

▪ NARRATIVE REVIEW

Adherence to Antiretroviral Therapy (ART) Among People Living with HIV/AIDS (PLWHA): A Structured Narrative Review

Nwankwo Victoria U¹, Ukwu David O^{3,8}, Ozomma Chizoba C⁵, Mbah Joseph O³, Chigozie Victor U², Ogbonna Chigozie A^{3,7}, Obila Mary U^{3,6}, Ofor Amala C⁴, Okpalanma Nneoma N^{3,6}, Anetoh Maureen U¹, Umeh Blessing I¹, Ogudu Friday O^{3,7}, Nnamani Monica N^{3,6}, Eze Daniel U², Ogbonna Brian O^{3,6,*} 

¹Department of Clinical Pharmacy and Pharmacy Management, Faculty of Pharmacy, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria

²Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmacy, David Umahi Federal University of Health Sciences, Uburu, Nigeria.

³International Institute for Health Policy, Systems and Knowledge Translation, David Umahi Federal University of Health Sciences, Uburu, Nigeria

⁴Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Enugu State University of Science and Technology, Enugu, Enugu State

⁵Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, University of Calabar, Nigeria

⁶Department of Clinical Pharmacy and Pharmacy Practice, College of Pharmacy, David Umahi Federal University of Health Sciences, Uburu, Nigeria

⁷Department of Anaesthesia, College of Medicine, David Umahi Federal University of Health Sciences, Nigeria.

⁸International Eye Center, David Umahi Federal University of Health Sciences, Uburu, Nigeria

***Corresponding author:** Ogbonna Brian O, Department of Clinical Pharmacy and Pharmacy Practice, College of Pharmacy, David Umahi Federal University of Health Sciences, Uburu, Nigeria. | Email: ogbonnabo@dufuhs.edu.ng | ORCID iD: <https://orcid.org/0000-0002-7015-8263>

Received: 14 September 2026 · Revised: 05 October 2026 · Accepted: 12 October 2026 · Published: 16 October 2026



© 2026 The Author(s). Published by Gnoscience Publishing House. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License.

ABSTRACT

Background. The advent of Highly Active Antiretroviral Therapy (HAART) has changed Human Immunodeficiency Virus (HIV) infection from an uncontrollable and lethal diagnosis into a manageable and controllable chronic condition. Overall, the clinical and epidemiological success of this therapeutic revolution hinges on strict patient adherence. This narrative review synthesized clinical data and public health perspectives to evaluate the critical thresholds of adherence, the biological mechanics of drug resistance, and the multi-tiered barriers that impede optimal treatment compliance across diverse global settings.

Main Text. A narrative synthesis of key literature was conducted, integrating foundational clinical trials, behavioral studies, and regional epidemiological reports detailing adherence challenges. A 95% adherence value remains the optimal benchmark for older or complex regimens, but newer agents offer slightly more pharmacokinetic flexibility to achieve good viral suppression and prevent CD4 count depletion. Drops below this benchmark trigger viral replication, creating sub-therapeutic pharmacokinetic windows that could select for drug-resistant mutant strains. This may induce cross-resistance that exhaust future line-of-defense therapies. Mechanistically, a drop in adherence could interfere with increase in drug resistance, complications, and mortality. While developed nations face barriers primarily driven by drug toxicities, psychiatric comorbidities, and lifestyle disruptions, resource-limited settings confront profound structural obstacles, including systemic supply chain failures, catastrophic out-of-pocket costs, and deep-seated psychosocial stigma.

Conclusion. Adherence is not merely an individual behavioral variable but a complex public health challenge. Maximizing the long-term durability of first-line regimens requires a paradigm shift: bridging precise clinical management with structural interventions that secure drug supply, alleviate financial burdens, and dismantle institutional stigma.

Keywords: Adherence; Highly Active Antiretroviral Therapy (HAART); HIV; PLWHA; Resistance

1. Introduction

The advent of Highly Active Antiretroviral Therapy (HAART) is one of the most remarkable achievements in modern clinical medicine, effectively shifting Human Immunodeficiency Virus (HIV) infection from an inevitably fatal condition to a containable chronic disease. Despite the availability of highly potent antiretroviral (ARV) agents, the real-world success of this therapeutic milestone does not rely solely on pharmacological efficacy. Instead, as established in foundational literature, patient adherence remains the single most critical determinant governing the success of anti-HIV management [1]. In the context of HIV therapeutics, adherence operates at a uniquely demanding intersection of clinical precision and public health infrastructure, representing an unforgiving clinical paradigm where even minor behavioral lapses yield catastrophic biological failures [2].

From a clinical medicine perspective, adherence dictates the precise pharmacokinetic equilibrium required to inhibit viral replication. The biological mechanics of HIV are distinct; when a patient skips even a single dose, blood concentrations of the drug fall below therapeutic thresholds, granting the virus an immediate window to replicate at an accelerated rate. Sub-optimal compliance triggers a predictable, destructive cascade: viral loads spike, CD4+ T-lymphocyte counts decline, and the patient faces rapid clinical progression toward Acquired Immunodeficiency Syndrome (AIDS), resulting in increased hospitalization rates and premature death. Beyond immediate clinical decline, sub-optimal adherence could trigger the negative public health issue called drug resistance. Because HIV possesses a high mutation rate, low drug levels fail to halt viral replication but provide enough selective pressure to kill off wild-type strains, giving drug-resistant mutants a distinct competitive advantage. These resistant strains quickly replicate to form the dominant viral population within the host. This biological shift may render the virus impervious to entirely different classes of ARVs that the patient has not yet even taken [2,3].

Consequently, the patient is left with highly complex, toxic, and expensive second- or third-line regimens. Because a patient's initial ARV regimen offers the absolute best statistical chance for long-term clinical success, preserving its durability through flawless adherence is a paramount medical priority. While clinical efficacy requires near-perfect adherence, typically defined as retaining at least 95% to 100% of prescribed doses, achieving this benchmark is exceptionally difficult. HIV is one of the most challenging chronic illnesses to manage due to severe medication toxicities (such as nausea, diarrhea, and vomiting), lifelong treatment durations, and complicated dosing schedules that must be strictly coordinated around dietary restrictions [2-4].

Furthermore, a sharp divide exists between the adherence barriers encountered in developed nations versus resource-limited settings. While patients in high-income countries are often constrained by lifestyle disruptions, forgetfulness, and psychiatric comorbidities like depression, individuals in developing regions face deep structural and socioeconomic crises. In resource-limited environments, adherence is profoundly undermined by weak drug procurement systems, manufacturer stockouts, catastrophic financial constraints, and severe social stigma [3,4]. This narrative review synthesized clinical data and public health perspectives to evaluate the critical thresholds of adherence, the biological mechanics of drug resistance, and the multi-tiered barriers that impede optimal treatment compliance across diverse global settings.

2. Methods

We searched three electronic databases, namely PubMed, Medline, and Google Scholar, focusing on peer-reviewed studies, clinical trials, and epidemiological reports published up to mid-2024. The primary search terms used in various Boolean combinations included: "antiretroviral therapy", "ART adherence", "highly active antiretroviral therapy", "HAART", "people living with HIV/AIDS", "PLWHA", "educational interventions", "integrated care management", "collaborative care", and "Nigeria". Studies were selected for primary synthesis if they evaluated

quantitative adherence rates (measured via self-reports, pill counts, pharmacy refills, or microelectronic monitoring systems), psychosocial or structural barriers to compliance, or the direct impact of educational and case-management models on viral suppression. A total of 36 papers were initially screened against these core criteria. Of these, 26 papers were excluded due to methodological inconsistencies, overlapping timelines, or duplication, leaving 10 primary papers that served as the foundational dataset for the core comparative analysis and tabular synthesis. To ensure a comprehensive narrative review, an additional 20 secondary references were integrated into the manuscript. These supplementary sources were utilized exclusively to ground the historical background in the introduction and to validate the molecular, virological, and epidemiological mechanisms of drug resistance discussed in the subsequent sections. The final synthesized literature was analyzed using a thematic narrative approach, categorizing findings into adherence metrics, global compliance barriers, and care integration strategies.

2.1. Literature Search Strategy Summary

The narrative review utilized a systematic search strategy to identify literature published up to mid-2024. While the authors screened 36 papers and formally included 10 primary studies for core synthesis, the manuscript lists 30 references in total. This difference exists because the extra 20 references provide clinical background, contextual frameworks, and biological descriptions in the introduction and discussion sections rather than serving as primary data sources for the review.

2.1.1. Breakdown of the Search Strategy

- Databases searched: PubMed, Medline, and Google Scholar.
- Search dates: publications up to mid-2024.
- Search terms: various Boolean combinations of terms including “antiretroviral therapy”, “ART adherence”, “highly active antiretroviral therapy”, “HAART”, “people living with HIV/AIDS”, “PLWHA”, “educational interventions”, “integrated care management”, “collaborative care”, and “Nigeria”.

2.1.2. Eligibility Criteria

Studies were eligible for inclusion if they evaluated:

- Adherence measurements: quantitative adherence rates measured via self-reports, pill counts, pharmacy refills, or microelectronic monitoring systems (MEMS).
- Barriers: psychosocial, socioeconomic, and clinical barriers to therapeutic adherence.
- Interventions: the impact of educational and case-management models on viral suppression.
- Geographic scope: global datasets to establish baseline thresholds, with focused extractions on sub-Saharan Africa and local Nigerian states.

2.1.3. Study Selection Process

1. Initial screening: a total of 36 papers were initially screened.
2. Exclusion: 26 papers were excluded due to duplicate entries, timing issues, or methodological inconsistencies.
3. Final selection: 10 papers were officially selected for core thematic analysis and narrative synthesis.

2.1.4. Resolving the Reference Discrepancy

The discrepancy between the 10 included papers and the 30 listed references is a standard characteristic of structured narrative reviews. It is resolved by distinguishing between core synthesized data and supporting literature. Core Review Studies (References 1–10): References 1 and 2 establish historical and foundational clinical trial contexts in the Introduction. These 10 selected papers (References 1–10), represent the primary studies evaluating adherence metrics, settings, and monitoring tools. These are directly synthesized inside the manuscript's main tables (Table 1 and Table 2) and thematic comparisons. Background and Discussion Literature (References 11–30): the remaining 20 references are used to build the narrative framework. References 11 through 30 are

utilized in the Discussion section to support statements regarding the biological mechanics of drug resistance, cross-resistance, and the clinical consequences of switching to second- or third-line therapies.

3. Results and Discussion

The table below outlines the divergent challenges encountered by patients across different socioeconomic landscapes.

Table 1. Comparative Barriers to HIV Adherence in Developed vs. Resource-Limited Settings.

Barrier Category	Developed Settings (e.g. Europe, North America)	Resource-Limited Settings (e.g. Sub-Saharan Africa)	Key Impact on Adherence
Primary Systemic Drivers	Behavioral, psychiatric, and lifestyle factors (New York State Department of Health AIDS Institute 2006) [4]	Structural, financial, and supply chain failures (Bangsberg 2008) [3]	Dictates whether interventions should target individual psychology or macro infrastructure.
Supply and Logistics	Consistent, uninterrupted access to medication via robust insurance or state programs.	Weak drug procurement, delayed shipments, and manufacturer stockouts (Laurent et al. 2005) [5]	Causes forced clinical interruptions, accelerating viral rebound.
Financial Constraints	Out-of-pocket costs for premium insurance plans; generally cushioned by state subsidies.	Direct treatment costs, lack of money for transport, and food insecurity (Afolabi et al., 2009) [6]	Forces patients to choose between purchasing food or securing daily life-saving ARV refills.
Clinical Environment	High provider-to-patient ratios allowing for tailored, long-term counseling sessions.	Overburdened clinics, short counseling windows, and poor provider attitudes.	Results in patient confusion due to inadequate instructions on complex dosing.
Socio-Cultural Context	Inconvenience, traveling away from home, or difficulty fitting medication into busy work schedules.	Deep-seated communal stigma, fear of status disclosure, and reliance on faith healing (Afolabi et al., 2009) [6]	Drives patients to miss doses to hide their status from family, friends, or coworkers.

Table 2. Comparison of ART Adherence Monitoring Tools.

Adherence Monitoring Tool	Accuracy Level	Cost & Feasibility	Key Advantages	Primary Limitations & Biases	Reference
Microelectronic Monitoring Systems (MEMS) Caps	Highly Accurate	Low Feasibility (Expensive)	Provides objective, precise, and highly reliable data.	Severely limited by high costs and logistical constraints in developing countries.	Mannheimer et al. (2002) [7]

Adherence Monitoring Tool	Accuracy Level	Cost & Feasibility	Key Advantages	Primary Limitations & Biases	Reference
Unannounced Pill Counts	Highly Accurate	Low Feasibility (Logistically Complex)	Delivers objective and highly accurate adherence measurements.	Restricted by high costs and severe logistical constraints in resource-limited settings.	Paterson et al. (2000) [8]
Pharmacy Refill Data Tracking	Practical, scalable adherence proxy; refill-rate changes track with viral load changes	High Practical Feasibility	Tracks adherence through routine pharmacy management information systems, without requiring expensive monitoring chips or protocols.	Requires organized pharmacy data infrastructure to remain functional.	Grossberg et al. (2004) [9]
Patient Self-Reports	Low Accuracy	High Feasibility (Inexpensive)	Most widely utilized method in low-income regions due to low cost and minimal patient burden.	Routinely overestimates adherence rates due to social desirability and recall biases.	Wagner (2002) [10]

MEMS, microelectronic monitoring systems.

Table 3. Methodological Profiling and Comparative Barriers to HIV Adherence.

Barrier Category	Study Design and Population Type	Developed Settings (e.g., North America, Europe)	Resource-Limited Settings (e.g., Sub-Saharan Africa)	Key Impact and Quantifiable Findings	Primary Systemic Drivers
Primary Systemic Baseline	Guidelines analysis and multi-center cohorts; population: mixed clinical cohorts across high-income vs. low- and middle-income countries (LMICs).	Behavioral, psychiatric, and lifestyle factors predominate.	Macro-structural, financial, and systemic supply disruptions drive the data.	Defines target vectors: determines whether compliance interventions should target individual psychology or macro-infrastructure.	Individual behavior vs. macro infrastructure (Bangsberg, 2008; NYSDOH, 2006 [4])

Barrier Category	Study Design and Population Type	Developed Settings (e.g., North America, Europe)	Resource-Limited Settings (e.g., Sub-Saharan Africa)	Key Impact and Quantifiable Findings	Primary Systemic Drivers
Supply Chain and Logistics	Open-label longitudinal cohort study; population: adults on HAART in West Africa (Senegal, N = 158).	Robust insurance or state-subsidized programs guarantee consistent, uninterrupted drug access.	Weak drug procurement networks, prolonged shipping delays, and frequent localized manufacturer stockouts.	Forced therapy interruptions: 21.5% of patients experienced clinical drug gaps; 58% of those gaps were driven entirely by pharmacy stockouts.	Operational infrastructure vs. market procurement instability (Laurent et al., 2005 [5])
Financial Constraints	Cross-sectional survey / mixed methods; population: outpatients at a tertiary clinic (Nigeria, N = 150).	Out-of-pocket costs are confined to premium insurance plans, heavily cushioned by state safety nets.	High direct treatment costs, complete lack of transport capital, and severe domestic food insecurity.	Binary survival choices: catastrophic out-of-pocket spending directly forces patients to choose between buying food or daily life-saving refills.	Household poverty index vs. healthcare subsidy distribution (Afolabi et al., 2009 [6])
Clinical Environment	Cross-sectional survey / quantitative audit; population: regional public health outpatients (Nigeria, N = 150).	High provider-to-patient ratios allowing for tailored, long-duration, multi-session counseling.	Severely overburdened public clinics, compressed counseling windows, and degraded provider attitudes.	Patient confusion and non-compliance: short consultation windows directly impair the delivery of critical instructions on complex dosing and dietary boundaries.	Professional workforce density vs. institutional employee burnout (Afolabi et al., 2009 [6])
Socio-Cultural Context	Cross-sectional survey / qualitative analysis; population: public health tracking cohorts (Nigeria, N = 150).	Inconvenience, traveling away from home, or difficulty fitting pill schedules into busy work routines.	Deeply institutionalized communal stigma, acute fear of status disclosure, and heavy reliance on spiritual faith healing.	Deliberate treatment boycott: stigma accounts for a significant proportion of missed clinic appointments, as patients skip collections to conceal status from peers.	Public health enlightenment vs. deep-seated cultural discrimination (Afolabi et al., 2009 [6])

Table 4. Empirical Quantifiable Metrics for the Core Tracking Studies.

Study Group and Reference	Study Design and Population	Quantifiable Findings and Statistical Intervals	Reference / Citation
Group A: Objective Longitudinal Tracking Methods	Design: prospective, multi-center longitudinal observational sub-study embedded within clinical trials. Population: US-based adult cohorts (N = 1,414).	Adherence rate ($\geq 95\%$) strongly correlates with viral suppression. Patients with $\geq 95\%$ execution rate had an Odds Ratio (OR) of 2.68 (95% CI: 1.89–3.81) for maintaining complete viral suppression compared to lower adherence levels.	Mannheimer et al., 2002 [7]
Group A: Objective Longitudinal Tracking Methods	Design: prospective observational cohort study tracking HIV-infected adults on protease inhibitor-based regimens. Population: North America (N = 81).	Established the landmark $\geq 95\%$ compliance threshold. Virologic failure occurred in 22% of patients with $\geq 95\%$ adherence, 61% with 80–94.9% adherence, and 80% with $< 80\%$ adherence ($p < 0.001$).	Paterson et al., 2000 [8]
Group B: Pragmatic Electronic Tracking Methods	Study Design: An observational cohort study designed to validate a pharmacy-based "time-to-refill" tracking method against traditional patient self-reporting. Population: HIV-infected individuals on HAART for at least 3 months. Setting: Medical Center in Philadelphia, Pennsylvania. (N = 110).	Pharmacy Refill Measure: For every 10% increase in adherence, the viral load decreased significantly by 0.12 log c/mL (95% CI: 0.01 to 0.23 log c/mL).	Grossberg et al., 2004 [9]
Group C: Subjective Behavioral Monitoring Methods	Design: comparative methodological evaluation cohort tracking adults on HAART over a 6-month period. Population: US-based (N = 114).	Patient self-reports consistently overestimated compliance by a mean margin of 10% to 15% when calibrated against objective microelectronic monitoring data. Found self-reporting to be highly feasible but heavily skewed by social desirability and cognitive recall biases.	Wagner, 2002 [10]

CI, confidence interval; HR, hazard ratio; OR, odds ratio.

4. Discussion

4.1. Key Clinical Context

The threshold: maintaining near-perfect medication adherence ($\geq 95\%$) is essential for adequate and sustained suppression of viral replication. Sub-optimal adherence: dropping below this threshold restarts viral replication, increases plasma viral load, drops CD4+ T-cell counts, accelerates progression to AIDS, and mutates drug-resistant

strains. The tables depict the vulnerabilities and limitations of the global health systems and infrastructures and the points of failure of the clinical strategies.

4.2. Barriers to HIV Adherence

Barriers to adherence are multi-dimensional and contextual. Globally, these are grouped into patient variables (age, forgetfulness, depression), treatment characteristics (pill burden, complex dosing schedules, severe side effects like diarrhea or nausea), and social-environmental parameters (HIV-related stigma, lack of disclosure, and weak family support). Strikingly, the review highlights clear disparities between developed and developing nations. In high-income countries, non-adherence is predominantly driven by drug side effects, substance use, and lifestyle inconveniences [5]. Conversely, in resource-limited settings like Nigeria, the primary barriers are structural and financial, including running out of medications, an inability to purchase companion treatments due to low per capita income, transport costs to clinics, and frequent supply chain disruptions or institutional stock-outs [3,6].

In addressing the barriers, integrated care management and collaborative care models offer substantial promise. Standard usual care can be enhanced by embedding case managers or health coaches such as trained nurses or pharmacists directly into primary HIV clinical settings. Evidence shows that clinics utilizing integrated services (offering psychological, social, and co-infection management alongside primary ART) help patients achieve higher viral suppression rates than single-service clinics. It can significantly improve adherence and narrow regional health disparities. However, the real-world effectiveness of these collaborative care models is highly variable when scaled outside controlled trial environments. In overburdened, low-income clinics characterized by low provider-to-patient ratios, the operational demands of intensive case-management can strain existing human resources and exacerbate poor provider attitudes. Implementing structured, case manager-led educational interventions within these clinics utilizes existing staff in a streamlined, cost-effective manner to systematically improve patient-reported compliance and narrow regional health disparities. The adherence intervention that is not individualized or tailored to the patient's needs is bound to fail with time. The utilization of strategies based on patients' lifestyle modifications, psychosocial and mental health peculiar to developed countries is bound to fail in developing countries. In resource-limited settings like sub-Saharan Africa, non-adherence is often associated predominantly with health system failures, e.g., poor drug supply chain and management systems, high cost of medications, catastrophic spending, dysfunctional health insurance systems, and poverty, more so than personal forgetfulness. Claims regarding the universal cost-effectiveness of these interventions are often overstated. While team-based collaborative care may offer long-term financial benefits by reducing hospitalization rates and preserving the durability of less expensive first-line regimens, they require substantial initial structural capital and steady public funding. Consequently, their short-term implementation lacks structural feasibility in health systems plagued by frequent supply chain failures, unless paired with macro-level policies addressing direct medication costs and procurement security.

Stigma, usually associated with poor enlightenment and negative attitude of the society on the PLWHIV, causes more havoc than the virus itself, since the PLWHIV are discriminated against, leading to psychological trauma and deliberate boycott of their clinic appointments to conceal their status from relatives and coworkers, leading to resistance development that further compounds their status [6]. Stigma is a powerful *confounding variable* or *indirect barrier*. It is statistically associated with non-disclosure and fear, which subsequently limits a patient's capacity to open medication or attend clinics safely in communal spaces. MEMS and unannounced pill counts are very effective tools in monitoring ART adherence. However, they are limited by non-affordability and ineffective supply chain services in developing countries. Hence, self-report still remains popular in these regions. It is usually limited by recall biases and the desirability of the social dimension, leading to overestimation of adherence. From Table 2, pharmacy refill tracking is ideal and stands as a middle ground among the rest. It simply shows that adherence could be tracked through proper management information systems that do not involve expensive chips and protocols, as opined by Grossberg et al. [9].

4.3. The Biological Mechanics of Drug Resistance

Inconsistent, suboptimal adherence or missed doses of Highly Active Antiretroviral Therapy (HAART) can permit viral replication under drug pressure, which may contribute to the selection of drug-resistant variants. The extent to which this compromises future treatment options or leads to cross-resistance is not an absolute certainty; rather, it depends on the specific drug regimen, its genetic barrier to resistance, and individual pharmacokinetic and pharmacogenomic factors. Because HIV-1 replicates at a rapid rate and lacks a proofreading mechanism during reverse transcription, it exists within the host as a dynamic pool of closely related genetic variants, known as a mutant quasi-species. When a patient maintains perfect adherence, circulating drug concentrations remain above the minimum inhibitory concentration (MIC) required to block viral replication. Under these optimal pharmacokinetic conditions, viral replication is completely suppressed, and the generation of new genetic mutants is halted [7,8].

Conversely, total non-adherence leads to the complete clearance of the drug from the plasma. While this causes a rapid rebound in viral load and a drop in CD4+ T-lymphocyte counts, it paradoxically exerts no selective impact on the Human Immunodeficiency Virus because there is no active drug present to restrict wild-type replication. So, 100% adherence leads to high plasma drug levels and total viral suppression. Sub-optimal adherence leads to low and fluctuating drug levels, selective pressure, and resistance. In the complete absence of a drug, wild-type HIV-1 has a significant replication fitness advantage over mutated strains. Mutant strains usually carry structural defects in viral enzymes (e.g., reverse transcriptase), making them replicate slower than wild-type virus when unhindered. When sub-therapeutic drug windows are introduced via skipped doses, that selective pressure neutralizes the wild-type virus while allowing the drug-resistant mutants to thrive.

When doses are skipped, taken late, or taken incorrectly, plasma drug concentrations fall into a sub-therapeutic window. This intermediate drug level is too low to stop the virus from reproducing, yet high enough to kill off the drug-sensitive wild-type strains. This creates a powerful evolutionary selection pressure. Mutant strains capable of replicating despite the presence of the drug gain a distinct competitive advantage. These drug-resistant strains quickly become the dominant viral population in the body, leading to clinical treatment failure [9,10].

The consequences of this resistance extend far beyond the failure of a single drug. Genetic mutations may alter the molecular structure of viral enzymes such as reverse transcriptase, protease, or integrase in ways that disrupt the binding mechanics of different therapeutic agents in different classes of medications. This may lead to cross-resistance, meaning the virus can become immune not only to the current drug being taken but may also affect other ARVs within the same therapeutic class that the patient has never even tried. This biological shift carries severe clinical consequences for the patient. It may lead to the compromise of first-line therapy. The patient may develop resistance leading to treatment failure. This may trigger an increase in viral load and a decline in CD4+ counts [11-16].

There is transition to complex regimens when adherence to ART is compromised. The patient is encouraged to switch to second- or third-line therapies. These alternative regimens often involve a much higher pill burden. They are challenging when considering daily schedules, and carry a higher risk of severe toxicities and adverse drug interactions [17-22]. Loss of the “first-regimen advantage” is often difficult to avoid. Many clinical data confirms that a patient's very first antiretroviral regimen offers the absolute best statistical chance for long-term clinical success and viral suppression. Once resistance compromises this initial regimen, managing the disease becomes progressively more difficult, expensive, and toxic, highlighting why near-perfect adherence from day one is absolutely vital [23-30]. Modern Integrase Strand Transfer Inhibitor (INSTI)-based regimens (like Dolutegravir or Bictegravir) have a much higher genetic barrier to resistance and prolonged plasma half-lives, making them significantly more “forgiving” at lower adherence rates (e.g., 80-90%) [24-30].

5. Conclusion

Achieving the international UNAIDS 95-95-95 targets, which dictate that 95% of people living with HIV know their status, 95% of those diagnosed receive sustained antiretroviral therapy (ART), and 95% of those on treatment

achieve viral suppression, requires a comprehensive public health framework. The findings of this review demonstrate that maximizing the clinical success of the final tier of this cascade—sustained viral suppression—relies heavily on minimizing structural and socio-behavioral barriers to medication compliance. Structured educational interventions and clinic-embedded, collaborative care management systems show distinct utility in optimizing adherence metrics within controlled clinical environments. However, a “one size fits all” strategy is structurally inadequate. While high-income infrastructure allows for highly individualized, technologically tracked behavioral coaching, resource-limited health systems face systemic supply chain failures and deep-seated communal stigma that demand macro-level public policy interventions rather than individual behavioral corrections alone. Clinic-embedded team care involving nurses and pharmacists shows promise in improving patient follow-up, but its broader implementation must be tailored carefully to prevent staff burnout in overburdened settings.

6. Limitations

Several critical methodological constraints limit the generalizability and scope of the findings compiled in this review:

Absence of Formal Quality Appraisal: The included primary literature did not undergo a structured, standardized risk-of-bias or quality appraisal protocol (such as the Cochrane Risk of Bias tool or the Newcastle-Ottawa Scale), meaning the baseline methodological rigor of the synthesized studies varies unchecked.

Literature Search and Selection Constraints: The search strategy was restricted to three electronic databases (PubMed, Medline, and Google Scholar) and published materials up to mid-2024, potentially omitting relevant grey literature, regional institutional reports, or very recent trials.

Adherence Measurement Heterogeneity: The reviewed studies utilize highly divergent compliance tracking methods. A substantial proportion of data from resource-limited regions relies entirely on patient self-reports, which carry profound recall and social desirability biases that routinely overstate true adherence rates. Conversely, highly accurate measures like Microelectronic Monitoring Systems (MEMS) are poorly represented due to their logistical infeasibility in low-income clinics.

Implementation Scalability Limitations: Many evaluated care-management models were executed as highly controlled, resource-intensive clinical trials. These models frequently lack structural feasibility and financial sustainability when scaled up within standard, public-sector health environments in high-burden, resource-limited states.

7. Recommendations

Based on the synthesized evidence, the following actions are recommended to optimize ART adherence programmatically:

Differentiate Socioeconomic Drivers: Policymakers and clinicians must design adherence support strategies that match the infrastructure of the local population. Interventions in resource-poor environments should prioritize mitigating macro-structural barriers, such as supply logistics, rather than relying strictly on individual behavioral modifications adapted from high-income countries.

Standardize Practical Compliance Metrics: Healthcare facilities in low- and middle-income regions should transition toward standardized pharmacy refill tracking as a primary, cost-effective programmatic indicator of adherence, supplementing it with structured, verbal verification drills during routine visits.

Qualify Collaborative Care Transitions: When deploying team-based care models that utilize pharmacists and nurse case managers for educational counseling, clinics must carefully audit baseline staff workloads to prevent operational bottlenecks and ensure that additional administrative demands do not degrade patient-provider interactions.

Dismantle Financial and Structural Barriers: Health ministries must prioritize securing uninterrupted drug procurement chains and expanding fully subsidized or free access to both first-line regimens and routine laboratory monitoring to minimize catastrophic out-of-pocket costs and forced clinical treatment interruptions.

AUTHOR CONTRIBUTIONS

NVU. and B.O.O conceived and developed the study and its framework. U.D.O, O.C.C, M.J.O, C.V.U, O.M.U, O.A.C, O.N.N, A.M.U, U.B.I., O.C.A, O.F.O, N.M.N, E.D.U, and N.V.U participated in the literature search. NVU. B.O.O, U.D.O, O.C.C, M.J.O, C.V.U, O.M.U, and O.A.C synthesized the tables. NVU. and B.O.O wrote the initial draft. NVU. and B.O.O prepared the final document. B.O.O proof-read and corrected the final manuscript.

ETHICS APPROVAL

Ethical approval was not required for this study.

CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study received no funds from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors have none to declare.

DATA AVAILABILITY

Not applicable.

REFERENCES

1. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence, Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care*. 2000;12(3):255-266.
2. Sepkowitz KA. AIDS—the first 20 years. *N Engl J Med*. 2001;344:1764-1772.
3. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. *J Infect Dis*. 2008;197(Suppl 3):S272-S278.
4. New York State Department of Health AIDS Institute. Pharmacists: Partners in Health Care for HIV-Infected Patients. [Accessed February 26, 2024]. Available from: hivguidelines.org
5. Laurent C, Ngom Gueye NF, Ndour CT, et al. Long-term benefits of highly active antiretroviral therapy in Senegalese HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2005;38:14-17. doi:10.1097/00126334-200501010-00003.
6. Afolabi MO, Ijadunola KT, Fatusi AO, et al. Determinants of adherence to antiretroviral drugs among people living with HIV/AIDS in the Ife-Ijesa zone of Osun state, Nigeria. *Afr J Prim Health Care Fam Med*. 2009;1(1):1-6.
7. Mannheimer S, Friedland G, Matts J, et al. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis*. 2002;34:1115-1121.
8. Paterson DL, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21-30.
9. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. *J Clin Epidemiol*. 2004;57(10):1107-1110. doi:10.1016/j.jclinepi.2004.04.002.
10. Wagner GJ. Predictors of antiretroviral adherence as measured by self-report, electronic monitoring, and medication diaries. *AIDS Patient Care STDS*. 2002;16:599-608.

11. Ibrahim GTW, Mustafe MA, Abdirahman KR. Non-adherence to antiretroviral therapy and associated factors among adult HIV patients in Somali region public hospitals, eastern Ethiopia. *Int J Afr Nurs Sci.* 2023;19:100645. doi:10.1016/j.ijans.2023.100645
12. Dzimbanhete MT, Shambira G, Tshimanga M, et al. Non-adherence and first line antiretroviral therapy failure among people living with HIV on antiretroviral therapy in Bulawayo city. *Afr Health Sci.* 2016;26(2):23-30. doi:10.4314/ahs.v26i2.4.
13. Onyedum CC, Iroezindu MO, Chukwuka CJ, et al. Profile of HIV-infected patients receiving second-line antiretroviral therapy in a resource-limited setting in Nigeria. *Trans R Soc Trop Med Hyg.* 2013;107(10). doi:10.1093/trstmh/trt071
14. Liegeois F. Virological failure rates and HIV-1 drug resistance patterns in patients on first-line antiretroviral treatment in semi-rural and rural Gabon. *J Int AIDS Soc.* 2012;15.
15. Kwobah CM, Mwangi AW, Koech JK, et al. Factors associated with first-line antiretroviral therapy failure amongst HIV-infected African patients: a case-control study. *World J AIDS.* 2012;2(4):271-278.
16. Dzangare J, Gonese E, Mugurungi O, et al. Monitoring of early warning indicators for HIV drug resistance in antiretroviral therapy clinics in Zimbabwe. *Clin Infect Dis.* 2012;54(Suppl 4):S313-S316. doi:10.1093/cid/cir1014.
17. Gardner EM, Burman WJ, Steiner JF, et al. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS.* 2009;23(9):1035-1046. Available at: <https://pubmed.ncbi.nlm.nih.gov/19381075>
18. Byrd KK, Hou JG, Hazen R, et al. Antiretroviral adherence level necessary for HIV viral suppression using real-world data. *J Acquir Immune Defic Syndr.* 2019;82(3):245-251. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31343455>
19. Castillo-Mancilla JR, Brown TT, Erlandson KM, et al. Suboptimal adherence to combination antiretroviral therapy is associated with higher levels of inflammation despite HIV suppression. *Clin Infect Dis.* 2016;63(12):1661-1667. Available at: <https://pubmed.ncbi.nlm.nih.gov/27660234>
20. Post WS, Haberlen SA, Witt MD, et al. Suboptimal HIV suppression is associated with progression of coronary artery stenosis: the Multicenter AIDS Cohort Study (MACS) longitudinal coronary CT angiography study. *Atherosclerosis.* 2022;353:33-40. Available at: <https://pubmed.ncbi.nlm.nih.gov/35577614>
21. Kacanek D, Huo Y, Malee K, et al. Nonadherence and unsuppressed viral load across adolescence among US youth with perinatally acquired HIV. *AIDS.* 2019;33(12):1923-1934. Available at: <https://pubmed.ncbi.nlm.nih.gov/31274538>
22. Akinwunmi B, Buchenberger D, Scherzer J, et al. Dose-related and contextual aspects of suboptimal adherence to antiretroviral therapy among persons living with HIV in Western Europe. *Eur J Public Health.* 2021;31(3):567-575. doi:10.1093/eurpub/ckaa229
23. Simpson KN, Baran RW, Kirbach SE, et al. Economics of switching to second-line antiretroviral therapy with lopinavir/ritonavir in Africa: estimates based on DART trial results and costs for Uganda and Kenya. *Value Health.* 2011;14(8):1048-1054. doi:10.1016/j.jval.2011.06.011.
24. Mantshonyane L, Roy J, Levy MZ, et al. Participants switching to second-line antiretroviral therapy with susceptible virus display inferior adherence and worse outcomes: an observational analysis. *AIDS Patient Care STDS.* 2021;35(12):467-473. doi:10.1089/apc.2021.0115.
25. Amstutz A, Nsaka BL, Vanobberghen F, et al. Switch to second-line versus continued first-line antiretroviral therapy for patients with low-level HIV-1 viremia: an open-label randomized controlled trial in Lesotho. *PLoS Med.* 2020;17(9):e1003325. doi:10.1371/journal.pmed.1003325.
26. Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration. Incidence of switching to second-line antiretroviral therapy and associated factors in children with HIV: an international cohort collaboration. *Lancet HIV.* 2019;6(2):e105-e115. doi:10.1016/S2352-3018(18)30319-9.
27. Sibhat MM, Mulugeta TN, Aklilu DW. Incidence of switching to second-line antiretroviral therapy and its predictors among children on antiretroviral therapy at general hospitals, Northern Ethiopia: a survival analysis. *PLoS One.* 2023;18(9):e0288132. doi:10.1371/journal.pone.0288132.
28. Tenza IS, Njuguna C, Sodo PP, et al. Exploring barriers to switching “on time” to second-line antiretroviral therapy among nurses in primary health care facilities, Ekurhuleni Health District, South Africa. *PLoS One.* 2023;18(4):e0284996. doi:10.1371/journal.pone.0284996.
29. Madec Y, Leroy S, Rey-Cuille MA, et al. Persistent difficulty in switching to second-line ART in sub-Saharan Africa—a systematic review and meta-analysis. *PLoS ONE.* 2013;8(12):e82724. doi:10.1371/journal.pone.0082724.
30. Al-Haidary NM, Radman EA. Brief communication: the rate of switching from first-line to second-line antiretroviral therapy among people living with HIV in Aden City, Yemen. *AIDS Res Ther.* 2024;21(1):49. doi:10.1186/s12981-024-00638-z.