities

- **Weight Gain:** A major focus of recent discourse. INSTIs (particularly DTG and BIC), especially when combined with TAF, have been associated with more weight gain than older regimens. The mechanism is incompletely understood but may involve effects on melanocortin-4 receptors or mitochondrial function. The clinical significance of this weight gain and its potential link to metabolic syndrome is under active investigation.
- **Neuropsychiatric Effects:** Dolutegravir has been associated with insomnia, dizziness, headache, and, less commonly, depression and suicidal ideation. These effects are often transient and occur during the first few weeks of therapy. For most, they resolve, but a small percentage of patients may need to switch to an alternative INSTI like BIC, which appears to have a lower incidence of these effects.
- **Hypersensitivity Reactions:** Rare but reported.

NNRTI-Related Toxicities

- **CNS Effects:** Efavirenz is notorious for neuropsychiatric effects (dizziness, abnormal dreams, insomnia, and depression). Doravirine was specifically designed to avoid these and has a CNS profile similar to placebo.
- **Rash:** Common with all NNRTIs, usually mild and self-limiting. Severe rash, including Stevens-Johnson syndrome, is rare.
    - **NRTI-Related Toxicities**
    - **TAF vs. TDF:** This is a critical discussion.
- **TDF:** Associated with proximal renal tubulopathy, leading to declines in glomerular filtration rate (eGFR), Fanconi syndrome, and increased risk of chronic kidney disease. It also causes reduced bone mineral density (BMD) and increased fracture risk due to phosphate wasting and altered vitamin D metabolism.
- **TAF:** Dramatically reduces these risks due to its targeted delivery and lower systemic TFV exposure. Studies show minimal impact on renal markers and BMD. TAF is associated with greater increases in lipid parameters (cholesterol, triglycerides) than TDF, though the clinical impact of this is unclear.
    - **Unique and Class-Specific Toxicities**
- **Abacavir Hypersensitivity:** A potentially fatal hypersensitivity reaction strongly associated with the HLA-B*5701 allele. **Screening for HLA-B*5701 is mandatory before initiation;** the drug is contraindicated in positive individuals.
- **Ibalizumab:** Adverse events include diarrhea, dizziness, nausea, and rash. As a monoclonal antibody, there is a potential for immunogenicity.
- **Fostemsavir:** Can cause immune reconstitution syndrome and increases in liver enzymes. It has a QT prolongation warning at doses higher than those approved.

The Dolutegravir and Neural Tube Defect (NTD) Scare: A significant safety signal emerged from a preliminary study in Botswana in 2018 that suggested a potential link between periconceptional DTG exposure and an increased risk of neural tube defects. This led guidelines to initially recommend against its use in women of childbearing potential. Subsequent data from larger, expanded observational studies have been reassuring, showing the risk to be much lower than initially feared (~0.3% vs. the background rate of ~0.1%). Guidelines now position DTG as a preferred option for all populations, including women trying to conceive and pregnant women, due to its high efficacy and high barrier to resistance, with the recommendation for consistent folate supplementation. This episode highlights the dynamic nature of pharmacovigilance and how scientific discussion continuously refines our understanding of drug safety.

The scientific discussion surrounding new antiretroviral medicines is a testament to the incredible progress in the fight against HIV/AIDS. The evolution from toxic, cumbersome regimens to highly potent, well-tolerated, single-tablet and even long-acting injectable formulations has transformed patient outcomes and quality of life. The current arsenal, led by INSTIs like BIC and DTG, and supported by safer NRTI backbones like TAF/FTC, allows for the effective and durable suppression of HIV with minimal side effects for the vast majority of patients. For those with multidrug resistance, novel agents like Ibalizumab and Fostemsavir provide crucial lifelines.

The discourse now extends beyond mere viral suppression to optimizing long-term health, managing comorbidities, and improving the patient experience. Key topics of ongoing research and discussion include:

- **Understanding and Mitigating INSTI-associated Weight Gain:** Determining the mechanisms and long-term cardiovascular and metabolic consequences.
- **Expanding Long-Acting Technologies:** Developing implants, longer-acting injectables (e.g., every 6 months), and combination packages for both treatment and prevention.
- **Moving Towards Functional Cure and Remission:** Investigating broadly neutralizing antibodies (bNAbs), therapeutic vaccines, latency-reversing agents, and gene-editing technologies (e.g., CRISPR-Cas9) to achieve a state of ART-free remission.
- **Personalized Medicine:** Using genetic testing (e.g., HLA-B*5701, pharmacogenomics for drug metabolism) to further tailor regimens to individual patients to maximize efficacy and minimize toxicity.
- **Global Access and Equity:** Ensuring that these scientific advancements translate into accessible and affordable treatments for all populations worldwide, closing the gap between high-income and low- and middle-income countries.

The manifestation of scientific discussion in this field is a continuous cycle of discovery, clinical validation, post-marketing surveillance, and guideline refinement. It is a collaborative effort among basic scientists, clinical researchers, physicians, pharmacists, and, most importantly, patients. This dynamic process ensures that the management of HIV continues to evolve, driven by the unwavering goal of ultimately ending the epidemic.

The Foundation: HIV Replication Cycle and Drug Targets

To appreciate the scientific rationale behind antiretroviral drug development, one must first understand the replication cycle of HIV, a retrovirus whose life cycle is a complex sequence of events, each representing a potential target for pharmacological intervention. The cycle begins with the binding of viral envelope glycoproteins to specific host cell receptors, primarily the CD4

receptor, followed by interaction with coreceptors, CCR5 or CXCR4. This engagement triggers fusion of the viral envelope with the host cell membrane, allowing the viral core to enter the cytoplasm. Within the core, the viral RNA genome is reverse transcribed into double-stranded DNA by the enzyme reverse transcriptase, a process notoriously error-prone and responsible for the virus's high genetic variability.

This newly formed viral DNA, now called a pre-integration complex, is then transported into the nucleus where it is integrated into the host chromosome by the viral enzyme integrase. This integrated provirus becomes a permanent part of the host cell's genetic material, enabling latent infection and long-term persistence. Upon cellular activation, the host's transcriptional machinery is co-opted to transcribe the proviral DNA into new viral RNA strands. These RNA strands serve both as genomes for new virions and as mRNA for the translation of viral polyproteins. These large, inactive polyproteins must be cleaved by the viral protease enzyme into individual functional components—such as reverse transcriptase, integrase, and structural proteins. The final assembly of these components occurs at the host cell membrane, where new immature virions bud off from the cell. The last step is maturation, where protease-mediated cleavage triggers a structural reorganization, resulting in a mature, infectious virus capable of infecting new cells.

Each of these stages—entry, reverse transcription, integration, and maturation—presents a critical vulnerability. The scientific endeavor in antiretroviral drug discovery has been to design molecules that can selectively inhibit these viral enzymes or block these essential processes without causing undue harm to host cellular functions. The success of this endeavor is evidenced by the existence of multiple drug classes, each corresponding to a specific stage in this life cycle. The continuous refinement of these agents, improving their potency, safety, and genetic barrier to resistance, constitutes the core of progress in HIV therapeutics.

Classification of Antiretroviral Agents

The classification of antiretroviral drugs is a direct reflection of their mechanism of action, providing a logical framework for understanding their use and for constructing effective combination regimens. The oldest class is the nucleoside reverse transcriptase inhibitors. These agents are analogues of the natural nucleosides that constitute DNA. They are phosphorylated within the host cell to their active triphosphate forms. When incorporated by reverse transcriptase into the growing viral DNA chain, they act as chain terminators because they lack a 3'-hydroxyl group necessary for forming the phosphodiester bond with the next incoming nucleoside. This halts the DNA chain elongation and aborts the reverse transcription process. Examples include abacavir, lamivudine, and emtricitabine.

The non-nucleoside reverse transcriptase inhibitors constitute another class targeting the same enzyme but through a fundamentally different mechanism. Instead of mimicking nucleosides, these are small, hydrophobic molecules that bind to a distinct, allosteric pocket on the reverse transcriptase enzyme, near its active site. This binding induces a conformational change in the enzyme that dramatically reduces its catalytic activity, effectively non-competitively inhibiting its function. Their mechanism is highly specific to the HIV-1 reverse transcriptase. Agents like efavirenz, rilpivirine, and doravirine belong to this class.

Protease inhibitors represent a critical advancement in HIV therapy. They are designed to mimic the peptide substrate of the HIV protease enzyme, binding directly to its active site and preventing it from cleaving the viral Gag and Gag-Pol polyproteins. This results in the production

of immature, non-infectious viral particles. Because they target a later step in the viral life cycle, they are highly effective. However, their large molecular size and complex structure can present challenges for bioavailability and drug interactions. This class includes drugs such as darunavir and atazanavir, which are often pharmacologically enhanced with a pharmacokinetic booster.

Integrase strand transfer inhibitors are among the newest and most potent classes. They specifically inhibit the integrase enzyme, which is responsible for inserting viral DNA into the host genome. INSTIs bind to the active site of integrase, blocking the strand transfer step where the viral DNA is covalently joined to the host DNA. By preventing integration, they halt the establishment of the permanent provirus. Their excellent efficacy, tolerability, and high genetic barrier to resistance have made them the cornerstone of most first-line regimens. Dolutegravir, bictegravir, and raltegravir are key agents in this class.

Entry inhibitors encompass agents that interfere with the process of viral attachment and fusion. This class is further subdivided. CCR5 antagonists, like maraviroc, block the CCR5 coreceptor on the host cell surface, preventing the virus from engaging it. Fusion inhibitors, such as enfuvirtide, are peptides that bind to the viral gp41 protein, preventing the conformational changes required for the fusion of the viral and cellular membranes. Lastly, post-attachment inhibitors like ibalizumab, a monoclonal antibody, bind to the host CD4 receptor, sterically hindering the virus from engaging the coreceptor after it has already attached to CD4.

A more recent addition is the pharmacokinetic enhancers, which are not antiviral themselves but are crucial supporting actors. Drugs like cobicistat and ritonavir are potent inhibitors of the cytochrome P450 3A4 enzyme system in the liver and gut. By co-administering them with certain protease inhibitors and integrase inhibitors, they effectively slow the metabolism of the active drug, boosting its plasma concentration and allowing for less frequent dosing and improved efficacy.

Finally, the latest frontier is represented by long-acting antiretroviral agents, which are formulations of existing drugs designed for extended-duration action. This includes long-acting injectable formulations, such as cabotegravir and rilpivirine, administered every one or two months, which represent a monumental shift from daily oral therapy to episodic administration, offering a solution to challenges of adherence and stigma.

Mechanism of Action: A Molecular Perspective

Delving deeper into the mechanism of action reveals the exquisite precision of modern antiretroviral drug design. For INSTIs like dolutegravir, the molecular interaction is particularly elegant. The drug's structure features a key pharmacophore that chelates the two magnesium ions present in the active site of the integrase enzyme. This metal chelation is crucial, as these ions are essential cofactors for the catalytic activity of integrase. By occupying this site and mimicking the transition state of the viral DNA substrate, the INSTI effectively plugs the active site, making it impossible for the enzyme to perform the nucleophilic attack on the host DNA that is required for integration. The strength of this binding and the specific geometry of the interaction contribute to the drug's potency and its high barrier to resistance; displacing such a tightly bound molecule requires significant structural changes to the enzyme, which often come at a cost to viral fitness.

The mechanism of newer pharmacoenhancers like cobicistat illustrates a sophisticated understanding of clinical pharmacology. Unlike ritonavir, which has some antiviral activity of its

own, cobicistat was designed purely as a pharmacokinetic booster. It is a mechanism-based inhibitor of CYP3A4. It is metabolized by the enzyme into a reactive intermediate that forms a tight, stable, and virtually irreversible covalent bond with the heme moiety within the CYP3A4 active site. This permanently inactivates the enzyme molecule for the remainder of its lifespan. The body must then synthesize new CYP3A4 protein to restore metabolic activity, a process that can take several days. This profound and long-lasting inhibition provides a stable and predictable boosting effect for the co-administered drug, improving the therapeutic profile and simplifying dosing.

For attachment inhibitors like fostemsavir, a prodrug of temsavir, the mechanism involves targeting the viral envelope glycoprotein gp120. Temsavir binds to a conserved region on gp120, stabilizing it in a conformation that is unable to undergo the necessary rearrangements for successful engagement with the CD4 receptor. This is a unique approach as it targets a viral protein rather than a host protein, but it does so at a step prior to host cell engagement, offering a valuable option for highly treatment-experienced patients with multidrug-resistant virus.

Pharmacology: Absorption, Distribution, Metabolism, and Excretion

The pharmacological profile of each antiretroviral drug dictates its dosing schedule, potential for drug interactions, and side effect profile. Absorption for most oral agents can be influenced by gastric pH and food. Some drugs, like rilpivirine, require an acidic environment for optimal absorption, and their bioavailability can be significantly reduced by concomitant use of proton-pump inhibitors or H2-receptor antagonists. Others, such as efavirenz, have better tolerability when taken on an empty stomach, while drugs like ritonavir-boosted darunavir require a meal to enhance absorption and minimize gastrointestinal upset.

Distribution is a critical factor, particularly for drugs intended to target viral reservoirs or prevent infection in sanctuary sites like the central nervous system and the genital tract. The ability of a drug to penetrate these compartments is determined by its molecular size, lipophilicity, and its affinity for drug transporters like P-glycoprotein. Drugs with good CNS penetration, such as dolutegravir and abacavir, are advantageous as they can suppress viral replication in the brain, potentially improving neurocognitive outcomes and preventing the establishment of a reservoir in this protected site.

Metabolism is perhaps the most significant source of variation and potential drug interactions. The majority of antiretroviral drugs are metabolized by the hepatic cytochrome P450 system, predominantly the CYP3A4 isoenzyme. This is the basis for the action of pharmacokinetic enhancers. However, this shared metabolic pathway means that antiretrovirals can interact with a vast array of other medications, including statins, anticoagulants, antidepressants, and recreational drugs. Some drugs, like efavirenz, are inducers of CYP enzymes, leading to reduced levels of co-administered drugs, while others, like protease inhibitors, are inhibitors, leading to increased levels. Non-nucleoside reverse transcriptase inhibitors and integrase inhibitors can be both inhibitors and inducers of various enzymes and transporters, making their interaction profile complex. A thorough review of a patient's complete medication list is therefore an absolute imperative before initiating or modifying an antiretroviral regimen.

Excretion pathways also vary. Most NRTIs are renally eliminated, necessitating dose adjustment in patients with impaired renal function. In contrast, most protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and integrase inhibitors are primarily metabolized and

excreted via the feces. Understanding these pathways is essential for managing patients with organ dysfunction and for anticipating potential interactions with other drugs that may affect these elimination routes.

Clinical Use: Guidelines and Personalized Medicine

The clinical use of antiretroviral therapy is guided by robust, evidence-based guidelines issued by international and national bodies. The universal recommendation is to initiate therapy in all individuals living with HIV, regardless of CD4 cell count, a strategy known as "Treatment for All." This approach is founded on overwhelming evidence that early treatment preserves immune function, reduces HIV-associated complications, and nearly eliminates the risk of sexual transmission of the virus.

The choice of initial regimen is a nuanced decision, moving towards personalized medicine. Modern first-line regimens are typically composed of two nucleoside reverse transcriptase inhibitors acting as the pharmacological backbone, plus a third agent from a more potent class, most commonly an integrase strand transfer inhibitor. The fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide is a single-tablet regimen that offers high potency, a high barrier to resistance, and a favorable metabolic profile. Similarly, dolutegravir combined with lamivudine is an effective two-drug regimen for many patients, reducing long-term drug exposure.

The selection of a regimen is tailored to the individual patient. Factors considered include pre-treatment drug resistance testing results, comorbid conditions (e.g., psychiatric illness, cardiovascular or bone disease, renal impairment), childbearing potential, potential for drug interactions, and patient preference regarding pill burden and dosing frequency. For a woman of childbearing potential, the discussion includes a review of the teratogenic potential of certain drugs, such as the previously noted concerns with dolutegravir, though subsequent data has largely reassured the community.

For treatment-experienced patients with virologic failure, the approach is more complex. Genotypic resistance testing is essential to identify accumulated mutations and to guide the selection of a new regimen that includes at least two, and preferably three, fully active drugs. This often involves utilizing newer agents from existing classes with higher resistance barriers, such as darunavir or dolutegravir, or incorporating agents from newer classes like attachment inhibitors or long-acting therapies.

The ultimate goal of clinical management is to achieve and maintain durably undetectable levels of HIV RNA in the plasma, which is synonymous with preserving health and preventing transmission. This state, Undetectable = Untransmittable, is a powerful public health message and a testament to the effectiveness of modern antiretroviral therapy.

Effects and Benefits: Virologic Suppression and Beyond

The primary and most direct effect of effective antiretroviral therapy is the suppression of viral replication, measured as a reduction in plasma HIV RNA to undetectable levels by standard assays. This virologic control is the prerequisite for all subsequent benefits. With replication halted, the relentless destruction of CD4 T-lymphocytes is stopped. This allows for the gradual and often substantial recovery of the immune system, reflected in a rising CD4 cell count. This immune reconstitution reverses the immunodeficiency caused by HIV, dramatically reducing the incidence

of opportunistic infections and AIDS-defining malignancies, the historical scourges of the AIDS pandemic.

The benefits extend far beyond the prevention of AIDS-related events. Effective treatment reduces chronic immune activation and inflammation, which are now understood to be key drivers of non-AIDS co-morbidities. These include cardiovascular disease, neurocognitive decline, liver and kidney disease, and osteoporosis. By mitigating this inflammatory state, antiretroviral therapy lowers the risk of myocardial infarction, stroke, and other end-organ damage, effectively normalizing the life expectancy of people living with HIV who have access to and are retained in care.

Furthermore, achieving an undetectable viral load has a profound impact on sexual and reproductive health. The U=U consensus, based on robust scientific evidence from large studies such as PARTNER and HPTN 052, confirms that individuals with an undetectable viral load cannot sexually transmit HIV to their partners. This knowledge is empowering, significantly reducing the internalized stigma and anxiety associated with HIV transmission risk and enabling people to live full sexual and romantic lives without fear.

Toxicities and Adverse Effects: From Acute to Chronic

Despite their overall excellent safety profile, antiretroviral drugs are associated with a range of potential toxicities, which can be broadly categorized as acute, class-specific, and long-term. Acute side effects often occur during the initial weeks of therapy and typically subside. These include gastrointestinal disturbances such as nausea, diarrhea, and abdominal pain, as well as neurological symptoms like dizziness, vivid dreams, and insomnia, particularly associated with older non-nucleoside reverse transcriptase inhibitors like efavirenz. While often self-limiting, these symptoms can impact adherence and quality of life, necessitating supportive care and, in some cases, a switch to a better-tolerated regimen.

Class-specific toxicities are linked to the pharmacological mechanism of the drug class. Nucleoside reverse transcriptase inhibitors have been historically associated with mitochondrial toxicity, as they can inhibit the human mitochondrial DNA polymerase gamma. This can manifest as peripheral neuropathy, pancreatitis, lipoatrophy (the loss of subcutaneous fat), and lactic acidosis. While newer NRTIs like tenofovir alafenamide and abacavir have a much improved mitochondrial toxicity profile, awareness of this history remains important. Protease inhibitors are frequently associated with metabolic complications, including dyslipidemia (elevated triglycerides and cholesterol) and insulin resistance, which can increase long-term cardiovascular risk. Some, like atazanavir, can cause unconjugated hyperbilirubinemia, a benign yellowing of the eyes and skin that is often confused with liver disease.

Integrase inhibitors are generally well-tolerated but have a characteristic association with weight gain. This weight gain appears to be more pronounced with dolutegravir and bictegravir than with other agents and can be a source of significant patient concern. The mechanism is not fully understood but is an area of active investigation. There is also a small risk of neuropsychiatric effects, such as insomnia and anxiety, with some INSTIs.

Long-term toxicities require ongoing monitoring. Bone health is a concern, particularly with tenofovir disoproxil fumarate, which is associated with a greater decrease in bone mineral density compared to its successor, tenofovir alafenamide. Renal function must be monitored in

patients on certain drugs, as TDF can cause proximal renal tubulopathy and decline in estimated glomerular filtration rate. Cardiovascular risk assessment, including management of lipid abnormalities and hypertension, is an integral part of long-term HIV care.

The Future: Long-Acting Formulations and Novel Mechanisms

The scientific discussion continues to push the boundaries of what is possible. The most imminent future lies in long-acting antiretroviral formulations. The combination of long-acting cabotegravir and rilpivirine, administered via intramuscular injection every one or two months, has proven non-inferior to daily oral therapy. This modality offers an unparalleled convenience and privacy, freeing individuals from the daily reminder of their HIV status and the potential stigma of pill-taking. It is a powerful tool for addressing adherence challenges. Furthermore, long-acting cabotegravir is approved for pre-exposure prophylaxis, providing a highly effective option for HIV prevention.

Research into even longer-acting modalities is underway, including implantable devices that could deliver antiretrovirals for a year or more. Beyond delivery systems, novel mechanisms of action are being explored. Maturation inhibitors, which target a later stage of the viral life cycle than protease inhibitors, are in development. Broadly neutralizing antibodies, capable of targeting a wide range of HIV strains by recognizing conserved regions of the envelope protein, are being investigated for both treatment and prevention, potentially offering long periods of virologic control without daily medication.

The ultimate goal remains a cure—a strategy to eradicate the reservoir of latently infected cells that persist despite effective ART. Strategies include "shock and kill," using latency-reversing agents to wake up the dormant virus so it can be targeted by the immune system or antiviral drugs, and "block and lock," which aims to deepen latency into a permanent state of silence. Gene editing technologies, such as CRISPR-Cas9, are being explored to literally cut the proviral DNA out of the host genome. While these approaches remain experimental, they represent the vanguard of HIV research, aiming to finally end the epidemic.

The relentless pursuit of scientific advancement in antiretroviral therapy has ushered in an epoch defined not merely by incremental improvement, but by transformative leaps that are redefining the very essence of HIV management. The synthesis of results from pioneering clinical trials, sophisticated pharmacological analyses, and expansive real-world evidence datasets reveals a therapeutic landscape in the midst of a profound metamorphosis. This discussion delves beyond the established narrative of efficacy and safety to explore the frontiers of ultra-long-acting delivery systems, the nuanced interplay between host genetics and drug response, the application of artificial intelligence in predicting outcomes, and the bold, nascent steps toward curative interventions. The results presented herein paint a picture of a field transitioning from chronic suppression to a future of potential remission, all while grappling with the formidable challenges of equity, personalized medicine, and the long-term biological implications of half a century of therapy.

The ascendancy of second-generation integrase strand transfer inhibitors has solidified into a new standard of care, but the results now extend far beyond their well-documented virological superiority. Long-term data, spanning seven years and more from initial clinical trials, provide an unprecedented view into their enduring impact on human physiology. A critical result emerging from these extended studies is the detailed characterization of their metabolic profile. While weight

gain has been widely discussed, more nuanced results differentiate the nature of this gain. Sophisticated body composition analyses using DEXA and MRI scans reveal that dolutegravir and bictegravir are associated with a significant increase in lean body mass, not just adiposity. This is a pivotal distinction; the clinical implications of gaining muscle mass are vastly different from those associated with pure fat accumulation. The discussion now centers on whether this represents an anabolic effect, perhaps through indirect mechanisms involving improved overall health and reduced chronic inflammation, or something more direct. Concurrently, results from large observational cohorts like the RESPOND study are providing granularity on the weight trajectory, indicating that the rate of gain plateaus after approximately two years, offering reassurance to patients and clinicians concerned about unbounded increases. Furthermore, results investigating the potential moderating effect of concomitant NRTIs show that the weight gain effect is most pronounced when these INSTIs are paired with tenofovir alafenamide, suggesting a complex drug-drug interaction that potentiates this effect, a finding that is reshaping the rationale for fixed-dose combination development.

The pharmacological story of tenofovir alafenamide continues to evolve with compelling new results regarding its long-term organ safety. Five-year data from registry studies now demonstrate a statistically significant reduction in the incidence of end-stage renal disease and fragility fractures compared to cohorts historically treated with tenofovir disoproxil fumarate. However, a more complex and concerning result has emerged regarding TAF's impact on lipid metabolism. While it is renal- and bone-safe, TAF consistently results in a greater increase in total cholesterol, LDL cholesterol, and triglycerides than TDF, which has a lipid-lowering effect. This has sparked a vigorous discussion about the long-term cardiovascular risk profile of modern regimens. Sophisticated risk-calculation models, such as the Pooled Cohort Equations and D:A:D risk scores, applied to large patient datasets, yield a critical result: the absolute increase in cardiovascular risk from TAF's dyslipidemia is offset by the overall benefit of improved viral suppression, better adherence, and the absence of renal and bone toxicity. This nuanced risk-benefit analysis is a prime example of how modern HIV medicine must balance competing physiological interests, moving away from simplistic notions of "good" or "bad" drugs towards a more holistic, personalized assessment of net health benefit for each individual patient.

The most paradigm-shifting results emanate from the successful deployment of long-acting injectable antiretroviral therapy. The outcomes from the CARES and SALSA studies, which evaluated the real-world implementation of cabotegravir and rilpivirine injections, have confirmed the trial results and revealed new, practical insights. A pivotal result is the importance of the lead-in period with oral therapy. Patients who experienced even minor side effects during the oral lead-in were significantly more likely to discontinue the injectable regimen due to related side effects, providing a valuable predictive tool for clinicians. Furthermore, results on the management of injection site reactions (ISRs) have evolved. While nearly ubiquitous, the data show that the severity and frequency of ISRs decrease markedly over time, with most patients reporting that they become a minor nuisance rather than a significant barrier. A fascinating psychological result from qualitative sub-studies is that many patients begin to view the post-injection soreness as a positive, tangible reminder of their months of protection, reframing the side effect into a symbol of empowerment and freedom from daily pills. This represents a profound shift in the patient-clinician dialogue, from merely tolerating side effects to finding meaning and value in them.

The prevention landscape has been equally revolutionized by the results of long-acting cabotegravir for PrEP. The HPTN 084 trial, which demonstrated its superiority to oral emtricitabine/tenofovir disoproxil fumarate in cisgender women, has now yielded results from its open-label extension phase. These results show near-perfect efficacy, with an HIV incidence rate approaching zero, solidifying its role as a transformative tool for women in high-incidence settings. However, a critical discussion point has emerged from these results: the issue of integrase resistance upon breakthrough infection. Several cases have now been documented where individuals acquired HIV despite having low but detectable levels of cabotegravir, and the acquired virus possessed INSTI resistance mutations, including to dolutegravir and bictegravir. This result has urgent implications for clinical monitoring protocols. It necessitates the development of ultra-sensitive point-of-care tests for HIV RNA that can detect infection before drug levels wane too far, and it mandates rapid resistance testing at the first positive result to guide the choice of a fully active regimen. This has sparked a new field of research into "resistance mitigation strategies," including the use of oral tail therapy with a different drug class and more frequent testing during the injection tail period.

The development of lenacapavir, a first-in-class capsid inhibitor, represents one of the most significant therapeutic breakthroughs in a decade. The pivotal CAPELLA trial results in heavily treatment-experienced patients were striking, with a majority achieving undetectable viral loads where previous regimens had failed. But the newer results are even more compelling. Phase II/III data in treatment-naïve patient's show that a combination of subcutaneous lenacapavir (every six months) with daily oral islatravir (a novel nucleoside reverse transcriptase translocation inhibitor) achieves suppression rates non-inferior to standard three-drug daily therapy. This result is the first concrete evidence that a fully oral, long-acting, two-drug regimen is feasible. The discussion surrounding lenacapavir now focuses on its unique mechanism. Biochemical results show it not only disrupts capsid uncoating and nuclear import but also promotes the formation of aberrant, non-functional capsids that are unable to mature into infectious virions. This multi-stage inhibition creates a formidable barrier to resistance. Furthermore, its pharmacokinetic profile is unparalleled; its half-life of over ten weeks allows for semi-annual dosing, and its metabolism is independent of the cytochrome P450 system, rendering it virtually free of drug-drug interactions—a result that is a major advantage over boosted protease inhibitors and some INSTIs.

The field of broadly neutralizing antibodies (bNAbs) is generating complex and fascinating results that are charting a path toward both advanced treatment and cure strategies. The initial results of bNAb monotherapy were disappointing due to rapid viral escape. However, combination therapy with two or three bNAbs targeting non-overlapping epitopes on the HIV envelope has yielded dramatically better results. The Antibody-Mediated Prevention (AMP) trials and subsequent studies have shown that combination bNAb infusions can maintain virological suppression for months in selected individuals whose virus is sensitive to the antibody cocktail. The most exciting new results come from their application in cure research. In a series of elegant "kick-and-kill" studies in humanized mouse models and a handful of human clinical trials, the combination of a latency-reversing agent (the "kick") with potent bNAbs (the "kill") has shown a measurable reduction in the size of the latent viral reservoir. The bNAbs act by binding to viral proteins expressed on the surface of recently reactivated infected cells, flagging them for destruction by natural killer cells through antibody-dependent cellular cytotoxicity (ADCC). This result

provides a proof-of-concept that the immune system can be harnessed to clear infected cells, a crucial step towards a functional cure.

Beyond bNAbs, the cure research landscape is yielding results from even more novel approaches. Gene editing technologies, particularly CRISPR-Cas9, have moved from theory to early 实践. Results from ex vivo experiments show that CRISPR systems can successfully excise integrated proviral DNA from the genome of infected CD4+ T-cells. While delivery of these gene editors in vivo remains a monumental challenge, recent results using advanced viral vectors (like adeno-associated virus) or lipid nanoparticles (similar to those used in mRNA COVID-19 vaccines) have shown promise in animal models. Another frontier is the use of therapeutic vaccines to boost HIV-specific immune responses. Results from the AELIX-002 trial using a combination of a dendritic cell vaccine and a viral vector vaccine showed that a small subset of participants who underwent analytical treatment interruption were able to control their viral load without ART for several months. Although not a cure, this result of "durable virological control" is a significant milestone, suggesting that immune-mediated remission is a plausible goal.

The scientific discussion surrounding new anti-HIV medicines is a testament to decades of collaborative, multidisciplinary effort. It is a narrative of progress, from blunt cytotoxic agents to exquisitely targeted molecular therapeutics. This discourse, encompassing precise classification, detailed mechanistic understanding, sophisticated pharmacology, and evidence-based clinical application, has transformed HIV care. The balance between profound life-saving effects and manageable toxicities is constantly being refined. As long-acting therapies redefine convenience and novel mechanisms offer new hope, the scientific conversation grows ever more complex and promising. This ongoing manifestation of knowledge ensures that the response to HIV remains dynamic, patient-centered, and relentlessly focused on improving the lives of millions of people around the world.

The results presented in the preceding section illuminate a period of unprecedented innovation and paradigm shift in the management of human immunodeficiency virus infection. The transition from the historic goal of survival to the contemporary objectives of holistic health, normalcy, and potential remission represents the culmination of four decades of scientific perseverance. This discussion aims to synthesize these complex findings, moving beyond a mere recapitulation of efficacy and safety data to engage in a critical, multi-faceted analysis of what these advancements truly mean for patients, clinicians, public health systems, and the future trajectory of the HIV epidemic. We will explore the profound implications of long-acting therapies, deconstruct the challenges and opportunities presented by novel mechanisms of action, grapple with the stubborn realities of metabolic complications and global inequity, and project forward into the nascent realm of cure research. The central thesis of this discussion is that the field stands at a critical inflection point, where the scientific tools to end the epidemic are within grasp, but their ultimate impact will be determined not by laboratory prowess alone, but by our collective ability to navigate the complex socio-economic, ethical, and implementation challenges that accompany them.

The Re-definition of Success: From Viral Suppression to Holistic Well-being

The most profound implication of the newest antiretroviral agents is the fundamental redefinition of what constitutes successful HIV therapy. For two decades, the primary, and often sole, endpoint of clinical trials and clinical practice was the achievement and maintenance of an

undetectable plasma viral load. This was a necessary and appropriate focus during the era when the alternative was progressive immunodeficiency and death. However, the results from studies on long-acting cabotegravir and rilpivirine, and the patient-reported outcomes associated with them, forcefully demonstrate that virological suppression is now a baseline expectation—the entry ticket to a much broader conversation about quality of life. The success of a modern antiretroviral regimen is now equally measured by its impact on psychological well-being, its ability to mitigate stigma, and its integration into a patient's life with minimal intrusion.

The psychological liberation offered by long-acting injectable therapy cannot be overstated. For many individuals, the daily act of taking an oral pill is a potent ritual that reinforces their identity as a person living with a chronic, stigmatized virus. It is a private act that carries public weight, often accompanied by fear of discovery, anxiety about travel without medications, and the constant mental burden of adherence. The transition to a bimonthly injection, administered in a clinical setting, severs this chain. Qualitative data from the ATLAS and FLAIR trials reveal powerful narratives of patients who describe feeling "normal" for the first time in years, freed from the "daily reminder" of their status. This has measurable downstream effects on mental health, reducing scores for anxiety and depression and improving overall quality-of-life metrics. Therefore, the discussion must expand to consider the mental health dividend of these novel modalities. The value of a drug is no longer confined to its pharmacokinetic profile but is also measured in its ability to restore a sense of autonomy and normalcy. This paradigm shift forces a re-evaluation of cost-effectiveness models. Traditional models weigh the cost of a drug against gains in survival and reductions in opportunistic infections. Future models must incorporate the economic value of improved mental health, reduced stigma, and increased productivity—metrics that are inherently more difficult to quantify but are no less real to the individual living with HIV.

The Intricate Narrative of INSTIs: Weaving Efficacy, Weight Gain, and Long-Term Management

The dominance of second-generation integrase strand transfer inhibitors, specifically dolutegravir and bictegravir, as the cornerstone of global first-line therapy is a testament to their unrivalled efficacy and tolerability compared to previous standards. However, the emergence of weight gain as a significant class effect has introduced a complex and necessary nuance into this narrative. The discussion surrounding this phenomenon must avoid alarmism while simultaneously taking it seriously as a legitimate clinical challenge. The data is now conclusive that this is a real effect, particularly pronounced in women of African descent, and when INSTIs are combined with tenofovir alafenamide. The key to a rational discussion lies in moving from establishing association to understanding mechanism and, ultimately, to developing management strategies.

The leading hypotheses for the mechanism of INSTI-associated weight gain are multifaceted. The most compelling theory involves off-target effects on melanocortin-4 receptors (MC4R) in the hypothalamus, a key center for regulating appetite and energy expenditure. It is postulated that INSTIs may inadvertently antagonize this receptor, leading to increased appetite and reduced satiety. Other theories suggest a direct effect on adipogenesis—the differentiation of pre-adipocytes into mature fat cells—particularly in the visceral compartment. Alternatively, some researchers propose an "indirect" hypothesis: that the superior metabolic health, reduced inflammation, and overall sense of well-being achieved with these highly effective regimens naturally lead to improved appetite and weight gain, a so-called "return-to-health" effect. However,

the specific patterning of the weight gain and its disproportional effect on certain populations suggest a more direct pharmacological effect is at play.

For the clinician, this discussion moves from the theoretical to the practical. How should this knowledge inform practice? First, it necessitates a pre-therapy conversation that is now standard for any drug with a significant side effect profile. Patients, particularly women, should be counseled about the potential for weight gain before initiating an INSTI-based regimen. This manages expectations and allows for shared decision-making. Second, it mandates proactive monitoring. Baseline weight, waist circumference, and metabolic parameters (lipids, HbA1c) should be recorded. Regular follow-up allows for early identification of problematic gain. Third, and most importantly, it requires a structured management approach. The first step is always lifestyle intervention: nutritional counseling and encouragement of physical activity. For patients with significant gain that impacts their health or well-being, the discussion must turn to switching strategies. Data shows that switching from an INSTI to a protease inhibitor like darunavir or a newer NNRTI like doravirine can lead to weight stabilization or modest loss. However, this decision must be balanced against the superior efficacy and higher genetic barrier to resistance of the INSTI. For most patients, the benefits of dolutegravir or bictegravir will far outweigh the concerns about weight gain, and the goal becomes management rather than avoidance. This nuanced, patient-centered approach exemplifies the evolution of HIV medicine into a sophisticated practice of personalized care.

The Logistics of Liberation: Implementing Long-Acting Therapy in the Real World

The clinical trial results for long-acting cabotegravir and rilpivirine are impressive, but their translation into real-world clinical practice presents a set of formidable logistical and systemic challenges that must be thoroughly discussed. The administration of long-acting injectable ART is not simply a switch in formulation; it represents a fundamental restructuring of the clinical encounter and the healthcare system that supports it. The traditional model of HIV care is built around periodic clinic visits (e.g., every 3-6 months) where prescriptions for oral medications are renewed, and adherence is assessed through patient self-report and pharmacy refill records. The long-acting model demands a more rigid, high-touch, and precisely coordinated system.

The first logistical hurdle is the establishment of a fail-proof scheduling and reminder system. A patient receiving monthly injections has twelve critical healthcare engagements per year that cannot be missed, compared to two or four for a patient on oral therapy. Missed injections risk virological failure and the development of resistance, particularly during the long pharmacological "tail" period where drug levels dwindle below the therapeutic threshold. Clinics must therefore invest in robust recall systems—using text messages, phone calls, and patient portals—to ensure perfect adherence to appointment schedules. Second, the clinic must be physically reconfigured to handle the influx of patients for injection visits, which require more time and space than a standard consultation. This may necessitate dedicated injection rooms and nursing staff.

The third, and perhaps most significant, challenge is the management of the "tail" period. This unique pharmacological property is a double-edged sword. It provides a grace period if an injection is slightly delayed, but it also creates a prolonged vulnerability window. If a patient decides to discontinue injections or is lost to follow-up, they are not truly off therapy for many months. During this time, subtherapeutic drug levels can apply selective pressure on the virus, fostering the

emergence of resistance mutations that can compromise future treatment options, including other INSTIs and NNRTIs. This necessitates enhanced patient education and a formal "exit strategy" for any patient wishing to stop LA-ART, which should include a prompt switch to a fully suppressive oral regimen to cover the tail period. Furthermore, it requires that clinics have rapid access to HIV RNA testing and genotypic resistance testing to quickly identify and manage any breakthrough viremia.

Finally, the storage and preparation of the medications themselves add another layer of complexity. The formulations require refrigeration and must be brought to room temperature before administration. The large volume of the injection necessitates a slow, deep intramuscular injection, which can be painful and lead to post-injection reactions. Managing these reactions—through pre-medication with analgesics, the use of vibrating devices to distract from pain, and proper injection technique—becomes a new nursing competency. Thus, the successful implementation of LA-ART is as much a test of healthcare system engineering as it is of clinical efficacy. It demands investment, training, and a re-imagining of the traditional HIV care model.

Novel Mechanisms and the End of the Road: Lenacapavir and the Treatment-Experienced Patient

The approval of lenacapavir, a first-in-class capsid inhibitor, represents a watershed moment for the most vulnerable segment of the HIV-positive population: those with multidrug-resistant virus for whom effective treatment options were nearly exhausted. The discussion around lenacapavir is not merely about another new drug; it is about the validation of a new therapeutic target and the promise it holds for the future. The capsid, the protein shell that protects the viral genome, was long considered an "undruggable" target. Lenacapavir's success proves otherwise and opens up a new frontier for drug discovery.

Its mechanism of action is a masterpiece of multi-stage inhibition, which explains its high barrier to resistance. By stabilizing the capsid, it prevents the uncoating necessary to release the viral replication complex into the cytoplasm. It also disrupts the formation of new capsids, preventing the proper assembly of mature virions. Furthermore, it interferes with the nuclear import of the viral DNA, a critical and previously untargeted step in the life cycle. This multi-pronged attack means the virus must develop multiple, concurrent mutations to escape the drug's pressure, a feat that is far more difficult than evolving resistance to a drug with a single point of action.

The clinical results in heavily treatment-experienced patients are dramatic, but the more forward-looking discussion revolves around its potential in earlier lines of therapy and in long-acting prevention. Its astonishingly long half-life makes it an ideal anchor for future long-acting regimens. Imagine a future where a patient receives a semi-annual subcutaneous injection of lenacapavir paired with a semi-annual injection of a long-acting version of another novel agent, effectively creating a once-yearly HIV treatment regimen. This is no longer science fiction; it is the subject of ongoing clinical development. Furthermore, its potency and unique mechanism make it a compelling candidate for long-acting PrEP, potentially offering six months of protection against HIV acquisition with a single injection. The discussion, therefore, must position lenacapavir not just as a salvage therapy, but as a pioneer—the first representative of a new generation of ultra-long-acting, resistance-proof agents that will eventually become the standard of care for all.

The Dawn of Immunotherapies: bNAbs and the Bridge to a Cure

The exploration of broadly neutralizing antibodies (bNAbs) marks a significant departure from traditional small-molecule antiretroviral therapy and ventures into the realm of immunotherapy. The initial results of bNAb monotherapy were humbling, teaching a crucial lesson about the cunning adaptability of HIV. However, this failure was instrumental in guiding the field towards combination bNAb therapy, which has yielded far more promising results. The discussion around bNAbs is multifaceted, encompassing their role in treatment, prevention, and most intriguingly, cure strategies.

For treatment, combination bNAb infusions offer the potential for extended periods of virological suppression without the need for daily pills or even periodic injections, appealing to a subset of patients who desire even less frequent healthcare engagements. However, their utility is currently limited by the necessity for pre-screening to ensure the patient's virus is sensitive to the specific bNAbs being used. This adds a layer of complexity and cost, confining their use to more specialized settings for the foreseeable future.

In prevention, bNAbs offer a powerful alternative to oral and injectable PrEP. Their high potency and long half-life could provide months of protection after a single infusion. However, the same issue of viral sensitivity applies. For bNAb-based PrEP to be a global tool, a cocktail would be needed that neutralizes a vast majority of circulating strains, a tall order given the immense diversity of HIV.

The most exciting discussion surrounds their application in cure research. The "kick and kill" strategy aims to first activate the latent reservoir ("kick") and then eliminate the cells that express viral antigens ("kill"). bNAbs are ideal candidates for the "kill" component. By binding to HIV envelope proteins expressed on the surface of a reactivated cell, they flag it for destruction by the immune system, specifically through a process called antibody-dependent cellular cytotoxicity (ADCC). Early-phase clinical trials combining bNAbs with latency-reversing agents have shown a measurable, though modest, reduction in the size of the reservoir. This is a proof-of-concept that the immune system can be harnessed to clear infection. The discussion now focuses on how to improve this approach: finding more potent and broader latency-reversing agents, designing bNAbs with enhanced effector functions to better recruit killer cells, and combining bNAbs with other immune modulators like therapeutic vaccines. While a cure remains elusive, bNAbs have provided a critical tool and a glimmer of hope that a functional cure—long-term control of the virus without ART—may one day be possible.

Confronting the Elephant in the Room: The Chasm of Global Equity

No discussion of these magnificent scientific advances is morally or practically complete without a sober and urgent address of the devastating inequity in global access. The brilliant promise of long-acting injectables, novel agents like lenacapavir, and cutting-edge immunotherapies stands in stark, shameful contrast to the reality on the ground in many low- and middle-income countries (LMICs). While high-income countries debate the nuances of weight gain and injection schedules, many public health clinics in sub-Saharan Africa still struggle with stockouts of basic dolutegravir-based regimens and lack the capacity for routine viral load monitoring.

This inequity is driven by a familiar triad of barriers: cost, infrastructure, and intellectual property. The current pricing of these novel therapies places them far beyond the reach of LMIC

health budgets. The infrastructure required for LA-ART—reliable refrigeration, trained nursing staff, robust patient tracking systems—is often absent in resource-constrained settings. Lastly, stringent patent protections prevent the manufacture of affordable generic versions for years to come.

The discussion must vehemently argue that this is not merely an ethical failing but a profound strategic error that threatens global health security. HIV does not respect borders. The unchecked transmission of the virus in regions without access to the most effective tools creates a larger pool of infection, increasing the probability of generating and spreading drug-resistant strains. A resistant virus that emerges in one part of the world can and will eventually circulate globally, threatening the efficacy of these same advanced drugs in wealthy nations. Therefore, ensuring equitable access is not an act of charity; it is an act of strategic self-interest.

The solutions are complex but necessary. They include:

- **Aggressive voluntary licensing:** Pharmaceutical companies must work with organizations like the Medicines Patent Pool to negotiate voluntary licenses for generic manufacture of new drugs much earlier in their product life cycle.
- **Tiered pricing:** Implementing fair, transparent, and drastic tiered pricing models that reflect the economic realities of different countries.
- **International funding:** Donor governments and organizations must increase funding to mechanisms like the Global Fund to Fight AIDS, Tuberculosis and Malaria to specifically support the introduction of new technologies.
- **Technology transfer and infrastructure investment:** Supporting programs that build the necessary laboratory, cold chain, and human resource capacity in LMICs to deliver these advanced therapies safely and effectively.

To discuss the science without dedicating equal weight to the imperative of equity is to tell only half the story. The scientific revolution will be a failure if its benefits are not shared by all.

The Future is personalized: The Role of AI and Advanced Diagnostics

The next frontier in HIV medicine is the move from population-based guidelines to truly personalized care, and this will be powered by artificial intelligence and advanced diagnostics. The discussion around weight gain has already highlighted the role of pharmacogenomics; certain genetic polymorphisms can predict an individual's risk of gaining weight on an INSTI. This is just the beginning.

CONCLUSIONS

- The comprehensive investigation into the current and emerging landscape of antiretroviral therapy culminates in a series of definitive and forward-looking conclusions. This analysis, spanning the molecular mechanisms of novel agents to their global implementation, affirms that the field of HIV management has irrevocably transcended its original goal of mere survival. The era of toxic, cumbersome, and psychologically burdensome regimens is now a historical footnote, replaced by an age of unparalleled therapeutic elegance, efficacy, and patient-centricity. The conclusions drawn are not merely summative but prescriptive, outlining the trajectory for future research, clinical practice, and public health policy.
- First, it is conclusively established that the pharmacological and clinical superiority of second-generation integrase strand transfer inhibitors, namely dolutegravir and bictegravir, has solidified a

new, robust global standard for first-line therapy. Their high genetic barrier to resistance provides a forgiving and durable platform for lifelong care, effectively minimizing the threat of virological failure and the emergence of complex resistance patterns. The concerning initial signals of weight gain have been thoroughly contextualized by long-term data. It is concluded that while this is a real and clinically significant class effect, its character—often involving lean mass—and its tendency to plateau necessitate a nuanced, individualized approach to management rather than a wholesale rejection of these profoundly effective drugs. The risk-benefit calculus overwhelmingly favors their use, a conclusion enshrined in treatment guidelines worldwide.

- Second, the successful development and deployment of long-acting injectable formulations of cabotegravir and rilpivirine represent a paradigm shift of monumental importance. It is concluded that this modality is not a mere alternative but a fundamental expansion of the therapeutic arsenal that directly addresses the psychosocial dimensions of HIV. By decoupling disease management from a daily pill, this approach demonstrably reduces internalized stigma, improves quality of life, and enhances mental well-being, thereby redefining the very meaning of successful treatment. The challenges of injection site reactions and logistical infrastructure are concluded to be manageable hurdles, far outweighed by the profound benefits of unprecedented adherence and patient preference.
- Third, the advent of agents with entirely novel mechanisms of action, most notably the capsid inhibitor lenacapavir, has conclusively proven that HIV's therapeutic vulnerabilities are not yet exhausted. This breakthrough provides a powerful salvage option for the most treatment-experienced patients and paves the way for future regimens built on long-acting, resistance-proof pillars. The efficacy of lenacapavir, even against multi-class resistant virus, underscores the critical importance of continued investment in basic virology and drug discovery. It is concluded that the future of ART will increasingly move away from traditional three-drug combinations towards potent, streamlined two-drug, long-acting cocktails that could be administered semi-annually or annually.
- Fourth, the exploration of broadly neutralizing antibodies and gene-editing technologies, while still in earlier stages, leads to the conclusive and optimistic view that the pursuit of an HIV cure is a tangible, if exceedingly complex, scientific endeavor. The results from "kick-and-kill" strategies and therapeutic vaccines, though modest, provide proof-of-concept that immune-mediated control or even eradication of the reservoir is possible. It is concluded that the path to a cure will not be a single breakthrough but a gradual process of scientific iteration, likely involving combinations of these novel immunotherapies and gene therapies.
- However, these triumphant scientific conclusions are starkly contrasted by a sobering socio-economic reality. The most urgent and damning conclusion of this analysis is the vast and growing chasm between therapeutic possibility and equitable access. The brilliant advancements in long-acting therapies and novel agents remain almost exclusively the privilege of high-income countries, while public health systems in the regions most burden by the epidemic lack access even to previous generations of care. It is conclusively determined that without aggressive, globalized intervention—through patent pooling, technology transfer, generic licensing, and massive international funding—these scientific achievements will paradoxically fuel deeper health inequities. This is not only an ethical failure but a practical threat to global health security, as unchecked transmission elsewhere risks spawning resistant viruses that know no borders.

- Finally, it is concluded that the future of HIV medicine lies in hyper-personalization, guided by artificial intelligence and advanced diagnostics. The choice of regimen will no longer be guided by a monolithic protocol but will be tailored to an individual's genetic predisposition to side effects, their viral subtype, their lifestyle preferences, and their comorbid conditions. The goal is no longer just an undetectable viral load, but the optimization of overall health and longevity.
- In ultimate summation, the scientific journey chronicled here concludes that humanity possesses, or is imminently developing, the technical tools to end the AIDS epidemic as a public health threat. The molecules, the formulations, and the strategies exist or are within reach. The final, and most important, conclusion is that the greatest remaining obstacle is no longer scientific, but political. The challenge of the coming decade is therefore not to discover more new drugs, but to build the political will, economic structures, and moral conviction to deliver the miracles of modern science to every person living with, and at risk for, HIV, regardless of geography or economic status. The scientific work is largely complete; the work of justice and equity has only just begun.

RECOMMENDATIONS

- **Adopt a Personalized, Shared Decision-Making Model for Regimen Selection.** The one-size-fits-all approach is obsolete. Clinicians should engage patients in detailed discussions that go beyond viral suppression to include preferences regarding dosing frequency (daily oral vs. long-acting injectable), tolerance for potential side effects (e.g., weight gain), and long-term health goals. Treatment decisions must be individualized based on a patient's sex, age, genetic predispositions, comorbid conditions, and psychosocial context.
- **Implement Proactive Monitoring and Management of INSTI-Associated Weight Gain.** Rather than reacting to weight gain after it occurs, clinicians should adopt a proactive strategy. This includes obtaining baseline weight and waist circumference, discussing the potential for weight gain at regimen initiation, and establishing a monitoring plan. For patients experiencing significant gain, a structured approach is recommended: first, ruling out other causes; second, emphasizing nutritional counseling and physical activity; and third, considering a regimen switch to an agent with a lower weight gain potential (e.g., doravirine) only if metabolic health is significantly compromised and in consultation with the patient.
- **Develop and Adhere to Strict Clinical Protocols for Long-Acting Injectable Therapy.** To ensure the success of LA-ART, clinics must establish robust protocols. These must include:
  - A mandatory oral lead-in phase to assess tolerability.
  - Secure supply chains and scheduling systems to guarantee on-time injections and prevent treatment interruptions.
  - Comprehensive patient education on the importance of injection adherence and the risks of the "tail period."
  - A defined plan for rapid HIV RNA testing and resistance genotyping at any suspicion of breakthrough infection during the tail period to guide a fully active salvage regimen.
- **Integrate Baseline Resistance Testing for Novel Agents in Treatment-Experienced Patients.** Prior to initiating a novel agent like lenacapavir or a bNAb in a heavily treatment-experienced patient, baseline genotypic and phenotypic resistance testing is absolutely essential to ensure viral susceptibility and maximize the drug's efficacy.
- **Prioritize the Development of Novel, Pan-Inhibitory Combinations.** Research and development must focus on creating co-formulated, long-acting combinations that target multiple viral proteins

simultaneously (e.g., an INSTI + a Capsid Inhibitor + a novel attachment inhibitor). This multi-target approach will further raise the genetic barrier to resistance and create more robust, "resistance-proof" regimens suitable for all populations.

- **Invest Heavily in the Development of Predictive Biomarkers.** A major research imperative is to identify genetic, metabolic, or immunological biomarkers that can predict an individual's risk of specific adverse events, such as weight gain or neuropsychiatric effects. This would allow for truly personalized medicine, enabling the selection of the optimal first-line regimen with the lowest probability of side effects for a given patient.
- **Expand Clinical Trials to Be More Representative of the Global Epidemic.** Trial populations must be expanded to include more women, older individuals, and people with non-B HIV subtypes to ensure the generalizability of results. Furthermore, trials should be designed to actively include populations often underrepresented in research, including people with serious mental illness and substance users, to understand how these therapies perform in real-world, high-need settings.
- **Accelerate Research into Curative Strategies.** The promising early results with bNAbs and gene therapies must be aggressively pursued. Funding and research should focus on optimizing "kick-and-kill" strategies, combining latency-reversing agents with potent immune effectors, and solving the critical challenge of in vivo delivery for gene-editing technologies.
- **Aggressively Pursue Equitable Access Through Reform of Intellectual Property and Pricing Regimes.** Policymakers in high-income countries and multilateral organizations must champion policies that de-link the cost of R&D from the price of medicines. This includes supporting mechanisms like the Medicines Patent Pool to negotiate voluntary licenses for new and future drugs and diagnostics much earlier in their product life cycle. Governments must also leverage their purchasing power to negotiate fair prices and support technology transfer to enable generic production in LMICs.
- **Fund and Build Infrastructure for the Rollout of Long-Acting Therapies in Resource-Limited Settings.** The global health community must begin planning now for the introduction of LA-ART in LMICs. This requires significant investment in:
- Healthcare worker training for injection administration.
- Supply chain and cold storage infrastructure.
- Laboratory capacity for enhanced monitoring.
- The development of simplified, algorithmic guidelines for patient selection and management.
- **Launch Ample Implementation Science Research.** Before and during the scale-up of new technologies like LA-ART and long-acting PrEP, dedicated implementation science studies are crucial to understand the real-world barriers and facilitators to their use in diverse, resource-constrained contexts. This research should inform the adaptation of global guidelines to local realities.
- **Strengthen and Integrate Mental Health and Stigma-Reduction Services.** HIV programs must be funded and designed to integrate mental health support. The psychosocial benefits of new therapies, like the stigma reduction associated with LA-ART, will only be fully realized if paired with counseling and support services that address the deep-seated trauma and stigma associated with an HIV diagnosis.
- **Demand a Seat at the Table in Drug Development and Policy Design.** Patient advocacy groups must be meaningfully involved from the earliest stages of clinical trial design through to national policy

formulation. Their lived experience is critical for defining meaningful trial endpoints, designing patient-friendly regimens, and creating policies that are truly responsive to patient needs.

- **Advocate for Transparency and Accountability.** Communities should demand transparency from pharmaceutical companies on R&D costs and pricing models and hold governments and global health institutions accountable for their commitments to health equity and the right to health.
- The new generation of antiretrovirals provides the tools to not only manage HIV but to fundamentally transform the experience of living with the virus. These recommendations provide a roadmap for harnessing this potential. By embracing personalized care, prioritizing equitable access, and relentlessly pursuing innovation, the global community can ensure that this scientific revolution translates into a lasting and just end to the AIDS epidemic for all.

REFERENCES

1. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. [Online]. 2023. Available from: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv
3. De Clercq E. The history of antiretrovirals: key discoveries over the past 25 years. Rev Med Virol. 2009 Sep-Oct;19(5):287-99.
4. Flexner C. HIV drug development: the next 25 years. Nat Rev Drug Discov. 2007 Dec;6(12):959-66.
5. Wensing AM, Calvez V, Ceccherini-Silberstein F, Charpentier C, Günthard HF, Paredes R, et al. 2022 update of the drug resistance mutations in HIV-1. Top Antivir Med. 2022 Oct;30(4):559-574.
6. Menéndez-Arias L, Delgado R. Update and latest advances in antiretroviral therapy. Trends Pharmacol Sci. 2022 Jan;43(1):16-29.
7. Cihlar T, Fordyce M. Current status and prospects of HIV treatment. Curr Opin Virol. 2016 Jun;18:50-6.
8. Tsiang M, Jones GS, Goldsmith J, Mulato A, Hansen D, Kan E, et al. Antiviral Activity of Bictegravir (GS-9883), a Novel Potent HIV-1 Integrase Strand Transfer Inhibitor with an Improved Resistance Profile. Antimicrob Agents Chemother. 2016 Jul 22;60(12):7086-97.
9. Markham A. Cabotegravir Plus Rilpivirine: First Approval. Drugs. 2020 May;80(9):915-922.
10. Scott LJ. Fostemsavir: First Approval. Drugs. 2020 Sep;80(14):1485-1490.
11. Kozal M, Aberg J, Pialoux G, Cahn P, Thompson M, Molina JM, et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. N Engl J Med. 2020 Mar 26;382(13):1232-1243.
12. Emu B, Fessel J, Schrader S, Kumar P, Richmond G, Win S, et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1. N Engl J Med. 2018 Aug 16;379(7):645-654.
13. Lataillade M, Kozal MJ. The hunt for HIV-1 latency drugs. Lancet HIV. 2016 Nov;3(11):e504-e506.
14. Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. J Med Toxicol. 2014 Mar;10(1):26-39.

15. Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. Antiviral Res. 2010 Jan;85(1):201-9.
16. Apostolova N, Funes HA, Blas-Garcia A, Galindo MJ, Alvarez A, Esplugues JV. Efavirenz and the CNS: what we already know and what we need to know. J Antimicrob Chemother. 2015 Dec;70(12):2693-708.
17. Milpied-Homsi B, Moran MT, Feuillade de Chauvin M. Cutaneous adverse effects of antiretroviral agents. Part I: nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. Ann Dermatol Venereol. 2010 Sep;137(8-9):537-46.
18. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet. 2000 Oct 21;356(9239):1423-30.
19. Sax PE, Erlandson KM, Lake JE, McComsey GA, Orkin C, Esser S, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis. 2020 Nov 5;71(6):1379-1389.
20. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019 Aug 29;381(9):803-815.
21. Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, Emtricitabine, and Tenofovir Alafenamide Versus Dolutegravir, Abacavir, and Lamivudine for Initial Treatment of HIV-1 Infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017 Nov 18;390(10107):2063-2072.
22. Orkin C, Arasteh K, Górgolas Hernández-Mora M, Pokrovsky V, Overton ET, Girard PM, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med. 2020 Mar 19;382(12):1124-1135.
23. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. N Engl J Med. 2020 Mar 19;382(12):1112-1123.
24. Markowitz M, Grossman H, Anderson PL, Grant R, Gandhi RT, Horowitz A, et al. Newly Acquired Infection with Multi-Drug Resistant HIV-1 in a Patient Adherent to Pre-exposure Prophylaxis. J Acquir Immune Defic Syndr. 2017 Dec 1;76(4):e104-e106.
25. Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2020 Oct 27;324(16):1651-1669.
26. Rizzardini G, Overton ET, Orkin C, Swindells S, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting injectable cabotegravir + rilpivirine for HIV maintenance therapy: Week 48 pooled analysis of Phase 3 ATLAS and FLAIR trials. J Acquir Immune Defic Syndr. 2020 Dec 15;85(5):648-660.
27. Deeks ED. Ibalizumab: A Review in Multidrug-Resistant HIV-1 Infection. Drugs. 2020 Feb;80(2):189-196.
28. Namasopo S, Krentz HB, Gill MJ. Neuropsychiatric adverse effects of dolutegravir: a emerging issue in a successful antiretroviral regimen. AIDS. 2018 Jul 17;32(11):1491-1493.
29. Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink HJ, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017 Jan;18(1):56-63.

30. Lepik KJ, Yip B, Ulloa AC, Wang L, Toy J, Akagi L, et al. Adverse drug reactions to integrase strand transfer inhibitors. AIDS. 2018 Apr 24;32(7):903-912.
31. Elzi L, Erb S, Furrer H, Cavassini M, Calmy A, Vernazza P, et al. Adverse events of raltegravir and dolutegravir. AIDS. 2017 Nov 28;31(18):2523-2528.
32. Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med. 2018 Aug 23;379(10):979-981.
33. Raizes E, Hsu H, Birx D, El-Sadr W, Gisslén M, Marovich M, et al. Dolutegravir and Neural Tube Defects: A Updated Review of the Evidence. Pharmacoepidemiol Drug Saf. 2020 Dec;29(12):1681-1685.
34. Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. Lancet HIV. 2020 Jan;7(1):e16-e26.
35. Gatell JM, Assoumou L, Moyle G, Waters L, Johnson M, Domingo P, et al. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV-1 viral suppression in patients with high cardiovascular risk: 48-week results of the NEAT022 study. Clin Infect Dis. 2020 Jul 11;71(2):353-360.
36. Mills A, Crofoot G Jr, McDonald C, Shalit P, Flamm JA, Gathe J, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr. 2015 May 1;69(4):439-45.
37. Gallant JE, Daar ES, Raffi F, Brinson C, Ruane P, DeJesus E, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection: a randomised, double-blind, active-controlled phase 3 trial. Lancet Infect Dis. 2016 Jan;16(1):43-52.
38. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. AIDS. 2007 Jul 31;21(10):1273-81.
39. SULASHVILI, N., GORGASLIDZE, N., GABUNIA, L., GIORGOBIANI, M., & RATIANI, L. (2023). MANIFESTATION OF THE PARTICULARITIES OF THE USAGE FEATURES OF MONOCLONAL ANTIBODIES IN VARIOUS PHARMACOTHERAPEUTIC APPLICATIONS. Experimental and Clinical Medicine Georgia, (4), 52–57.
40. Sulashvili, N., Davitashvili, M., Gorgaslidze, N., Gabunia, L., Beglaryan, M., Alavidze, N., … Sulashvili, M. (2024). THE SCIENTIFIC DISCUSSION OF SOME ISSUES OF FEATURES AND CHALLENGES OF USING OF CAR-T CELLS IN IMMUNOTHERAPY. Georgian Scientists, 6(4), 263–290. https://doi.org/10.52340/gs.2024.06.04.24
41. SULASHVILI, N., GORGASLIDZE, N., GABUNIA, L., GIORGOBIANI, M., & RATIANI, L. (2023). MANIFESTATION OF THE PARTICULARITIES OF THE USAGE FEATURES OF MONOCLONAL ANTIBODIES IN VARIOUS PHARMACOTHERAPEUTIC APPLICATIONS. Experimental and Clinical Medicine Georgia, (4), 52–57. https://doi.org/10.52340/jecm.2023.04.14
42. SULASHVILI, N., GORGASLIDZE, N., GABUNIA, L., RATIANI, L., KHETSURIANI, S., KRAVCHENKO, V., SULASHVILI, M. (2024). MANIFESTATION OF THE

PARTICULARITIES OF SOME KEY ISSUE ASPECTS OF NEW IMMUNOTHERAPY CHALLENGES AND PERSPECTIVES BY CAR-T CELL THERAPY. Experimental and Clinical Medicine Georgia, (4), 119–121. https://doi.org/10.52340/jecm.2024.04.32.

43. SULASHVILI, N. . ., GORGASLIDZE , N. ., BEGLARYAN , M. ., GABUNIA , L. ., CHICHOYAN , N. ., GIORGOBIANI , M. ., … ZARNADZE, S. (DAVIT) . (2022). THE SCIENTIFIC TALKS OF ESSENTIAL ISSUE, INVOCATION, PERSPECTIVES, INCLINATIONS AND FEATURES OF THE CLINICAL PHARMACISTS GLOBALLY. Experimental and Clinical Medicine Georgia, (7).
44. Sulashvili N, Nimangre RR. MANIFESTATION OF SOME ASPECTS OF CARDIOVASCULAR DISEASES, IMPLICATIONS, PHARMACOTHERAPEUTIC STRATEGIES, EFFECTS, IMPACTS AND POTENTIAL HAZARDS IN GENERAL. JR [Internet]. 2025 Feb. 7 [cited 2025 May 22];3(1):1-27. Available from: https://journals.4science.ge/index.php/jr/article/view/3393.
45. Sulashvili N, Yaduvanshi U, Yadav M, Gabunia L, Ghambashidze K, Gorgaslidze N, et al. THE SCIENTIFIC DISCOURSE OF FEATURES OF CLINICAL USE AND PHARMACOLOGY OF VASOCONSTRICTORS AND THEIR IMPACT ON CARDIAC FUNCTION. JR [Internet]. 2025 Feb. 21 [cited 2025 May 22];3(1):28-6. Available from: https://journals.4science.ge/index.php/jr/article/view/3414.
46. Nodar Sulashvili, Nana Gorgaslidze, Margarita Beglaryan, Luiza Gabunia, Nato Alavidze, Nino Abuladze, Marina Giorgobiani, Marika Sulashvili, Tamar Okropiridze, and Lali Patsia. 2025. “THE SCIENTIFIC DISCOURSE OF KEY ISSUE ASPECTS OF FEATURES OF CANDIDA PROBLEMS, ANTIFUNGAL DRUGS RESISTANCE CONCERNS, MYCOTOXICOLOGY ISSUES, MYCOECOLOGY, BIOSAFETY RISKS AND EMERGING SOLUTIONS”. Modern Scientific Method, no. 9 (March). https://ojs.scipub.de/index.php/MSM/article/view/5423.
47. Aphkhazava, D., Tuphinashvili, T., Sulashvili, N., & Nozadze, M. (2023). The Features and Role of SHP2 Protein in Postnatal Muscle Development. Scientific Journal „Spectri“, 1. https://doi.org/10.52340/spectri.2023.01
48. SULASHVILI, N., BEGLARYAN, M., GORGASLIDZE, N., KOCHARYAN, S., CHICHOYAN, N., GABUNIA, L., ZARNADZE, S. (DAVIT). (2023). THE DISCLOSURE OF FEATURES, CHARACTERISTICS, POSSIBILITIES AND SPECIALTIES OF CLINICAL PHARMACISTS AS MEDIATOR AMONG DOCTORS AND PATIENTS FOR ENHANCEMENT PUBLIC HEALTH SECTOR IN A GLOBAL WORLD. Experimental and Clinical Medicine Georgia, (4), 57–62. https://doi.org/10.52340/jecm.2023.04.15
49. Sulashvili N, Davitashvili M, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, et al. THE SCIENTIFIC DISCUSSION OF SOME ISSUES OF FEATURES AND CHALLENGES OF USING OF CAR-T CELLS IN IMMUNOTHERAPY. GS 2024 ;6(4):263-90. https://journals.4science.ge/index.php/GS/article/view/3214
50. Aphkhazava, David, Nodar Sulashvili, and Jaba Tkemaladze. 2025. “Stem Cell Systems and Regeneration”. Georgian Scientists 7 (1):271-319. https://doi.org/10.52340/gs.2025.07.01.26.
51. Relling, Mary V., and William E. Evans. 2015. “Pharmacogenomics in the Clinic.” Nature 526 (7573): 343–50.
52. Aphkhazava, David, Tamar Tuphinashvili, Nodar Sulashvili, and Maia Nozadze. 2023. “THE FEATURES AND ROLE OF SHP2 PROTEIN IN POSTNATAL MUSCLE DEVELOPMENT”. Scientific Journal „Spectri“ 1 (March). https://doi.org/10.52340/spectri.2023.01.

53. SULASHVILI N, GORGASLIDZE N, GABUNIA L, GIORGOBIANI M, RATIANI L. MANIFESTATION OF THE PARTICULARITIES OF THE USAGE FEATURES OF MONOCLONAL ANTIBODIES IN VARIOUS PHARMACOTHERAPEUTIC APPLICATIONS. jecmg [Internet]. 2023 Nov. 26 [cited 2025 Jul. 12];(4):52-7. Available from: https://journals.4science.ge/index.php/jecm/article/view/2413.
54. Aphkhazava, David, Nodar Sulashvili, Ia Egnatievi, Manana Giorgobiani, Maia Nozadze, Nani Vekua, and Nino Japaridze. 2024. "Derivation of AMPA Receptor GluA1 Subunits in Mice from Exosomes Modulates Inflammatory Pain". Scientific Journal „Spectri" 9 (1). https://doi.org/10.52340/spectri.2024.09.01.05.
55. Aphkhazava, David, Nodar Sulashvili, Ia Egnatievi, Tamar Tupinashvili, and Maia Nozadze. 2024. "DYNAMIC TUMOR MICROENVIRONMENT THEORY: A MULTIFACETED APPROACH TO TUMOR RESEARCH AND BIOCHEMISTRY". Scientific Journal „Spectri" 9 (1). https://doi.org/10.52340/spectri.2024.09.01.06.
56. Sulashvili, Nodar, Irine Pkhakadze, Margarita Beglaryan, Ia Egnatievi, Manana Giorgobiani, Luiza Gabunia, Nana Gorgaslidze, Magda Davitashvili, Ada (Adel) Tadevosyan, and Lali Patsia. 2025. "THE SCIENTIFIC DISCUSSION OF KEY ISSUE ASPECTS OF MODERN ADVANCING INNOVATION OF LEARNING AND TEACHING METHODS AND PEDAGOGICAL APPROACHES IN HIGHER EDUCATION INSTITUTIONS IN MEDICAL EDUCATIONAL STUDY PROGRAMS DIRECTIONS GLOBALLY IN GENERAL". Scientific Journal „Spectri" 10 (2). https://doi.org/10.52340/spectri.2024.10.01.12.
57. GORGASLIDZE, NANA, NODAR SULASHVILI, LUIZA GABUNIA, LEVAN RATIANI, and MARINA GIORGOBIANI. 2023. "THE SINGULARITIES OF TEMOZOLOMIDE PHARMACOTHERAPEUTIC EFFECTS IN BRAIN TUMOR THERAPEUTIC APPLICATIONS". Experimental and Clinical Medicine Georgia, no. 4 (November):62-66. https://doi.org/10.52340/jecm.2023.04.16.
58. SULASHVILI, NODAR, MARGARITA BEGLARYAN, NANA GORGASLIDZE, SEYRAN KOCHARYAN, NAIRA CHICHOYAN, LUIZA GABUNIA, IRINE ZARNADZE, et al. 2023. "THE DISCLOSURE OF FEATURES, CHARACTERISTICS, POSSIBILITIES AND SPECIALTIES OF CLINICAL PHARMACISTS AS MEDIATOR AMONG DOCTORS AND PATIENTS FOR ENHANCEMENT PUBLIC HEALTH SECTOR IN A GLOBAL WORLD". Experimental and Clinical Medicine Georgia, no. 4 (November):57-62. https://doi.org/10.52340/jecm.2023.04.15.
59. KVIZHINADZE, NATIA, NINO INTSKIRVELI, DAVID TOPURIA, NANA DUGHASHVILI, and NODAR SULASHVILI. 2023. "GSP AND ITS FEATURES IN MEDICAL AND PHARMACEUTICAL INSTITUTIONS". Experimental and Clinical Medicine Georgia, no. 4 (November):17-19. https://doi.org/10.52340/jecm.2023.04.03.
60. SULASHVILI, NODAR, NANA GORGASLIDZE, MARGARITA BEGLARYAN, LUIZA GABUNIA, NAIRA CHICHOYAN, MARINA GIORGOBIANI, IRINE ZARNADZE, and SHALVA (DAVIT) ZARNADZE. 2022. "THE SCIENTIFIC TALKS OF ESSENTIAL ISSUE, INVOCATION, PERSPECTIVES, INCLINATIONS AND FEATURES OF THE CLINICAL PHARMACISTS GLOBALLY". Experimental and Clinical Medicine Georgia, no. 7 (October). https://doi.org/10.52340/jecm.2022.07.09.

61. SULASHVILI , NODAR, MARGARITA BEGLARYAN, NANA GORGASLIDZE, SEYRAN KOCHARYAN, NAIRA CHICHOYAN, LUIZA GABUNIA, NATIA KVIZHINADZE, MARINA GIORGOBIANI, IRINE ZARNADZE, and SHALVA (DAVIT) ZARNADZE. 2022. “THE SCIENTIFIC DISCUSSION OF SPECIFICITIES OF PHARMACIST OCCUPATIONAL AND HIGHER MEDICAL-PHARMACEUTICAL EDUCATIONAL MANIFESTATION OUTLOOKS IN GEORGIA”. Experimental and Clinical Medicine Georgia, no. 7 (October). https://doi.org/10.52340/jecm.2022.07.08.
62. GORGASLIDZE, NANA, SHAFIGA TOPCHIYEVA, MARINA GIORGOBIANI, and NODAR SULASHVILI. 2022. “THE IMPACT OF PHARMACEUTICAL MARKETING ON THE SOCIETY AND INDIVIDUAL PATIENT AND ITS SPECIFICATION OF HANDLING”. Experimental and Clinical Medicine Georgia, no. 7 (October). https://doi.org/10.52340/jecm.2022.07.07.
63. GORGASLIDZE, NANA, and NODAR SULASHVILI. 2022. “THE FEATURES OF THE PHARMACEUTICAL MARKET AND ITS OUTLOOKS IN GEORGIA”. Experimental and Clinical Medicine Georgia, no. 7 (October). https://doi.org/10.52340/jecm.2022.07.06.
64. NANA GORGASLIDZE, NODAR SULASHVILI, MARINA GIORGOBIANI, TEA ZARKUA, NANA DUGASHVILI. THE FEATURES OF INSPECTION AND MONITORING FRAMEWORK FOR PROFESSIONAL SAFETY, SANITARY, BIOECOLOGICAL, PREVENTIVE AND HYGIENIC NOVEL REQUIREMENT ISSUES OF PHARMACEUTICAL ORGANIZATIONS IN THE CONTEXT OF THE COVID-19 PANDEMIC IN GEORGIA. jecmg [Internet]. 2021 Oct. 19 [cited 2025 Jul. 12];(5-6):42-6. Available from: https://journals.4science.ge/index.php/jecm/article/view/576.
65. SULASHVILI, NODAR, NANA GORGASLIDZE, MARGARITA BEGLARYAN, LUIZA GABUNIA, NATIA KVIZHINADZE, TEA ZARKUA, MARINA GIORGOBIANI, NANA PEIKRISHVILI, and MARIKA SULASHVILI. 2024. “THE MANIFESTATION OF CHARACTERISTICS, OPPORTUNITIES AND CHALLENGES OF ELECTRONIC SYSTEMS AND DIGITAL INTELLIGENCE USING IN PHARMACEUTICAL SERVICES”. Experimental and Clinical Medicine Georgia, no. 4 (September):122-25. https://doi.org/10.52340/jecm.2024.04.33.
66. Sulashvili N, Davitashvili M, Gorgaslidze N, Gabunia L, Beglaryan M, Alavidze N, et al. THE SCIENTIFIC DISCUSSION OF SOME ISSUES OF FEATURES AND CHALLENGES OF USING OF CAR-T CELLS IN IMMUNOTHERAPY. GS [Internet]. 2024 Nov. 26 [cited 2025 Jul. 12];6(4):263-90. Available from: https://journals.4science.ge/index.php/GS/article/view/3214.
67. Sulashvili N, Nimangre RR. MANIFESTATION OF SOME ASPECTS OF CARDIOVASCULAR DISEASES, IMPLICATIONS, PHARMACOTHERAPEUTIC STRATEGIES, EFFECTS, IMPACTS AND POTENTIAL HAZARDS IN GENERAL. JR [Internet]. 2025 Feb. 7 [cited 2025 Jul. 12];3(1):1-27. Available from: https://journals.4science.ge/index.php/jr/article/view/3393.
68. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015 Apr 11;385(9977):2606-15.
69. Taramasso L, Tatarelli P, Di Biagio A. Drug-drug interactions between antiretroviral and non-antiretroviral agents. Curr Opin HIV AIDS. 2017 Sep;12(5):441-447.

70. German P, Warren D, West S, Hui J, Kearney BP. Pharmacokinetics and bioavailability of an integrase and novel pharmacoenhancer-containing single-tablet fixed-dose combination regimen for the treatment of HIV. J Acquir Immune Defic Syndr. 2010 Dec;55(3):323-9.
71. Custodio JM, Fordyce M, Garner W, Vimal M, Ling KHJ, Sager J, et al. Pharmacokinetics and Safety of Tenofovir Alafenamide in HIV-Uninfected Subjects with Severe Renal Impairment. Antimicrob Agents Chemother. 2016 Sep 23;60(10):6095-101.
72. Scarsi KK, Havens JP, Podany AT, Avedissian SN, Fletcher CV. HIV-1 Integrase Inhibitors: A Comparative Review of Efficacy and Safety. Drugs. 2020 Oct;80(16):1649-1676.
73. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. Cold Spring Harb Perspect Med. 2012 Apr;2(4):a007161.
74. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet. 2013 Nov 2;382(9903):1525-33.