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PATTERNS OF WHO HIV DRUG RESISTANCE EARLY WARNING INDICATOR PERFORMANCE ACROSS ART PROGRAMS IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW

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ABSTRACT

Human immunodeficiency virus drug resistance (HIVDR) remains a major threat to the long-term success of antiretroviral therapy (ART) programs, particularly in Sub-Saharan Africa, where the HIV burden remains high and ART coverage continues to expand. In many low-resource settings, limited access to routine HIVDR testing increases reliance on program-level monitoring to identify conditions associated with HIVDR emergence. The World Health Organization (WHO) developed HIVDR Early Warning Indicators (EWIs) to monitor ART program performance and identify vulnerabilities linked to increased HIVDR risk. The objective is to systematically review evidence on the performance of WHO HIVDR EWIs across ART programs in Sub-Saharan Africa and identify recurring program and health system challenges associated with poor EWI performance. A systematic review was conducted in accordance with a PROSPERO-registered protocol. Electronic database searches were conducted in PubMed, Scopus, and Google Scholar for studies published between 1 January 2013 and 31 December 2023. Eligible studies included surveillance studies, operational research, program evaluations, and facility- or program-level assessments reporting WHO HIVDR EWI outcomes in Sub-Saharan Africa. Country-level observations from WHO multi-country HIVDR reports were also included. Study screening, eligibility assessment, and data extraction were conducted systematically using Covidence. Two reviewers independently screened titles, abstracts, and full-text articles and extracted data using standardized tools. Disagreements were resolved through discussion and consultation with a third reviewer. Findings were synthesized narratively due to heterogeneity in study designs, EWI frameworks, and reporting approaches. A total of 13 studies met the inclusion criteria, representing 37 country-level observations across 25 countries in Sub-Saharan Africa. Retention in care met WHO-recommended targets in 14 of 37 observations (37.8%), while 22 (59.5%) failed to meet targets. Adherence/on-time ARV pick-up performed the poorest, with only 1 of 31 observations (3.2%) meeting targets and 30 (96.8%) failing. Viral load suppression was assessed in only five observations, of which one (20.0%) met targets and two (40.0%) failed

to meet targets. No observation assessing viral load testing coverage/completion met the WHO-recommended targets (0/3; 0%), while all three (100%) failed to meet targets. ARV stock continuity met targets in only 3 of 26 observations (11.5%), compared with 23 (88.5%) that failed to meet targets. In contrast, prescribing and dispensing practices consistently performed well, meeting WHO-recommended targets in 35 of 36 observations (97.2%). Reported challenges evolved over time. Studies conducted between 2004 and 2010 primarily reported challenges with adherence, retention, stock-outs, and routine monitoring. Between 2011 and 2015, laboratory, viral load monitoring, workforce, and information systems challenges became more prominent. Studies conducted between 2016 and 2023 reported broader systems-level challenges related to data integration, laboratory capacity, supply chain management, patient follow-up, and program sustainability. Although substantial progress was made in ART scale-up and in implementing standardized treatment practices across Sub-Saharan Africa, as reflected in consistently strong prescribing and dispensing performance, critical program and health-system weaknesses persisted. Poor performance in adherence monitoring, treatment continuity, ARV stock continuity, viral load monitoring, and patient follow-up systems was reported across multiple countries and reporting periods, suggesting that ART scale-up was not consistently matched by equivalent system strengthening. Reported challenges evolved from early ART access and continuity-of-care constraints to broader laboratory, information-system, and program sustainability challenges, yet poor EWI performance persisted across successive reporting periods.

KEYWORDS: HIV Drug Resistance, Early Warning Indicators; Antiretroviral Therapy, ART Program Performance, Sub-Saharan Africa, Viral Load Monitoring, Systematic Review.

1. INTRODUCTION

The rapid expansion of antiretroviral therapy (ART) programs has substantially reduced HIV-related morbidity and mortality globally and transformed HIV infection into a manageable chronic condition. Sub-Saharan Africa remains the region most heavily affected by HIV and accounts for the largest proportion of people receiving ART worldwide. Despite major progress in treatment access, the emergence and transmission of HIV drug resistance (HIVDR) threaten long-term treatment effectiveness, program sustainability, and progress toward global HIV epidemic control targets (World Health Organization [WHO], 2021).

HIVDR can compromise virological suppression, increase treatment failure, reduce future treatment options, and increase healthcare costs. The emergence of HIVDR is influenced by multiple interacting factors, including poor adherence, interruptions in ART supply continuity, delayed viral load monitoring, weak retention systems, and limitations in routine program monitoring systems (Bertagnolio et al., 2012; WHO, 2016). Many of these factors are preventable and may be addressed through strengthened program monitoring and health-system interventions.

To support monitoring of program-level factors associated with HIVDR emergence, WHO introduced HIVDR Early Warning Indicators (EWIs) as standardized tools to assess ART program performance and identify weaknesses that increase HIVDR risk (WHO, 2010; WHO, 2016). Commonly monitored EWIs include retention in care, loss to follow-up, on-time pill pick-up, appointment keeping, pharmacy stock-outs, prescribing and dispensing practices, viral load coverage, viral load suppression, and timely switching to second-line ART.

Several countries in Sub-Saharan Africa have implemented WHO HIVDR EWI monitoring using routine program data and surveillance systems. However, reported EWI performance has varied considerably across countries and settings, and recurring program and health-system challenges continue to affect HIVDR surveillance and program performance. In addition, WHO HIVDR EWI frameworks have evolved over time, resulting in differences in indicator definitions, thresholds, and reporting approaches across studies.

Although previous studies and WHO reports have described HIVDR EWI performance in individual countries and regions, evidence remains fragmented across settings and reporting periods. To date, few reviews have comprehensively synthesized patterns of WHO HIVDR EWI performance across ART programs in Sub-Saharan Africa, particularly in the context of expanding dolutegravir-based treatment programs and evolving ART service delivery models.

This systematic review, therefore, aimed to synthesize evidence on the performance of the WHO HIVDR Early Warning Indicator across ART programs in Sub-Saharan Africa and to identify recurring program- and health system-related challenges associated with poor EWI performance.

1.1. Review Objectives

Primary Objective

To systematically review published evidence on the performance of the WHO HIVDR Early Warning Indicators across ART programs in Sub-Saharan Africa.

Secondary objectives

- To summarize reported patterns in WHO HIVDR EWI performance across different Sub-Saharan African countries.
- To identify commonly underperforming EWIs associated with increased HIVDR risk.
- To examine program and health system-related factors associated with poor EWI performance across Sub-Saharan African settings.

2. METHODS

2.1. Protocol Registration

This systematic review was conducted according to a prospectively developed protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the title "Patterns of WHO HIV Drug Resistance Early Warning Indicator Performance Across ART Programs in Sub-Saharan Africa: A Systematic Review". The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting principles.

2.2. Review Design

A systematic review of published studies and program reports assessing WHO HIVDR EWIs across ART programs in Sub-Saharan Africa was conducted. For multi-country WHO technical reports, country-specific EWI findings were extracted and synthesized as individual country observations to improve comparability across ART program settings.

2.3. Eligibility Criteria

2.3.1. Population And Setting

Studies involving ART programs, ART facilities, and HIV-positive populations receiving ART in Sub-Saharan Africa were eligible for inclusion. Included studies consisted of national, regional, district-level, facility-level, and multi-country ART program assessments. Multi-country surveillance reports were eligible if country-level EWI findings were reported separately.

2.3.2. Exposure Of Interest

Studies reporting WHO HIVDR EWIs or related ART program performance measures associated with HIVDR risk were included. Relevant indicators included:

- adherence or on-time ARV drug pick-up indicators
- retention in care and attrition indicators
- viral load testing coverage
- viral load suppression
- ARV stock-outs and supply continuity indicators
- prescribing and dispensing practices
- treatment interruption indicators
- and timely switching to second-line ART.

2.3.3. Study Designs

Eligible study designs included surveillance studies, program evaluations, operational research studies, observational studies, cross-sectional studies, cohort studies, and facility- or program-level assessments reporting WHO HIVDR EWI outcomes.

2.4. Exclusion Criteria

Studies were excluded if they:
did not report WHO HIVDR EWI findings

- focused exclusively on laboratory-confirmed HIVDR mutations without program-level assessment
- were conducted outside Sub-Saharan Africa
- were reviews, editorials, commentaries, or conference abstracts without sufficient data
- were not available in English
- or lacked an accessible full text

2.5. Information Sources and Search Strategy

Electronic database searches were conducted using PubMed, Scopus, and Google Scholar. Additional studies were identified through backward citation searching of included studies and relevant reports. Searches included studies published between 1 January 2013 and 31 December 2023.

Search terms included combinations of:

- "HIV drug resistance"
- "Early Warning Indicators" OR "EWI"
- "Antiretroviral therapy"
- "ART program performance"
- "Viral load monitoring"
- and "Sub-Saharan Africa"

2.6. Study Selection

Retrieved references were imported into Covidence for duplicate removal and screening. Title and abstract screening were followed by full-text eligibility assessment using predefined inclusion and exclusion criteria. Screening was conducted independently by at least two reviewers, with disagreements resolved through discussion.

A total of 43 records were identified through database searching, including 21 from PubMed, 16 from Scopus, and 6 from Google Scholar. Eighteen duplicates were removed, including 14 identified manually and 4 identified using Covidence. Twenty-five studies underwent title and abstract screening; 9 were excluded. Sixteen full-text articles were assessed for eligibility, and 3 studies were excluded because of inappropriate study design (n = 2) or publication language restrictions (n = 1). Thirteen studies were included in the final synthesis, one of which was a WHO multi-country surveillance report containing country-specific EWI findings, which were extracted and synthesized individually in the narrative analysis.

Figure 1: PRISMA Flow Diagram.

Flow diagram summarizing study identification, duplicate removal, screening, eligibility assessment, and inclusion process for studies included in the systematic review.

2.7. Data Extraction

Data extraction was conducted independently by at least two reviewers using a standardized data extraction form developed specifically for this review. Extracted variables included:
study characteristics;

- country and reporting level
- WHO HIVDR EWI framework/version used
- study design and data sources
- EWI performance outcomes
- underperforming and well-performing indicators
- program and health system-related challenges

- and reported data quality limitations.

For multi-country reports and regional WHO surveillance reports, country-level EWI findings were additionally extracted and synthesized where reported separately within the source document. Discrepancies in extracted data were resolved through discussion and review of source publications.

Indicator findings and programmatic challenges were harmonized across studies to improve comparability in reporting terminology and thematic categorization. Interpretation of EWI performance was conducted according to the WHO threshold criteria applicable to the framework version used in each study. For multi-country WHO technical reports, aggregate country-level EWI performance findings were extracted separately and treated as individual country observations during synthesis

2.8. Quality Assessment and Risk of Bias

Methodological quality and risk of bias were assessed narratively due to substantial heterogeneity among the included studies. Assessment considered completeness of reporting, missing EWI data, representativeness of included facilities, consistency of findings, and limitations in routine program monitoring systems.

Reporting bias associated with missing routine data, selective indicator reporting, and incomplete methodological reporting was also accounted for.

- variability in routine monitoring systems
- incomplete VL data
- missing pharmacy records
- paper-based systems
- inconsistent reporting standards

2.9. Data Synthesis

A formal narrative synthesis was conducted in accordance with the registered protocol. Findings were grouped according to WHO HIVDR EWI domains, including:

- retention in care and attrition
- adherence and on-time ARV drug pick-up
- viral load testing coverage
- viral load suppression
- ARV stock-outs and supply continuity
- prescribing and dispensing practices
- and timely switching to second-line ART.

Study characteristics and EWI performance findings were summarized descriptively using tables and narrative comparisons across countries and settings. Recurring program and health-system challenges were synthesized thematically. A meta-analysis was not performed due to substantial heterogeneity in study designs, EWI definitions, reporting approaches, and implementation contexts.

Where multi-country reports presented country-specific EWI findings, these were synthesized descriptively to improve comparability of EWI performance patterns across Sub-Saharan African ART programs. However, where individual countries were stated, in multi-country reports remained classified as single included sources within the review.

A structured narrative synthesis approach was used to identify recurring patterns in EWI performance, underperforming indicators, and health-system-related challenges across studies and countries. Recurring programmatic and health-system challenges were grouped into five harmonized thematic domains.

- Health system, workforce, and program capacity challenges
- Laboratory, viral load monitoring, and diagnostic capacity challenges
- Health information, monitoring, and data system challenges
- Supply chain and pharmacy system challenges
- Adherence, retention, and patient follow-up challenges

Reported data quality limitations were additionally synthesized across studies to identify recurring weaknesses in routine ART monitoring systems.

3. RESULTS

3.1. Study Selection

Database searching identified 43 records. Following duplicate removal and screening, thirteen (13) studies met the inclusion criteria and were included in the final synthesis. Please refer to Figure 1.

3.2. Characteristics Of Included Studies

A total of 13 studies were included in the review, comprising 11 single-country studies and 2 multi-country studies. One of the multi-country studies was a WHO HIVDR EWI report that contributed multiple country-specific observations to the analysis.

Together, the included studies represented 25 countries across Sub-Saharan Africa, including Cameroon, the Democratic Republic of Congo (DRC), Burundi, Ethiopia, Kenya, Mozambique, Rwanda, Uganda, Tanzania, Angola, Lesotho, Namibia, South Africa, Eswatini, Zimbabwe, Benin, Burkina Faso, Côte d'Ivoire, Ghana, Guinea, Mali, Niger, Nigeria, Senegal, and Togo. This is summarised in Figure 2. Several countries

contributed more than one survey or assessment. Consequently, the final synthesis comprised 37 country-level observations, which served as the unit of analysis for the review.

All included studies used retrospective routine program-based EWI assessment designs. Seven studies (53.8%) used the revised WHO HIVDR EWI framework, while 6 studies (46.2%) used the earlier WHO EWI framework. Study periods ranged from 2004 to 2017. The number of assessed facilities ranged from 2 to 334 facilities. Five studies (38.5%) used only paper-based records, while 8 studies (61.5%) used combined paper and electronic data systems.

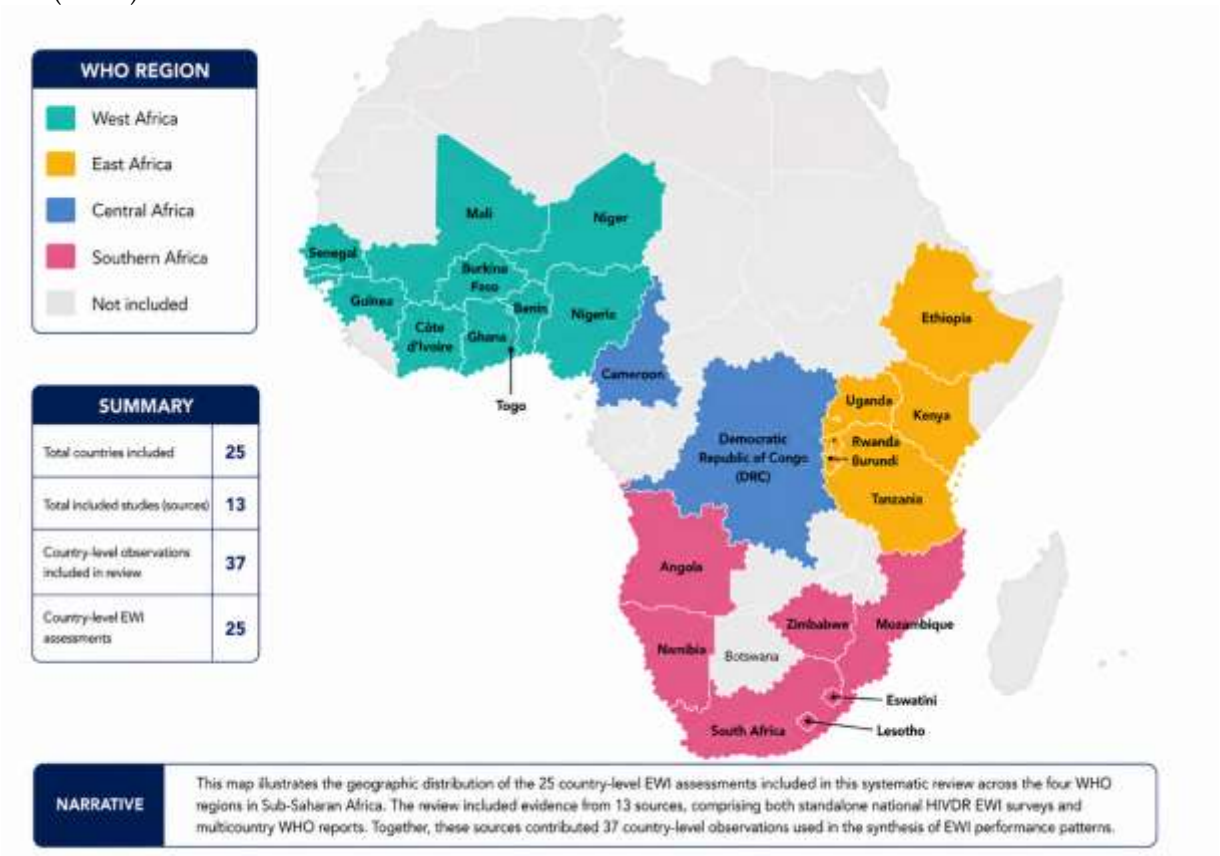

Figure 2: Geographic Distribution of Included Studies.

Geographic distribution of included WHO HIVDR EWI studies conducted across Sub-Saharan Africa between 2013 and 2023.

3.3. Patterns Of EWI Performance Across Included Studies

This section summarizes patterns of EWI performance across included studies, including the proportion of studies assessing each indicator, the proportion meeting or not meeting WHO-recommended thresholds, and notable country-level findings reported across included studies.

Table 1: Summary of WHO HIVDR Early Warning Indicator Performance Patterns Reported Across Included Studies in Sub-Saharan Africa.

EWI Domain (Indicator)	Countries With Data n (%)	Met Who Target n (%)	Did Not Meet Who Target n (%)	Not Assessed / Not Reported n (%)
Retention in care	37 (100%)	14 (37.8%)	22 (59.5%)	1 (2.7%)
Adherence / On-time ARV pick-up	31 (83.8%)	1 (3.2%)	30 (96.8%)	6 (16.2%)
Viral load suppression	5 (13.5%)	1 (20.0%)	2 (40.0%)	32 (86.5%)
Viral load testing coverage / completion	3 (8.1%)	0 (0%)	3 (100%)	34 (91.9%)
ARV stock-outs / supply continuity	26 (70.3%)	3 (11.5%)	23 (88.5%)	11 (29.7%)
Prescribing / dispensing practices	36 (97.3%)	35 (97.2%)	1 (2.8%)	1 (2.7%)

Percentages for "Met WHO Target" and "Did Not Meet WHO Target" were calculated using only country/program observations with available data for the respective EWI indicator. "Not assessed / not reported" percentages were calculated using the total number of country/program observations included in the review (N = 37).

Heat map illustrating patterns of the WHO HIV Drug Resistance Early Warning Indicator (EWI) performance across included country-level observations. Indicator performance classifications were based on reported WHO-recommended thresholds and study-specific findings. Green indicates indicators that achieved WHO-recommended thresholds, red indicates indicators that did not achieve WHO-recommended thresholds, orange indicates mixed performance across facilities, program settings, or reporting periods, grey indicates indicators assessed but with insufficient or unreliable data available for classification, and white indicates indicators that were not assessed or not reported.

Figure 3: Summary Heat Map of EWI Performance Across Included Studies

Each row represents an independent country-level observation extracted from either standalone national studies or WHO multi-country reports. Duplicate country entries (a–b) represent independent country-level observations extracted from different studies or reporting sources conducted during the same reporting period.

3.4. Health System and Program Challenges Across the Included Studies

Figure 4 presents the reported health system and program challenges identified across the included HIVDR EWI studies and country-level observations, grouped by study/survey reporting periods (2004–2010, 2011–2015, and 2016–2023). The figure summarizes the types of challenges reported across the respective study periods, including challenges related to adherence and patient follow-up systems, laboratory and viral load monitoring systems, health information and data systems, supply chain and pharmacy systems, and broader health system and workforce capacity.

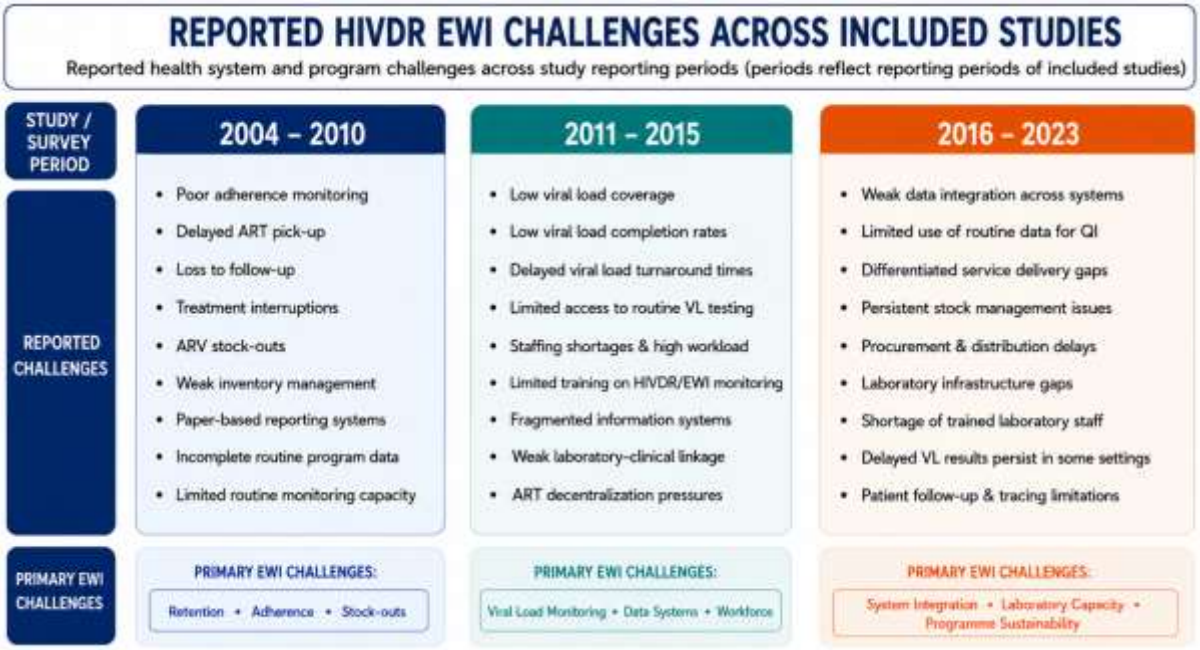

Figure 4: Reported HIVDR EWI Challenges Across the Included Studies.

4. DISCUSSION AND CONCLUSION

4.1. Overview Of Included Evidence

This systematic review synthesized evidence from 13 included studies, representing 37 country-level observations across 25 countries in Sub-Saharan Africa. The included evidence covered all four Sub-Saharan African regions: West Africa, Central Africa, East Africa, and Southern Africa. West Africa was represented by Benin, Burkina Faso, Côte d'Ivoire, Ghana, Guinea, Mali, Niger, Nigeria, Senegal, and Togo; Central Africa by Cameroon and the Democratic Republic of Congo; East Africa by Burundi, Ethiopia, Kenya, Rwanda, Uganda, Tanzania, and Mozambique; and Southern Africa by Angola, Lesotho, Namibia, South Africa, Eswatini, and Zimbabwe.

4.2. What Worked Across Art Programs in Sub-Saharan Africa

The strength across the review was the prescribing and dispensing practice. This indicator met WHO-recommended targets in 35 of 36 country-level observations, showing that many ART programs had successfully adopted standardized treatment guidelines and maintained appropriate ART prescribing practices across facilities and countries. This finding was consistent across the sub-

Saharan region (WHO, 2016; Fokam et al., 2015; Getaneh et al., 2020).

Retention in care performed better than most other indicators, but less consistently. Fourteen of 37 observations met WHO retention targets. Countries such as Burundi, Rwanda, Lesotho, Angola, Eswatini, Guinea, and Mozambique also reported retention performance that met WHO thresholds in some assessments (WHO, 2016). Mali stood out as the strongest-performing country observation, meeting targets across retention, adherence, ARV stock continuity, and prescribing indicators (WHO, 2016).

4.3. Program Vulnerabilities and Underperforming Indicators

Most other EWIs showed weak performance – adherence, stock-outs, retention, viral load suppression, and coverage. Adherence was the poorest-performing indicator, with 30 of 31 observations that assessed it failing to meet WHO-recommended thresholds. Poor on-time ARV pick-up or ARV stock continuity was also a major weakness, with 23 of 26 observations failing to meet WHO targets. Stock-outs were reported across West, Central, East, and Southern Africa, pointing to persistent gaps in forecasting, procurement, inventory management, and distribution systems (WHO, 2016; Mungati et al., 2016; Khamadi et al., 2023).

Viral load indicators were both poorly assessed and weak where data were available. Viral load suppression was assessed in only five observations, and viral load coverage or completion in only three. Among the observations assessing viral load suppression, only one met the WHO-recommended thresholds, while two did not meet targets, and two had insufficient or unreliable data for classification. No country-level observation assessing viral load coverage or completion met the WHO-recommended thresholds; all three observations reported poor performance.

Taken together, the findings show that ART scale-up achieved treatment access and prescribing standardization more successfully than it strengthened the systems required to sustain quality ART delivery. Adherence support, patient follow-up, viral load monitoring, supply chains, and routine data systems remained persistent vulnerabilities. This imbalance has also been described in wider HIV program literature, where rapid ART expansion in resource-limited settings has often outpaced health-system strengthening (Bertagnolio et al., 2012; Phillips et al., 2019; UNAIDS, 2023).

4.4. Evolution Of Reported Program and Health System Challenges

The review demonstrated a clear shift in the types of reported HIVDR EWI-related challenges across successive study and survey reporting periods. Earlier studies conducted between 2004 and 2010 predominantly reported operational challenges related to ART program expansion, including poor adherence monitoring, treatment interruption, weak retention systems, ARV stock-outs, paper-based reporting systems, and incomplete routine program documentation (Sigaloff et al., 2012; Juma et al., 2014).

Studies conducted between 2011 and 2015 increasingly identified laboratory and monitoring-system weaknesses, including limited routine viral load testing, low viral load completion rates, delayed return of viral load results, fragmented information systems, staffing shortages, and weak integration between laboratory and clinical monitoring systems (Fokam et al., 2015; Jonas et al., 2014; Dube et al., 2014).

More recent studies conducted between 2016 and 2023 reported broader and more complex systems-level challenges affecting long-term ART program performance, including weak data integration systems, procurement and distribution delays, differentiated service delivery implementation gaps, specimen transport constraints, laboratory infrastructure limitations, and shortages of trained personnel supporting viral load monitoring and routine programme monitoring systems (Asio et al., 2020; Getaneh et al., 2020; WHO, 2016).

Collectively, these findings suggest that the nature of reported challenges related to EWI for HIVDR shifted over time from early ART access and continuity-of-care challenges to broader laboratory, information-system, and program sustainability challenges as ART programs grow across the region. However, despite this progression in the complexity and type of reported program challenges, overall EWI performance remained largely poor across multiple reporting periods. This suggests that while ART programs evolved and expanded over time, many underlying operational and health-system weaknesses persisted rather than being fully resolved, as reflected by the continued poor performance of several HIVDR EWIs across successive reporting periods. In particular, adherence monitoring, viral load systems, patient follow-up mechanisms, and ARV stock continuity continued to perform poorly across several countries and reporting periods, despite broader growth in ART programs and increasing treatment access.

4.5. Conclusion

This systematic review found that although ART access and treatment delivery expanded substantially across Sub-Saharan Africa, as reflected in consistently strong prescribing and dispensing performance indicators, several critical program and health-system weaknesses persisted. Poor performance in adherence monitoring, treatment continuity, ARV stock continuity, viral load monitoring, and patient follow-up systems was reported across multiple countries and reporting periods. These findings suggest that gains in ART scale-up and treatment standardization were not consistently matched by equivalent strengthening of the systems required to sustain long-term treatment effectiveness and prevent HIV drug resistance.

The review further found that the nature of reported HIVDR EWI-related challenges evolved over time, shifting from early ART access and continuity-of-care challenges to broader laboratory, information-system, and program sustainability challenges as ART programs expanded across the region. Despite this progression, performance across several key HIVDR EWIs remained persistently poor. These findings suggest that while ART programs expanded and became more complex, many underlying operational and health-system weaknesses were not fully resolved; instead, they persisted, manifesting in poor EWI performance across successive reporting periods.

Overall, the review reinforces the continued importance of WHO HIVDR EWIs as program-level tools for identifying weaknesses in ART program performance and monitoring systems, while also providing evidence to support targeted program strengthening and health-system improvement efforts. Strengthening adherence support, viral load monitoring systems, supply chain systems, patient follow-up mechanisms, laboratory infrastructure, and routine health information systems will remain critical to sustaining long-term ART effectiveness and supporting HIVDR prevention efforts across Sub-Saharan Africa.

4.6 Limitations

Several limitations should be considered when interpreting the findings. Included studies varied in EWI frameworks, reporting approaches, facility coverage, indicator definitions, and reporting periods, reflecting the diversity of HIV program implementation contexts across Sub-Saharan Africa. However, the use of WHO HIVDR EWI frameworks across studies provided a common structure that enabled broader comparison of recurring program performance patterns and health-system challenges across countries and reporting periods.

Second, many included studies relied on routine program data systems that were affected by incomplete records, missing data, paper-based reporting, inconsistent documentation practices, and limited capacity for routine monitoring. These limitations affected the completeness and availability of several HIVDR EWIs, particularly viral load-related indicators, and reduced the ability to assess some indicators consistently across studies and reporting periods.

Finally, several newer HIVDR-related indicators, including viral load monitoring, second viral load testing after enhanced adherence counselling, and timely switching indicators, were infrequently assessed or inconsistently reported across included studies, particularly within earlier WHO EWI frameworks. This limited the review's ability to comprehensively assess DTG-era program performance and evolving HIVDR monitoring priorities across ART programs in the region.

Declarations

Ethics Approval and Consent to Participate

Not applicable. This study was a systematic review of published literature and did not involve human participants, patient data, or biological specimens.

Consent for Publication: Not applicable.

Availability of Data and Materials: All data generated or analysed during this study are included in this published article and its supplementary materials. Additional materials, including the data extraction form, quality assessment checklist, and detailed search strategies, are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

Authors' Contributions: Mosa Mabataung Monyake conceived the study, developed the review protocol,

conducted the literature search, extracted and analysed the data, performed the data synthesis, and drafted the manuscript. Mosa Mabataung Monyake, Palesa Khotso, Mamajalla Mofelehetsi, Thato Seotsa, and independently screened and reviewed studies for inclusion using Covidence. Prof P. Makhoahle and Prof J. Manasa provided academic supervision, contributed to methodological guidance, reviewed the findings, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Supplementary Materials

Supplementary materials associated with this review include:

- **Supplementary File 1:** PROSPERO registration record and protocol
- **Supplementary File 2:** Data extraction form
- **Supplementary File 3:** Covidence data extraction spreadsheet (raw extracted study data)
- **Supplementary File 4:** Quality assessment checklist and assessment results
- **Supplementary File 5** Harmonised dataset of included studies and country-level observations used for analysis and synthesis
- **Supplementary File 6:** Additional summary tables and supporting data

These materials are available from the corresponding author upon reasonable request.

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ANNEXTURE

Annex A: Full Search Strategy

Databases Searched

- PubMed
- Scopus
- Google Scholar

Search Period

Studies published between 1 January 2013 and 31 December 2023 were searched.

Search Concepts

The search strategy combined terms related to:

- HIV drug resistance early warning indicators
- Antiretroviral therapy programs
- HIV drug resistance
- Sub-Saharan Africa

PubMed Search Strategy

("HIV drug resistance"[Title/Abstract]
OR HIVDR[Title/Abstract]
OR "HIV drug resistance early warning indicators"[Title/Abstract]
OR "early warning indicators"[Title/Abstract]
OR EWI[Title/Abstract])
AND
("antiretroviral therapy"[Title/Abstract]
OR ART[Title/Abstract]
OR "HIV treatment programme"[Title/Abstract]
OR "HIV care programme"[Title/Abstract])
AND
("Sub-Saharan Africa"[Title/Abstract]

Scopus Search Strategy

("HIV drug resistance" OR HIVDR OR
"HIV drug resistance early warning indicators" OR
"Early warning indicators" OR EWI)
AND
("antiretroviral therapy" OR ART OR
"HIV treatment program" OR
"HIV care program")
AND
("Sub-Saharan Africa")

Google Scholar Search Strategy

"HIV drug resistance early warning indicators"
AND Africa
"HIVDR EWI" AND ART program

"WHO HIVDR early warning indicators."
AND "Sub-Saharan Africa"
"HIV drug resistance surveillance"
AND ART program Africa
Additional Search Approaches

- Reference list screening of included studies
- Manual searching of the WHO HIVDR technical reports
- Citation tracking of relevant studies

Eligibility Criteria
Inclusion Criteria

- Studies conducted in Sub-Saharan Africa
- Studies reporting WHO HIVDR EWI outcomes
- Surveillance studies, program evaluations, operational research studies, and observational studies
- Facility-level, program-level, or national-level assessments
- Studies published in English
- Studies published between 2013 and 2023

Exclusion Criteria

- Studies conducted outside Sub-Saharan Africa
- Studies not reporting HIVDR EWIs
- Reviews, editorials, commentaries, and conference abstracts without sufficient data
- Studies without an accessible full text
- Non-English publications

Annex B: Quality Assessment Checklist

Quality Assessment Tool for Included Studies
Included studies were assessed for methodological quality and reporting completeness using an adapted appraisal checklist developed for observational and programme evaluation studies.

Quality Assessment Domain	Assessment Criteria
Study objectives clearly stated	Yes / No
Study setting and population adequately described	Yes / No
WHO HIVDR EWI framework clearly described	Yes / No
EWI definitions appropriately applied	Yes / No
Sampling approach adequately described	Yes / No
Data collection methods clearly described	Yes / No
Data sources adequately described	Yes / No
Outcome measures clearly reported	Yes / No
Results adequately presented	Yes / No
Limitations acknowledged	Yes / No
Data quality issues discussed	Yes / No
Ethical considerations reported where applicable	Yes / No

Additional Considerations for EWI Studies
The following HIVDR EWI-specific issues were also considered during quality assessment:

- Completeness of routine program data
- Availability of viral load data
- Representativeness of included facilities
- Use of standardized WHO EWI definitions
- Presence of missing or incomplete monitoring data
- Reliability of pharmacy and stock management records
- Strength of routine monitoring systems
- Use of electronic versus paper-based reporting systems

Annex C: Data Extraction Form

Annex B: PROSPERO registration
Annex C: Characteristics of Included Sources and Country-Level HIVDR EWI Observations Across Sub-Saharan Africa

Author (Year)	Country/Region	Study Scope	Study Period	WHO EWI Framework	Study Design	No. of Facilities	Data Collection Method
Sigaloff et al. (2012)	Multicountry, Sub-Saharan Africa	Multicountry	2007–2009	Earlier WHO EWI framework	Retrospective routine programme-based EWI assessment	13	Paper electronic systems
WHO (2016)	Multicountry, Sub-Saharan Africa	Multicountry	2004 onward	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	Not stated	Paper + electronic systems
Juma et al. (2014)	Tanzania	Single-country	2010	Earlier WHO EWI framework	Retrospective routine programme-based EWI assessment	35	Paper-based records
Billong et al. (2016)	Cameroon	Single-country	2015	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	56	Paper-based records
Mungati et al. (2016)	Zimbabwe	Single-country	2012	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	74	Paper-based records
Mutenda et al. (2016)	Namibia	Single-country	2012–2014	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	50	Paper + electronic systems
Fokam et al. (2013)	Cameroon	Single-country	2008–2010	Earlier WHO EWI framework	Retrospective routine programme-based EWI assessment	10	Paper-based records
Dube et al. (2014)	South Africa	Single-country	2008–2010	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	2	Paper + electronic systems
Fokam et al. (2015)	Cameroon	Single-country	2012–2014	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	15	Paper + electronic systems
Asio et al. (2020)	Uganda	Single-country	2015–2017	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	334	Paper + electronic systems
Jonas et al. (2014)	Namibia	Single-country	2012–2013	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	50	Paper + electronic systems
Getaneh et al. (2020)	Ethiopia	Single-country	2014–2015	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	90	Paper + electronic systems
Khamadi et al. (2023)	Tanzania	Single-country	2013	Revised WHO EWI framework	Retrospective routine programme-based EWI assessment	50	Paper-based records