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(Review Article)

Developing adaptive HIV treatment guidelines incorporating drug resistance surveillance and genotype-tailored therapies

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Abstract

The persistent global burden of HIV demands treatment frameworks that are both responsive and personalized, particularly in the face of rising drug resistance. Current antiretroviral therapy (ART) guidelines, while effective in many contexts, often lag behind the rapid emergence of HIV drug-resistant mutations and fail to account for inter-individual genetic variability that influences therapeutic response. This article examines the imperative to develop adaptive HIV treatment guidelines that integrate real-time drug resistance surveillance and genotype-tailored therapeutic strategies. Beginning from a global overview of ART evolution, the discussion narrows to highlight the challenges posed by acquired and transmitted resistance patterns, especially in resource-limited settings with high viral diversity and limited genomic monitoring infrastructure. We evaluate the benefits of incorporating routine resistance testing into national treatment protocols, including improved regimen durability, reduced treatment failure, and better alignment with WHO 95-95-95 targets. In parallel, we explore the potential of pharmacogenomic data such as host CYP450 polymorphisms and HLA profiles to optimize drug selection and dosing, minimizing toxicity and enhancing adherence. Using case studies from sub-Saharan Africa, Asia, and the U.S., we demonstrate the feasibility and clinical utility of integrating drug resistance data and host genomics into national HIV guidelines. The article concludes with a framework for adaptive policy design, leveraging artificial intelligence, electronic health records, and regional surveillance networks to support dynamic, patient-centric HIV treatment pathways. Such an approach represents a paradigm shift towards precision public health, where real-world data directly inform equitable, effective HIV care across diverse populations.

Keywords: HIV Drug Resistance; Genotype-Guided Therapy; Adaptive Treatment Guidelines; Precision Public Health; Antiretroviral Therapy; Surveillance Systems

1. Introduction

1.1. Global Burden and Evolution of HIV Treatment

The HIV/AIDS pandemic has continued to exert profound public health, economic, and social burdens across the globe. Sub-Saharan Africa, in particular, accounts for over two-thirds of the global population living with HIV, underscoring a critical need for scalable treatment infrastructure and sustained community-based interventions [1]. Over the decades, antiretroviral therapy (ART) has emerged as the primary modality for HIV management, offering prolonged viral suppression, restored immune function, and reduced transmission rates when administered consistently [2].

The transition from monotherapy to combination ART marked a paradigm shift, allowing for the targeting of multiple stages of viral replication and delaying resistance onset [3]. The introduction of fixed-dose combinations and once-daily

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regimens significantly improved adherence outcomes and simplified delivery systems for resource-limited settings [4]. Programs such as PEPFAR and the Global Fund have contributed extensively to treatment scale-up and infrastructure development, particularly in high-burden regions.

Despite these advancements, the virus has continued to evolve, generating subtypes and drug-resistant strains that challenge standardized therapeutic regimens [5]. These adaptations have been especially pronounced in regions with interrupted treatment adherence or inconsistent drug supply chains, where selective pressure drives the emergence of resistance mutations.

Figure 1 will later illustrate the historical timeline of ART evolution alongside key resistance milestones. The global burden of disease is not merely a numerical concern but reflects the dynamic interplay between treatment innovations, resistance surveillance, and health system readiness. As ART programs expand, the clinical and virologic monitoring strategies must evolve in parallel to avoid therapeutic obsolescence and public health setbacks.

1.2. Challenges with Static ART Guidelines in a Dynamic Resistance Landscape

Standardized treatment guidelines for ART have been instrumental in establishing uniform care protocols and facilitating training and procurement. However, the emergence of drug resistance presents a significant challenge to the effectiveness of these static guidelines, particularly in environments where treatment initiation is decoupled from resistance testing [6]. In many low- and middle-income countries, first-line regimens are often deployed without real-time genotypic insight, resulting in mismatched therapy and suboptimal viral suppression [7].

Resistance mutations, such as K65R and M184V, compromise the efficacy of core reverse transcriptase inhibitors and are often undetected until virologic failure becomes clinically evident [8]. Without integrated resistance surveillance systems, these mutations can spread across populations, silently undermining treatment programs. Static guidelines, by nature, do not accommodate the localized evolution of resistance patterns, and this limitation disproportionately affects high-burden regions with diverse HIV subtypes [9].

Another complication stems from policy inertia guidelines are often updated based on global evidence rather than real-time national surveillance. Consequently, countries may implement regimens that no longer align with circulating resistance profiles [10]. Table 1, which will be presented later, compares ART regimen failure rates and resistance mutation prevalence across selected African and Asian countries.

The rapidly shifting genetic landscape of HIV demands agile and responsive treatment strategies. In the absence of such adaptability, standardized ART policies may inadvertently contribute to increased resistance prevalence, reduced population-level viral suppression, and long-term treatment program inefficiencies.

1.3. Aim and Scope: Integrating Surveillance and Genomic Personalization

This article seeks to examine the intersection of ART policy, resistance surveillance, and the growing imperative for genomic personalization of HIV treatment. The central thesis is that effective long-term ART delivery requires a shift from static, one-size-fits-all guidelines toward integrated, data-driven models that consider resistance profiles and patient-level genomic insights [11].

Public health surveillance systems capable of real-time genotypic and phenotypic resistance mapping are central to this transformation. Such systems allow for the identification of high-risk clusters, inform targeted interventions, and help refine national treatment algorithms before population-wide failure rates increase [12]. However, current infrastructure for this level of surveillance remains underdeveloped in most high-burden regions, and implementation gaps persist in terms of laboratory capacity, data sharing, and workforce training [13].

By incorporating patient-derived resistance profiles and leveraging machine learning to predict treatment responses, health systems can begin to implement stratified ART plans rather than blanket approaches. This is especially critical in areas with circulating recombinant forms (CRFs) and other non-B subtypes, where drug resistance pathways may deviate from those characterized in high-income countries [14].

The scope of this article will encompass three key components: a critical review of resistance surveillance practices, an analysis of ART outcomes across genetic variants, and a discussion on policy adaptations required to implement precision-guided treatment models in resource-constrained settings. Figure 2, to follow, will visualize the conceptual framework of surveillance-integrated ART personalization.

In doing so, this work aims to bridge the gap between epidemiologic realities and therapeutic responsiveness in global HIV policy.

2. Understanding HIV drug resistance

2.1. Mechanisms and Types of Resistance: Acquired vs. Transmitted

HIV drug resistance arises from two principal pathways: acquired resistance and transmitted resistance. Acquired resistance develops when a person undergoing antiretroviral therapy (ART) experiences suboptimal suppression of viral replication, allowing resistant mutations to emerge through selective pressure [5]. This may result from inconsistent adherence, inadequate drug potency, or delayed switching of failing regimens. Over time, the virus accumulates mutations that diminish the efficacy of first- or second-line treatments [6].

Transmitted resistance, on the other hand, occurs when individuals are infected with a strain of HIV that already carries resistance mutations, often due to prior propagation through treatment-experienced individuals [7]. This form of resistance complicates initial regimen effectiveness and poses challenges to public health programs that rely on empirical first-line prescriptions without baseline resistance testing.

The mutations themselves are typically located in the reverse transcriptase and protease genes, where alterations like M184V, K103N, or Y181C confer resistance to lamivudine, efavirenz, and nevirapine, respectively [8]. The dynamics of resistance evolution vary depending on subtype, host factors, drug half-life, and pharmacogenetics.

Compounding the issue, resistant strains may maintain robust transmission potential without significant loss of viral fitness, allowing them to persist and circulate within populations for extended periods [9]. Consequently, both acquired and transmitted resistance contribute to the erosion of treatment effectiveness and complicate ART scale-up efforts.

Public health strategies must distinguish between these mechanisms, as interventions for acquired resistance (e.g., adherence support) differ significantly from those targeting transmitted resistance (e.g., surveillance testing in newly diagnosed individuals) [10]. This foundational distinction underpins much of the analysis that follows in this section.

2.2. Epidemiological Trends of Resistance Across Regions

The global landscape of HIV drug resistance reveals considerable regional heterogeneity, influenced by treatment policies, monitoring infrastructure, and local epidemic dynamics. In high-prevalence areas across sub-Saharan Africa, rates of pre-treatment drug resistance (PDR) to non-nucleoside reverse transcriptase inhibitors (NNRTIs) have surpassed critical thresholds in several countries, with some exceeding 10% prevalence among newly infected individuals [11].

These figures have prompted policy shifts toward dolutegravir-based regimens in some regions, as integrase strand transfer inhibitors (INSTIs) have demonstrated a higher barrier to resistance [12]. However, implementation of such policies has been uneven, with rural health systems lagging behind urban centers in transitioning regimens and diagnostic protocols [13].

Southeast Asia has reported rising trends in dual-class resistance, particularly in populations with a history of exposure to older regimens like d4T and AZT. In Latin America and the Caribbean, pockets of transmitted resistance are emerging in concentrated epidemics, particularly among men who have sex with men and sex workers [14].

High-income countries have generally managed resistance rates more effectively through routine viral load monitoring and genotypic testing, although recent concerns have emerged regarding INSTI resistance in patients with long-term exposure to dolutegravir [15]. Moreover, treatment tourism and migration dynamics contribute to the cross-border spread of resistant strains, complicating national-level resistance containment strategies.

Table 1 Prevalence of HIV Drug Resistance by Region and Regimen Type

Region	NNRTI Resistance (%)	NRTI Resistance (%)	PI Resistance (%)	Integrase Inhibitor Resistance (%)
West Africa	14.2	6.3	1.1	0.5
East Africa	17.5	8.1	1.4	0.7
Southern Africa	21.8	9.7	2.3	1.2
Asia	12.6	5.9	1.0	0.4
Latin America	10.3	4.8	0.9	0.3

2.3. Impact of Resistance on First- and Second-Line ART Outcomes

Resistance undermines ART efficacy by enabling viral replication in the presence of therapeutic drug concentrations, thereby facilitating continued immune decline and increasing the likelihood of transmission. In clinical terms, patients harboring resistant virus often fail to achieve viral suppression, even when nominally adherent to therapy [16]. This has significant implications for both first-line and second-line ART outcomes.

First-line regimens based on NNRTIs are particularly susceptible to failure in the presence of common mutations such as K103N or Y181C, which confer high-level resistance with a single point mutation [17]. This vulnerability has contributed to widespread regimen failure in some settings, necessitating premature transition to second-line therapy a move that increases both costs and complexity of care.

Second-line regimens, typically based on protease inhibitors (PIs), exhibit a higher genetic barrier to resistance but are not impervious. The presence of resistance mutations such as L90M or V82A can significantly reduce the effectiveness of PI-based regimens, especially when compounded by NRTI mutations carried over from first-line failure [18].

Furthermore, patients failing first-line therapy are often switched without prior resistance testing, increasing the likelihood of functional monotherapy and further resistance accumulation [19]. This is particularly problematic in resource-limited settings where routine viral load monitoring and genotypic assays are not universally available.

Even in regions with robust health systems, the silent accumulation of resistance mutations can precede clinical failure, emphasizing the need for early detection strategies. In summary, resistance represents a pivotal determinant of long-term ART success and must be addressed proactively through prevention, monitoring, and responsive regimen design [20].

2.4. Limitations of Current Surveillance Practices

Despite the centrality of resistance data in informing ART policy and clinical decisions, global surveillance systems remain fragmented, under-resourced, and unevenly implemented. Many countries lack national resistance surveillance frameworks, relying instead on ad hoc academic studies or donor-driven programs with limited geographic and temporal scope [21].

Even where surveillance exists, delays in data reporting, lack of standardization across genotyping protocols, and inconsistent patient metadata undermine the utility of the findings for real-time policy decisions [22]. Cross-sectional sampling further limits the ability to track temporal trends, while insufficient integration with national health information systems prevents meaningful linkage to clinical outcomes.

Additionally, resistance data often reflect sentinel sites or urban referral centers, omitting rural or marginalized populations where treatment access and adherence may be poorest [23]. This sampling bias reduces the generalizability of surveillance outputs and conceals pockets of high resistance transmission risk.

The cost and technical complexity of genotypic resistance testing have also inhibited scale-up. Laboratory capacity remains concentrated in few national reference centers, leading to bottlenecks in processing and reporting [24]. Moreover, without routine viral load testing, many programs fail to identify candidates for resistance testing until well after virologic failure, missing opportunities for early intervention.

Emerging technologies such as dried blood spot genotyping and pooled resistance sequencing hold promise but require policy backing and financial investment to be operationalized at scale [25]. Until these structural constraints are addressed, resistance surveillance will continue to lag behind the evolving epidemiologic landscape, limiting its role as a frontline tool in the global response to HIV.

3. Genotype-tailored therapies in HIV care

3.1. Role of Host Pharmacogenomics in ART Response

The variability in antiretroviral therapy (ART) outcomes among individuals is significantly influenced by genetic differences in drug metabolism, transport, and immune response pathways. Pharmacogenomics, which explores the interaction between an individual's genome and drug response, has become essential to understanding ART efficacy and tolerability [11]. One of the most critical genetic pathways implicated in ART metabolism is the cytochrome P450 (CYP450) enzyme system, particularly CYP2B6, CYP3A4, and CYP2A6.

Polymorphisms in **CYP2B6**, for example, modulate the metabolism of efavirenz and nevirapine, resulting in significant differences in plasma concentrations and, consequently, treatment outcomes [12]. Individuals with the *CYP2B6 516G>T* variant often experience higher plasma levels of efavirenz, increasing the risk of neurotoxicity and early discontinuation [13]. Similarly, variations in *CYP3A4* and *CYP2A6* influence protease inhibitor clearance and pharmacokinetics of integrase inhibitors.

Pharmacogenomic differences also affect drug transport proteins, such as P-glycoprotein (encoded by *ABCB1*), which alter intracellular concentrations of ARTs, thereby impacting viral suppression success rates [14]. Additionally, host immune-genetic profiles, including HLA alleles, shape susceptibility to hypersensitivity reactions and modulate immune restoration under ART.

Understanding these genomic underpinnings provides insight into why some patients experience virologic failure or toxicities despite standard adherence and dosing protocols. It has also opened pathways for predictive treatment selection and dose optimization tailored to individual metabolic profiles.

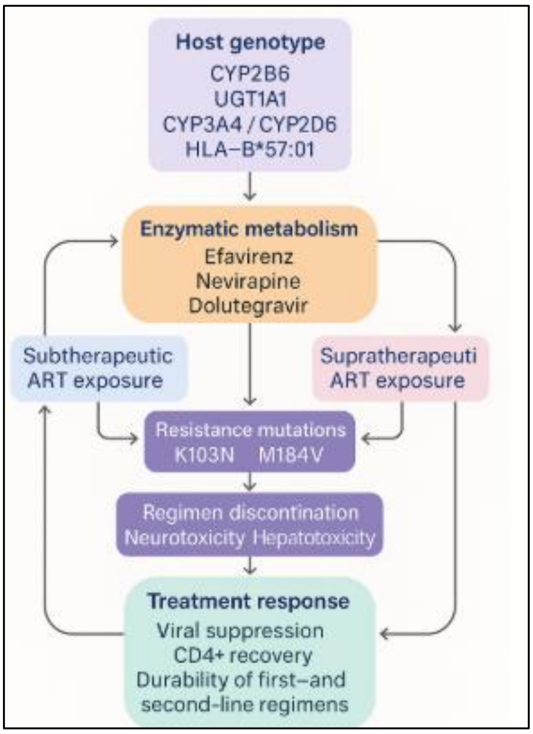

Figure 1 The mechanistic relationship between host genotype, enzymatic metabolism, and downstream effects on ART exposure, resistance development, and treatment response. Incorporating pharmacogenomics into HIV care aligns with precision medicine principles and has the potential to improve ART durability and long-term outcomes [15]

3.2. Genomic Markers of Adverse Drug Reactions and Efficacy

The identification of genomic biomarkers has substantially advanced the prevention of adverse drug reactions (ADRs) and improved treatment outcomes in HIV therapy. One of the most clinically significant associations is between the *HLA-B*5701 allele and hypersensitivity reactions to abacavir. Individuals carrying this allele have a markedly increased risk of developing a potentially fatal hypersensitivity syndrome upon exposure to abacavir [16].

Pre-treatment screening for *HLA-B*5701 has become a routine practice in several healthcare systems, enabling clinicians to preemptively exclude abacavir from the regimen and avoid associated toxicities [17]. Similarly, *HLA-B*3505 and *HLA-C*04:01 have been linked to nevirapine-induced hepatotoxicity and skin rashes, underscoring the need for ethnic-specific pharmacogenomic data [18].

Beyond hypersensitivity, markers of drug efficacy are also genetically modulated. For instance, slow metabolizers with *CYP2B6* polymorphisms exhibit higher plasma concentrations of efavirenz, leading to both neurotoxicity and, paradoxically, enhanced viral suppression in some cases [19]. Conversely, ultra-rapid metabolizers may subtherapeutically clear drugs, increasing the likelihood of treatment failure and resistance emergence.

Genetic variation in *UGT1A1* also affects the metabolism of dolutegravir and atazanavir, influencing bilirubin levels and treatment tolerability [20]. These findings highlight the necessity of integrating genotype data into ART decision-making to balance efficacy with safety.

Current genomic testing platforms have evolved to identify multiple actionable markers in a single assay, enabling clinicians to make informed, evidence-based decisions prior to ART initiation. However, access to such platforms remains limited in many HIV-endemic regions, constraining the full realization of their clinical utility.

Together, these genomic insights represent a critical axis in personalized HIV care, enabling safer and more durable treatment regimens adapted to individual genetic profiles [21].

3.3. Case Studies: Implementation of Genotype-Guided Therapy (Africa, Asia, U.S.)

The application of genotype-guided ART selection has gained traction globally, although adoption rates vary based on infrastructure, regulatory frameworks, and financial investment. In the United States, pharmacogenomic screening for *HLA-B*5701* has been standard practice since the mid-2000s, endorsed by both the Department of Health and Human Services (DHHS) and the FDA [22]. This screening significantly reduced abacavir hypersensitivity incidences and demonstrated cost-effectiveness in diverse clinical settings.

Several university hospitals also offer expanded pharmacogenomic panels covering *CYP2B6*, *UGT1A1*, and *ABCB1*, allowing for individualized dose adjustments and regimen design. Clinical decision support systems integrated into electronic health records help clinicians interpret genomic results and translate them into ART modifications [23].

In Asia, particularly Thailand and Vietnam, regional pharmacogenomic databases have guided national HIV programs in adopting genotype-informed nevirapine and efavirenz dosing. Research from Bangkok's Mahidol University has shown that *CYP2B6* polymorphisms are common in Southeast Asian populations and that reduced efavirenz dosing can mitigate neuropsychiatric side effects without compromising efficacy [24].

African settings have begun to pilot pharmacogenomic initiatives, although coverage remains limited. In South Africa, studies conducted in KwaZulu-Natal have identified high prevalence of *CYP2B6* 516G>T and demonstrated its impact on efavirenz plasma levels and central nervous system toxicity [25]. Pilot programs led by academic consortia have tested the feasibility of deploying point-of-care genotyping using dried blood spots, revealing promise in rural HIV clinics.

Table 2 ART Adjustments Based on CYP450 and HLA Genotyping

Region	**Key Genotype(s)**	**Affected Drug(s)**	**Allele Frequency (%)**	**Clinical Adjustment**
West Africa	CYP2B6*6	Efavirenz (EFV)	~38	Dose reduction to avoid neurotoxicity
East Africa	HLA-B*5701	Abacavir (ABC)	<1	Limited use of ABC; genetic screening optional
Southern Africa	CYP2B6*6, HLA-B*5701	EFV, ABC	36–40 / <2	EFV dose reduction; ABC used cautiously
Asia	HLA-B*1502, CYP2C19 variants	Nevirapine, EFV	5–15	Alternative drugs recommended
U.S.	HLA-B*5701, UGT1A1*28	ABC, Atazanavir (ATV)	~6 / ~10	Avoid ABC in carriers; monitor bilirubin levels

Table 2 compares genotype-based ART adjustments across these regions, highlighting allele frequencies, associated drugs, and resulting clinical decisions. These case studies illustrate that implementation of pharmacogenomics is feasible even in resource-constrained settings when aligned with national priorities and supported by donor partnerships.

Despite different rates of adoption, all regions affirm the clinical and economic benefits of tailoring ART using genetic data, particularly in minimizing ADRs and optimizing long-term adherence [26].

3.4. Barriers to Scaling Genomic Medicine in HIV Care

Despite its potential, several barriers hinder the widespread integration of genomic medicine into routine HIV care. The foremost challenge remains the high cost of genotyping technologies and the lack of reimbursement models in many low- and middle-income countries. Without subsidized funding, even basic HLA or CYP450 testing remains inaccessible to the majority of patients [27].

Another major constraint is the shortage of trained personnel capable of interpreting pharmacogenomic results and integrating them into clinical workflows. Most HIV programs do not include pharmacogenomics in provider training curricula, leading to gaps in awareness and confidence in using genomic data for ART decisions [28].

Furthermore, many national health information systems are not designed to store or process genomic data, creating integration barriers and privacy concerns. Standardization of nomenclature, data-sharing protocols, and ethical governance frameworks is still evolving, particularly in settings without prior genomic infrastructure [29].

Regulatory inertia also plays a role. In several countries, genomic testing panels are not approved by national regulatory bodies or lack clinical guidelines for use. This leads to variability in quality, limited oversight, and hesitancy among clinicians to incorporate results into care decisions.

Cultural and linguistic factors may also affect patient consent and understanding of genomic testing, particularly in indigenous or marginalized communities. Misconceptions about genetic determinism or fears of discrimination may reduce participation in testing initiatives [30].

To scale genomic HIV medicine, coordinated investments are needed across workforce development, digital infrastructure, regulatory reform, and community engagement. Pilot projects that demonstrate feasibility and impact in real-world settings can act as catalysts for broader adoption, especially if supported by regional consortia and global funders.

4. Adaptive treatment guidelines: theory and design

4.1. Static vs. Adaptive Guidelines: A Comparative Analysis

Antiretroviral therapy (ART) guidelines have historically been static, with fixed schedules for revisions based on cumulative clinical evidence. While such models offered consistency and regulatory clarity, they often lagged behind emerging resistance patterns, drug developments, and real-world treatment outcomes [15]. Static frameworks typically relied on periodic expert consensus, often resulting in outdated regimens being retained longer than necessary, particularly in low-resource settings where evidence generation lagged behind implementation timelines.

Adaptive guidelines, by contrast, allow for dynamic updating based on real-time data from virologic monitoring, pharmacovigilance systems, and genotypic resistance surveillance. These frameworks are iterative, integrating new evidence into policy more fluidly, thereby narrowing the gap between research and practice [16]. Adaptive protocols can incorporate patient-level variables such as host genotype, comorbidities, and viral subtypes, aligning more closely with principles of precision medicine.

Comparative analysis of programs implementing adaptive models such as those piloted in South-East Asia and select Southern African districts shows reduced incidence of late-stage regimen switches, fewer adverse drug reactions, and improved patient adherence [17]. Moreover, adaptive protocols have proven valuable in accelerating the introduction of new drug formulations when local resistance trends diverge from global norms.

However, the success of adaptive guidelines depends on infrastructure to collect, analyze, and act on large volumes of clinical and molecular data. Without such systems, even the most well-intentioned adaptive frameworks risk becoming inconsistent or fragmented in application [18].

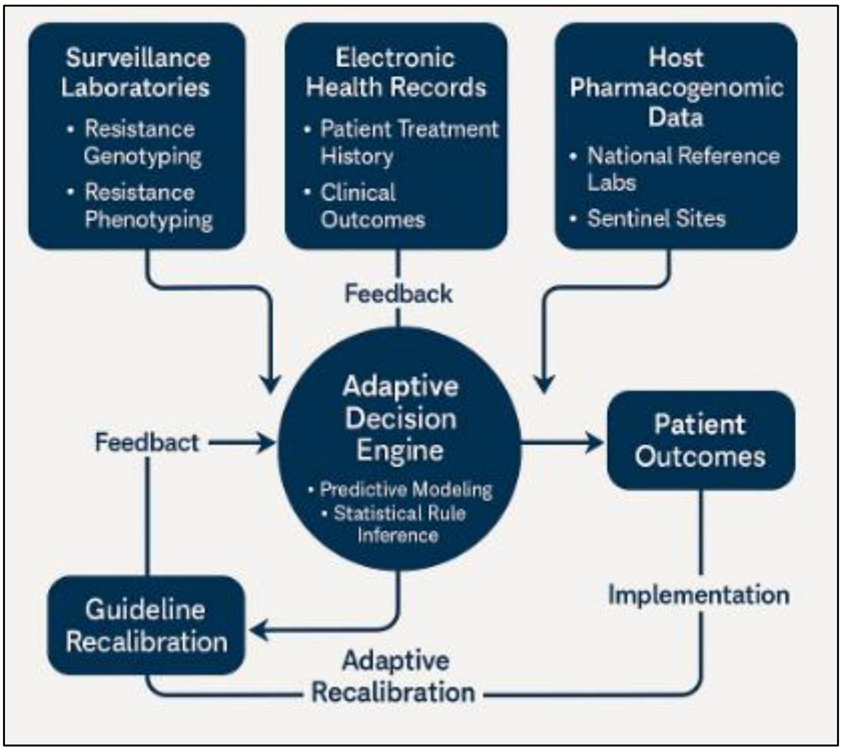

Figure 2 A schematic flowchart illustrating how real-time data inputs from surveillance labs, digital records, and pharmacogenomics are synthesized to guide adaptive HIV treatment guidelines. This model supports continuous evolution and contextual relevance, contrasting with the episodic updates typical of static approaches [19]

4.2. Data-Driven Decision Models and Real-Time Updates

Data-driven decision-making represents a transformative shift in the way HIV treatment policies are designed and maintained. Rather than relying exclusively on published randomized controlled trials or retrospective reviews, adaptive models utilize near real-time inputs from electronic medical records (EMRs), drug stock databases, and laboratory surveillance platforms to recalibrate guideline recommendations [20].

Bayesian networks, decision trees, and regression models can be employed to detect early warning signs of ART failure, toxicity clusters, or regional spikes in drug resistance. These analytic models synthesize patient-level variables and population trends to generate actionable outputs for program managers and clinicians. For instance, regional alerts based on rising NNRTI resistance can prompt guideline revisions that down-prioritize those regimens in affected zones [21].

Digital health technologies such as DHIS2, OpenMRS, and SMART guidelines interfaces have enabled automation of this evidence synthesis in some pilot settings. These platforms serve as repositories for structured clinical inputs, linking genomic surveillance outputs with treatment data to support adaptive policy revisions [22].

Real-time decision models have shown particular promise during public health emergencies, where rapid evidence assimilation and protocol changes are critical. While primarily used for outbreak response, their applicability to HIV treatment optimization has gained recognition in sub-national programs where data infrastructure has matured.

Challenges persist in harmonizing heterogeneous data sources, ensuring data completeness, and avoiding overfitting in models. Furthermore, ethical governance surrounding algorithmic bias and patient privacy remains underdeveloped in most national programs [23].

Nonetheless, the shift toward data-driven guideline updates provides a responsive mechanism to keep pace with the evolving clinical landscape. By combining surveillance data with machine learning insights, health authorities can enhance the timeliness, precision, and contextual alignment of HIV treatment protocols [24].

4.3. Policy Considerations for Flexibility and Responsiveness

Embedding flexibility into HIV treatment policy requires a recalibration of traditional policymaking paradigms that favor standardization over contextual agility. Conventional ART policies are often influenced by regulatory conservatism, donor stipulations, and procurement cycles, which delay the uptake of new drugs or resistance-informed adjustments [25]. To overcome this inertia, policies must be restructured to permit conditional approvals and provisional updates based on interim data.

One successful approach has been tiered policy layering, where core treatment algorithms are maintained, but modular components (e.g., dosing, sequencing, substitution options) are updated more frequently based on localized evidence. This layered framework supports national consistency while enabling subnational responsiveness, particularly in regions with unique resistance or demographic profiles [26].

Additionally, policy flexibility is facilitated through institutional mechanisms such as standing expert committees, rapid evidence review units, and decentralized regulatory oversight. For example, ministries of health that established real-time advisory panels for ART guidance were better equipped to implement timely changes in response to programmatic feedback and emerging resistance threats [27].

Financial and legal levers must also support flexibility. Framework contracts with pharmaceutical suppliers should include clauses that accommodate mid-cycle drug substitutions without penalty. Similarly, national formularies must allow provisional listing of promising treatments pending full approval.

Importantly, community involvement and transparency are vital. Rapid guideline shifts without stakeholder consultation risk eroding trust or triggering confusion. Participatory policy models that include frontline providers, PLHIV (people living with HIV) networks, and civil society actors have proven effective in managing transitions smoothly [28].

By embedding responsive design into policy architecture, national HIV programs can balance consistency with agility, ensuring that guidelines remain clinically relevant, contextually grounded, and ethically sound amidst evolving resistance landscapes [29].

4.4. Integration with WHO Recommendations and National Protocols

The World Health Organization (WHO) has historically played a central role in shaping HIV treatment guidelines, providing normative guidance, model regimens, and implementation tools for resource-limited settings. However, aligning national adaptive frameworks with WHO recommendations requires careful balance between global consistency and local specificity [30].

WHO guidelines, typically revised every two to four years, establish baseline expectations for safety and efficacy, often based on multicenter trials and meta-analyses. National protocols traditionally mirror these recommendations to maintain donor alignment and procurement eligibility. Yet, this synchronization can become a constraint when local resistance patterns or host genomic data call for earlier or different interventions [31].

One solution involves framing national guidelines as WHO-aligned but context-modified. For instance, while WHO recommends dolutegravir-based first-line therapy universally, countries with documented integrase inhibitor resistance have amended rollout schedules or introduced alternative agents for specific populations [32]. These context-driven variations reflect adaptive integration rather than deviation.

Another promising avenue is joint evidence review initiatives. Several regions have launched mechanisms whereby local surveillance data are fed into WHO regional offices, informing both local adaptations and potentially accelerating global revisions. Examples include Africa CDC–WHO collaborations on pharmacovigilance and resistance tracking [33].

Technology also facilitates integration. Digital platforms such as WHO's SMART Guidelines architecture support country-level tailoring of content, while maintaining alignment with international standards. These platforms allow seamless updates, track implementation fidelity, and support policy harmonization across diverse health system tiers.

Ultimately, effective integration hinges on mutual respect between global bodies and national authorities, transparent data sharing, and co-investment in adaptive capacity. When executed well, this integration allows for responsive, scientifically grounded HIV treatment policies that leverage both international best practices and indigenous evidence [34].

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5. Strengthening HIV drug resistance surveillance systems

5.1. Role of Sentinel Sites, National Labs, and Community Testing

The effectiveness of HIV drug resistance (HIVDR) surveillance relies heavily on a multilayered architecture that includes sentinel surveillance sites, national reference laboratories, and community-based testing hubs. Sentinel sites provide periodic, structured sampling from select geographic zones and population cohorts. These are often hospital-based ART clinics, maternal health centers, or regional referral facilities where routine virological monitoring can be paired with genotypic analysis [21].

National reference laboratories serve as the central nexus for genotyping and resistance interpretation. These facilities typically house trained personnel, sequencing platforms, and curated bioinformatics pipelines for tracking resistance mutations. When adequately resourced, national labs enable centralized validation, external quality assurance, and policy feedback loops based on emerging resistance profiles [22].

Community testing initiatives, including mobile outreach programs and key population-targeted diagnostics, have also been instrumental in expanding early detection. They capture data from otherwise hard-to-reach groups, including sex workers, MSM (men who have sex with men), and individuals lost to formal follow-up. In areas where community testing is tightly integrated with sample referral systems, resistance surveillance has benefited from broader epidemiological coverage [23].

The synergy between these three layers forms the backbone of an inclusive and resilient HIVDR surveillance network. However, continuity depends on regular supply of test kits, uninterrupted sample transport, and feedback mechanisms that allow community stakeholders to act on findings. Ensuring sustainability of this integrated surveillance system requires both domestic investment and harmonized external support [24].

5.2. Data Collection Standards and Challenges in Low-Resource Settings

Robust HIVDR surveillance hinges not only on clinical infrastructure but also on the standardization and completeness of data collection. In low-resource environments, inconsistent data formats, incomplete case reporting, and irregular sampling schedules frequently undermine surveillance fidelity [25]. National HIV programs have long struggled to balance the need for comprehensive coverage with logistical feasibility.

Standardized data elements such as ART history, viral load results, patient age, and adherence levels must be consistently recorded to ensure meaningful interpretation of genotypic resistance. The WHO has issued minimum datasets for surveillance, yet local health workers often face challenges with manual entries, fragmented paper records, and lack of real-time validation tools [26].

Many programs still rely on batch data abstraction from patient registers and laboratory logbooks. This delay between sample collection and data capture reduces responsiveness and increases the risk of transcription errors. Furthermore, linkage between viral load testing records and genotyping outcomes is frequently inadequate, particularly where different facilities operate under separate vertical reporting systems [27].

Table 3 Comparison of National HIVDR Surveillance Models in LMICs

Country	Surveillance Model Type	Data Integration Approach	Avg. Lab Turnaround (Days)	Reporting Mechanism	Notable Gaps Identified
Kenya	Sentinel Site + National Lab	Manual + Partial Electronic	10–14	Annual summary reports	Delayed feedback to ART clinics
Nigeria	Centralized Surveillance	Paper-based with limited linkage	14–21	Ad hoc donor-based updates	Lack of real-time sequencing
Uganda	Hybrid (National + Community)	Digital records + DHIS2	7–10	Biannual national bulletin	Inconsistent sample transport infrastructure
Cambodia	National Reference Lab Model	Excel-based registry	10–12	Routine MoH updates	Weak integration with clinical care platforms
Zambia	Decentralized Testing Model	Full EMR linkage (pilot phase)	5–7	Integrated dashboard	Limited scale of interoperable data systems

Table 3 presents a comparative overview of HIVDR surveillance frameworks across selected low- and middle-income countries (LMICs). It highlights variation in data integration approaches, lab turnaround times, and reporting mechanisms exposing key structural and operational gaps that influence resistance detection and response capabilities [28].

Efforts to improve data quality must focus on training, digital record systems, and incentives for timely, accurate entry. Without addressing these foundational issues, even well-designed surveillance protocols risk generating incomplete or non-actionable insights [29].

5.3. Innovations in Sample Transport, Sequencing, and Data Sharing

Technological innovation has brought substantial improvements to the logistics of HIVDR surveillance, particularly in sample collection, sequencing methodology, and secure data exchange. One of the most significant advancements has been the deployment of dried blood spots (DBS) for sample collection in remote areas. DBS enables non-cold-chain transport, expanding access to genotyping in rural and underserved populations [30].

For sequencing, the shift from Sanger to next-generation sequencing (NGS) technologies has significantly enhanced throughput and mutation detection sensitivity. Miniaturized sequencers, such as nanopore-based devices, have further lowered the barrier to decentralized testing, enabling select district labs to perform partial genotyping with adequate fidelity [31]. This decentralization has reduced turnaround time for resistance data, supporting faster clinical decision-making.

Data sharing innovations have included cloud-hosted surveillance dashboards, encrypted data portals, and interoperability frameworks that facilitate cross-institutional collaboration. Some national labs have implemented shared bioinformatics pipelines that anonymize and upload sequence data for pooled regional analysis. These systems enable pattern recognition and trend mapping across epidemiologically similar geographies [32].

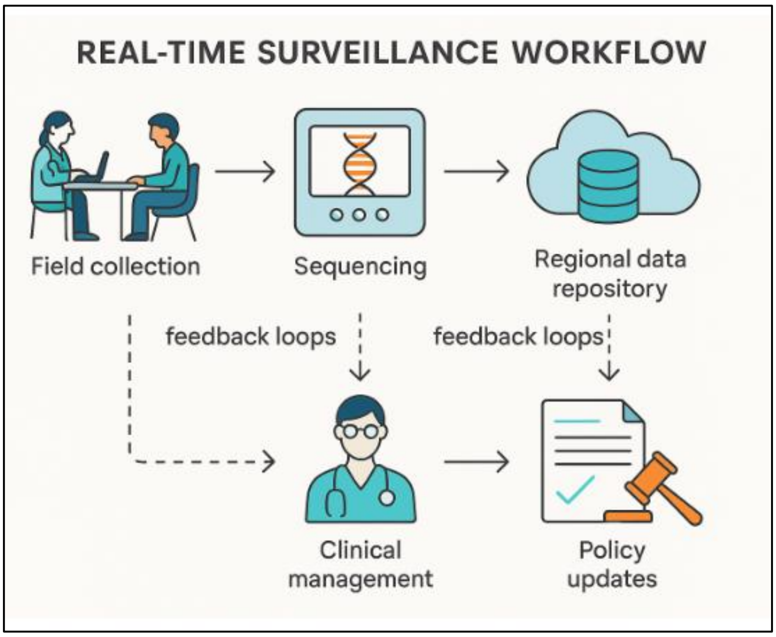

Figure 3 A real-time surveillance workflow that integrates field collection, sequencing, and regional data repositories. The model emphasizes the importance of feedback loops where resistance trends inform both clinical management and policy updates in near real-time [33]

Despite these advances, challenges remain. Limited internet bandwidth, data privacy regulations, and bioinformatics expertise shortages continue to affect the scale-up of these technologies. Strategic partnerships and cloud infrastructure investments are essential for operationalizing these systems more broadly [34].

5.4. Importance of Interoperable Data Systems and Cloud Infrastructure

Interoperable data systems form the backbone of any scalable HIVDR surveillance program, allowing disparate data sources from clinical records and sequencing labs to pharmacy inventory systems to function as a cohesive analytical unit. However, many national programs are encumbered by fragmented digital platforms that lack common protocols, making integration and cross-comparison difficult [35].

Establishing interoperability requires adherence to standardized health information exchange formats such as HL7, FHIR, and openHIE frameworks. These protocols support seamless communication between EMRs, laboratory information systems (LIS), and central databases. In countries where digital health strategies have prioritized modular interoperability, HIVDR surveillance has demonstrated greater consistency and real-time visibility [36].

Cloud-based infrastructure has further enabled elasticity in data storage and processing. National HIV programs can leverage secure, scalable hosting environments to centralize sequence data, automate resistance interpretation, and generate surveillance dashboards accessible to policymakers and clinicians alike. Cloud systems also support automated de-identification and data encryption, which are critical for ensuring patient confidentiality and ethical data sharing [37].

The development of regional cloud repositories, supported by multi-country agreements, has facilitated shared learning and resistance trend comparison. Such repositories are increasingly being used to inform pooled procurement strategies and cross-border treatment harmonization efforts.

To function effectively, these systems require investments in broadband connectivity, cybersecurity capacity, and IT governance frameworks. Without such enablers, the promise of interoperability remains theoretical. Countries that have made strategic cloud and interoperability investments report faster decision cycles, better outbreak preparedness, and more adaptive ART program responses [38].

6. Clinical decision support tools and AI integration

6.1. Role of Electronic Health Records in Monitoring ART Resistance

Electronic Health Records (EHRs) have emerged as essential tools in enhancing HIV care, particularly in monitoring antiretroviral therapy (ART) effectiveness and identifying emerging drug resistance. Properly integrated EHR systems allow clinicians to track a patient's ART history, lab results, adherence patterns, and virological failure trends across time points, enabling earlier detection of resistance-linked anomalies [25].

At their core, EHRs facilitate longitudinal data capture, centralizing patient information from diverse service delivery points community health centers, district hospitals, and national laboratories. When EHRs are synchronized with pharmacy dispensing and viral load systems, they help flag late refills, unsuppressed viral loads, and missed appointments, all of which are indirect indicators of potential treatment failure or resistance [26].

In addition to enhancing individual case management, EHR-based analytics have supported population-level surveillance. Health ministries can extract de-identified datasets to assess regional ART outcomes, resistance patterns, and regimen durability. In several programs, routine viral load and resistance testing have been automatically linked to patient records, triggering alerts when resistance thresholds are exceeded [27].

One of the most transformative applications has been the embedding of clinical decision support tools within EHR platforms. These tools guide clinicians to consider resistance risk factors when switching regimens. For example, alerts might prompt the re-evaluation of patients on non-nucleoside reverse transcriptase inhibitors (NNRTIs) if persistent low-level viremia is detected.

Nonetheless, many health systems continue to operate hybrid or paper-based systems, undermining continuity of care. Expanding full-function EHR platforms remains critical for delivering responsive, resistance-informed HIV treatment and ensuring optimal therapeutic outcomes across diverse settings [28].

6.2. Machine Learning for Predicting Treatment Failure and Recommending Regimens

Machine learning (ML) has demonstrated significant potential in predicting ART treatment failure and offering regimen recommendations based on individual and population-level resistance data. By training on historical patient records, virological outcomes, and resistance mutations, ML algorithms can identify subtle risk patterns that precede clinical failure, enabling pre-emptive intervention [29].

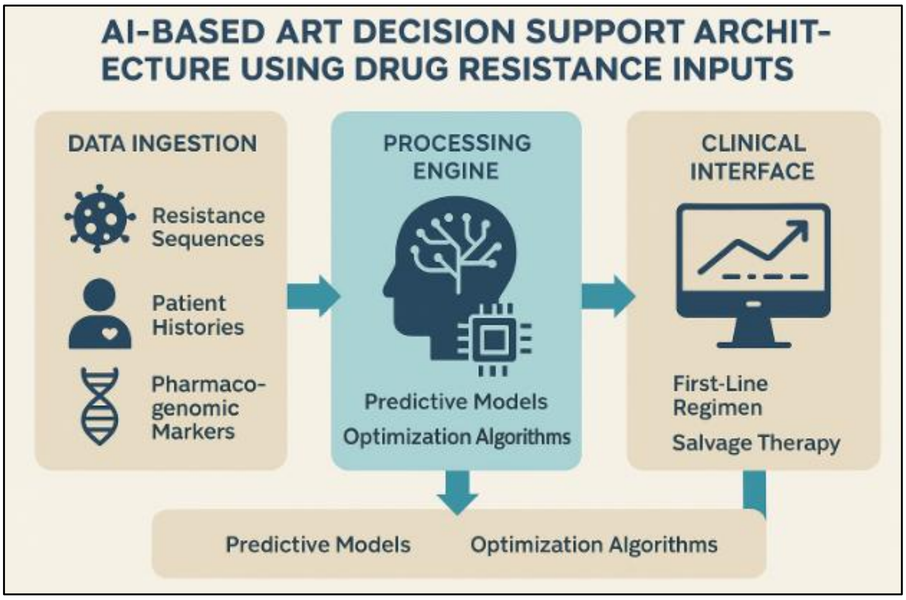

Figure 4 An AI-based ART decision support architecture that integrates drug resistance inputs, patient histories, and pharmacogenomic markers. The architecture includes a data ingestion layer for resistance sequences, a processing engine with predictive models, and a clinical interface that suggests optimized ART regimens for both first-line and salvage therapy [31]

Commonly used techniques include decision trees, support vector machines (SVM), random forests, and neural networks. These models have been developed to assess risk of virologic failure based on factors such as baseline CD4 count, adherence scores, mutation profiles, and ART history. When deployed effectively, ML classifiers have outperformed rule-based systems in predicting regimen durability and failure risk [30].

Moreover, ensemble models and hybrid frameworks have been used to recommend individualized treatment strategies in cases of multidrug resistance. These models learn from large genomic datasets and use probabilistic simulations to forecast mutation pathways under different regimens. In settings where resistance testing is limited, surrogate indicators from clinical and adherence data can still feed predictive algorithms [32].

Real-world implementation remains constrained by poor data quality, limited interoperability, and computational infrastructure. However, pilot studies in high-burden settings have shown promising outcomes in reducing time-to-switch and improving regimen efficacy when ML tools are integrated into clinical workflows [33].

6.3. Validation, Bias, and Ethical Use of AI in HIV Treatment

The deployment of AI and machine learning in HIV care introduces critical challenges around algorithm validation, bias, and ethical application. These issues are particularly acute in resistance prediction models, where decisions have direct implications for regimen selection and long-term patient outcomes [34].

Validation of AI models necessitates rigorous testing across independent datasets to ensure generalizability. However, most existing models have been trained on narrow, often geographically biased datasets, limiting their applicability in diverse epidemiological contexts. For instance, models trained in urban clinics may fail to capture resistance profiles prevalent in rural or migratory populations [35]. Without stratified validation, the risk of recommending suboptimal or toxic regimens increases, especially in vulnerable groups.

Bias can also be embedded in training data due to systemic disparities in healthcare access, adherence monitoring, and laboratory availability. Models may disproportionately misclassify women, children, or key populations if these groups are underrepresented in training cohorts. Ethical deployment thus requires both algorithmic fairness audits and stakeholder review to prevent unintended harm [36].

Further complicating the ethical landscape is the opacity of some predictive models, particularly deep learning networks. Clinicians may struggle to interpret or contest black-box recommendations, eroding trust and accountability. Transparent model documentation, performance metrics, and decision pathways must therefore accompany AI integration in clinical care.

There are also data privacy concerns. The aggregation of genomic, behavioral, and clinical data poses risks of re-identification, especially in stigmatized populations. Strong encryption, anonymization protocols, and data governance frameworks are essential to protect patient confidentiality [37].

Clinical acceptability is another key factor. Resistance-based recommendations must align with national treatment guidelines and consider drug availability. AI systems should enhance, not replace, clinician judgment. Feedback loops, where clinicians can refine or override model outputs, are vital to ensure contextual sensitivity and maintain provider agency [38].

When ethically designed and locally validated, AI systems offer transformative potential to personalize ART, reduce resistance-related morbidity, and accelerate regimen optimization. However, careful implementation and continuous oversight remain imperative to mitigate risks and uphold equity.

7. Multistakeholder engagement and policy development

7.1. Role of Ministries of Health, Donors, and Civil Society

The coordinated engagement of Ministries of Health (MoH), international donors, and civil society organizations (CSOs) has been pivotal in shaping national HIV drug resistance (HIVDR) responses. Ministries of Health serve as the central regulatory and implementation bodies, guiding clinical policies, overseeing laboratory systems, and integrating resistance surveillance into national strategic plans [29]. Their stewardship is essential in aligning donor-funded projects with public health goals and ensuring sustainable integration of surveillance tools within national HIV programs.

Donors, including multilateral agencies and bilateral partnerships, have provided catalytic funding for laboratory upgrades, sequencing platforms, and digital infrastructure. However, the donor landscape is often fragmented, with overlapping priorities and reporting frameworks that sometimes misalign with national systems [30]. Harmonization efforts where donor investments support nationally led objectives are essential to avoid duplication and resource inefficiencies.

Civil society plays a complementary and equally critical role. CSOs are often embedded in communities and offer culturally sensitive advocacy and service delivery. They help to demystify resistance testing, mobilize at-risk populations, and ensure transparency and accountability in public health interventions [31]. Civil society's advocacy has also been influential in pressuring for greater equity in access to genotypic testing and treatment adaptation, particularly for marginalized groups.

Ultimately, resilient HIVDR systems depend on effective coordination among these actors. National ownership, donor alignment with public strategies, and civil society participation collectively strengthen policy coherence and programmatic reach. Failure to engage any one stakeholder risks weakening the entire surveillance and response chain. The strategic collaboration across these spheres has been instrumental in maintaining progress in resistance monitoring, particularly in resource-limited settings [32].

7.2. Building Political Will and Cross-Border Collaboration

Sustaining HIVDR surveillance and response efforts requires robust political will at both national and regional levels. Political commitment manifests through budgetary allocations, regulatory reforms, and strategic prioritization of resistance surveillance as an essential element of HIV control [33]. In many contexts, political inertia has hindered the mainstreaming of resistance testing, often perceived as secondary to more immediate ART scale-up efforts.

Champions within health ministries, parliaments, and regional bodies can play decisive roles in elevating HIVDR to the policy agenda. Legislating dedicated budget lines for genomic surveillance and diagnostic infrastructure ensures long-term sustainability and reduces reliance on external funding. Political will is also expressed through investment in human capital and operational research capacity [34].

Regional cross-border collaboration is equally critical. HIVDR mutations and transmission networks do not conform to national boundaries. Shared procurement platforms, synchronized treatment protocols, and mutual recognition of diagnostic standards can help manage resistance more effectively across countries [35]. Regional Economic Communities (RECs) and intergovernmental organizations have spearheaded some of these initiatives, promoting pooled procurement and integrated surveillance systems.

Cross-border efforts also enhance early detection of emerging resistant strains, especially in border towns and mobile populations. Data harmonization through regional observatories allows timely analysis of resistance trends and facilitates coordinated action [36].

Political and diplomatic mechanisms must complement technical ones. Memoranda of understanding, joint declarations, and harmonized legal frameworks formalize commitments. Ensuring continuity despite political transitions remains a challenge, requiring institutionalized governance mechanisms rather than ad hoc arrangements. By embedding HIVDR collaboration into broader health security frameworks, political will can be both cultivated and preserved [37].

7.3. Capacity Building: Workforce, Training, and Diagnostic Infrastructure

Building resilient HIVDR surveillance and response systems requires sustained investment in workforce development, specialized training, and robust diagnostic infrastructure. One of the foremost limitations in many low-resource settings is the shortage of trained personnel capable of performing and interpreting resistance genotyping [38]. Strengthening the human resource pipeline involves not just laboratory technicians, but also clinicians, data analysts, bioinformaticians, and logistics coordinators.

National training institutions, in partnership with international agencies, have initiated short courses, mentorship programs, and laboratory attachments to close this skills gap. A key area of focus is the operationalization of next-generation sequencing (NGS) workflows, which require distinct competencies in molecular biology, quality control, and data interpretation [39]. Embedding this training into national medical curricula and continuous professional development programs enhances retention and institutional memory.

Diagnostic infrastructure underpins the entire surveillance ecosystem. Many countries still rely on centralized labs located in capital cities, leading to logistical delays in sample transport and turnaround time. Establishing decentralized, tiered laboratory networks with appropriate equipment and cold-chain capacity enhances accessibility and resilience [40]. This is especially crucial in remote or conflict-affected regions where delayed diagnosis translates into prolonged treatment failure.

Procurement of reagents and supplies must also be streamlined. Stockouts of key reagents and breakdowns in procurement systems have periodically disrupted sequencing activities. To mitigate this, buffer stock policies and framework contracts with suppliers can stabilize inputs [31].

Digital connectivity further amplifies capacity. Cloud-based platforms allow real-time data sharing between peripheral labs and national reference centers. Integration with EHRs and surveillance dashboards ensures that resistance data are promptly visualized and acted upon. However, the digital divide manifested through bandwidth constraints and cybersecurity vulnerabilities requires dedicated investment and policy attention [22].

Ultimately, capacity building is not a one-off event but a continuous process. Strong institutions, empowered staff, and robust systems are the cornerstone of an effective HIVDR response and broader health system resilience.

Figure 5 Feedback Loop from Surveillance to Guideline Adaptation and Patient-Level Change

8. Conclusion, implementation roadmap and future outlook

8.1. Pilot Programs and Phased Rollout of Adaptive Guidelines

Implementing adaptive HIV treatment guidelines requires careful piloting and phased deployment to ensure contextual fit and clinical effectiveness. Pilot programs have proven instrumental in translating surveillance insights into actionable policy and care innovations. These pilots typically begin in sentinel sites or high-burden urban centers where clinical data systems, laboratory capacity, and trained personnel are more readily available. This controlled environment allows for safe experimentation and provides a platform for iterative refinement of guideline algorithms.

In early-stage programs, adaptation mechanisms are often embedded into existing care protocols. For example, dynamic switches in ART regimens based on resistance thresholds, side effect profiles, or patient genotypes have been introduced using decision support tools. These pilots are monitored for feasibility, patient adherence, and cost-effectiveness, and often yield valuable lessons on scalability and patient acceptability.

Phased rollouts mitigate the risks of systemic disruptions that can arise from abrupt nationwide implementation. In many cases, pilot findings inform the design of staged expansions into rural or resource-limited settings. These expansions often coincide with workforce training efforts, EHR system upgrades, and stakeholder engagement campaigns to ensure local ownership. Regional adaptation committees, composed of clinicians, policymakers, and laboratory experts, typically oversee the scale-up and contextual customization of the evolving protocols.

Crucially, pilots are designed to account for variation in local epidemiology, resistance patterns, and infrastructure readiness. Lessons learned from one country or region do not automatically apply elsewhere. The iterative nature of pilot programs fosters a culture of evidence-driven guideline development. This approach aligns public health interventions with clinical realities and prepares the health system for resilient adaptation in response to evolving resistance dynamics.

8.2. Monitoring, Evaluation, and Feedback Loops for Guideline Refinement

Monitoring and evaluation (M&E) are fundamental pillars of adaptive HIV care systems. As guidelines become more dynamic, continuous feedback loops must be embedded into programmatic frameworks to ensure that changes lead to tangible improvements in patient outcomes. M&E systems go beyond periodic reviews; they operate in real-time to detect trends in treatment failure, genotypic resistance, regimen toxicity, and service delivery bottlenecks.

At the core of effective M&E are digital health records and centralized dashboards that aggregate patient-level data from multiple care settings. These systems provide disaggregated insights by demographic factors, treatment duration, and geography. Key performance indicators (KPIs), such as viral suppression rates post-regimen change or the frequency of resistance mutation recurrence, are tracked continuously to evaluate the clinical impact of adaptive protocols.

Feedback loops are closed through national technical working groups or HIV guideline committees that convene periodically to review data and revise policies. Such revisions may include updating regimen prioritization, modifying diagnostic thresholds, or introducing new genotyping requirements. In more advanced systems, machine learning algorithms assist in flagging anomalies or emerging trends, offering predictive insights that can inform proactive interventions.

Evaluation efforts also include stakeholder consultations, patient feedback surveys, and cost-effectiveness analyses. These inputs ensure that guideline changes remain patient-centered and equitable. Institutionalizing these loops fosters transparency, strengthens accountability, and accelerates learning within the health system.

Ultimately, adaptive guideline systems cannot succeed without robust M&E infrastructure. They depend on real-time information, interdisciplinary decision-making, and a willingness to iterate based on data. This continuous improvement approach is what enables HIV care models to evolve responsively and maintain clinical relevance amidst a changing resistance landscape.

8.3. Envisioning the Role of Adaptive HIV Care in Universal Health Coverage

Adaptive HIV care holds transformative potential for advancing universal health coverage (UHC) in low- and middle-income countries. The shift toward personalized, evidence-driven protocols aligns with the broader ethos of UHC: delivering high-quality, equitable, and people-centered care. Unlike static guideline systems that offer one-size-fits-all approaches, adaptive HIV care is responsive to local epidemiological realities, genetic diversity, and patient needs. This responsiveness ensures that services not only reach more people but also achieve better outcomes.

As health systems grapple with resource constraints, adaptive care offers a path to smarter allocation. By tailoring treatment regimens to individuals based on resistance profiles or pharmacogenomic markers, systems reduce unnecessary drug switches, prevent costly treatment failures, and extend the utility of existing antiretroviral formulations. This optimization is especially crucial where second- and third-line therapies are scarce or prohibitively expensive.

The integration of real-time surveillance, digital health platforms, and clinical decision tools enables a more agile response to shifts in resistance patterns. Such systems promote early detection of emerging challenges and facilitate targeted interventions, ultimately enhancing program efficiency. Importantly, these tools can be scaled beyond HIV care to other disease programs, thereby strengthening the broader digital health ecosystem.

From a governance standpoint, adaptive care requires decentralization, transparency, and community engagement. Empowering regional clinics to adjust protocols based on real-time data enhances local accountability and reinforces the trust of service users. It also catalyzes the transition from donor-dependent models to nationally owned and led systems.

Lastly, adaptive HIV care reinforces the equity dimension of UHC. Vulnerable populations such as adolescents, women, and key populations often experience higher rates of resistance and treatment discontinuation. By enabling individualized and timely interventions, adaptive models reduce disparities and advance health justice.

In envisioning HIV care that is both flexible and inclusive, health systems take a significant step toward achieving the promise of universal coverage. Adaptive guidelines thus serve as both a technical innovation and a moral imperative.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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