Adherence to Antiretroviral Therapy (ART) Among HIV-1 Patients From Sub-Saharan Africa: A Systematic Review

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Article

Adherence to Antiretroviral Therapy (ART) among HIV-1 Patients from Sub-Saharan Africa: A Systematic Review

Running Title: Adherence to ART in African HIV Patients

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Abstract: Two decades after the antiretroviral therapy (ART) introduction, several challenges still prevail in maintaining people living with HIV (PLHIV), even with "Test and Treat" and/or "Rapid Start of ART" initiatives, as well as the scale-up of ART worldwide to promote access and adherence to treatment. This review examined articles on ART adherence in Africa between 2016 and 2023, published in English and indexed in PubMed. A total of 16 articles out of 2415 were eligible and included for analyses. Overall, ART adherence rates in SSA regions ranged from 43% to 84%. Rates in the centre of the SSA region ranged from 58% to 80%, in the north from 50% to 83%, in the south from 77% to 84%, in the west from 43% to 60% and in the east from 69% to 73%. Most African countries use the self-report to assess treatment adherence, although unreliable. The main factors with negative influence on ART adherence were comorbidities, lack of motivation, socioeconomic difficulties or side effects. Conclusion: Adherence to ART is a good indicator for controlling the spread of HIV. It is important to overcome the barriers that make it difficult to comply with ART and reinforce the factors that facilitate the accession of medication.

Keywords: HIV-1; antiretroviral therapy; treatment adherence; sub-Saharan Africa

Introduction

Currently, there are still major challenges in starting and maintaining HIV-positive people on antiretroviral therapy (ART) throughout their infection, even with awareness-raising actions and initiatives that promote adherence to therapy, such as the "Test and Treat" and "Test and Treat" campaigns [1].

The success of ART in HIV-positive patients varies according to the patient's daily adherence to medication. This adherence is essential to ensure viral suppression, prevent the emergence of drug resistance mutations (DRMs) and minimize further HIV transmission. Previous studies reported that factors such as gender, age, residence, educational status, occupation, marital status, income, disclosure status, history of substance abuse, and clinical and medication-related factors frequently influence patient medication adherence, mainly in resource-limited settings [2,3]. The WHO defines treatment adherence as the degree to which a person's behaviour is consistent with standardized recommendations made by a trained health professional. The behaviour consists of taking medication,

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adhering to a diet and/or implementing lifestyle changes [4]. ART adherence interventions must therefore recognize this cultural diversity during the research development, evaluation and implementation phases [4]. To assess adherence to ART, laboratory investigations and clinical assessments must be carried out to verify tolerance and the appearance of adverse drug effects. Factors related to patients, healthcare professionals and the drugs themselves also have a major impact on adherence to ART. Several "patient-centred" interventions are currently in development and being implemented, however, few offer highly effective solutions, particularly for vulnerable groups such as women and children, key populations, men and young adults [1,4] The existence of high levels of discrimination in employment, fear of being abandoned by family members or divorce, and communication difficulties There have been some strategies to be broken down to maximize treatment adherence [5].

Considering the scarcity of data related to factors associated with adherence to ART or its rejection, we set out to qualitatively explore and review adherence to ART among HIV-infected adults and the differences depending on the characteristics of the population studied in Sub-Saharan African (SSA) countries, to provide approaches that maximize ART adherence in different regions of Africa [6].

Systematic Literature Review

The bibliographic search included the PubMed database, particularly articles published in English between 2016 and 2023. The search was performed using the Boolean operators “AND”, “OR” and “NOT”; and, the search keywords combining the medical subject headings (MeSH): " (i) Antiretroviral therapy" or " (ii) highly active antiretroviral therapy" or " (iii) antiretroviral” or “ (iii) antiretroviral agents HIV” or “ (iv) ART or ARV” and “ (v) treatment adherence” or “ (vi) adherence” and “ (vii) Sub-Saharan Africa”. Reporting of the results of this systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which provide guidelines for this type of research that allow the identification, selection, evaluation and synthesis of studies.

Study Selection

This review involved studies evaluating adherence to ART in adults from the SSA region. The definition of adherence in this review was operationally restricted to adherence to ART, which implied the degree of antiretroviral (ARV) intake by HIV-positive patients, as recommended by their healthcare providers. Studies related to the different concepts of adherence, such as attendance or consultation and retention, were also included. There was no restriction on measures to assess adherence to ART. Information on the year of publication, type of intervention, country where the study was conducted, and healthcare setting was obtained from each study. Subjective and objective measures of adherence were recorded, including biological correlates of adherence, for example, viral load and CD4 count. The guide used for inclusion criteria covered the population, intervention, comparison, outcome and time. Studies conducted in the SSA region, involving HIV-positive adults on adult correlates of adherence were included. On the other hand, meta-analysis and systematic review studies involving children and/or adolescents were excluded. Studies were reviewed based on strict adherence to ART appointments and medication as scheduled by healthcare professionals. In sequence, (i) articles were selected according to title, (ii) abstract and (iii) full-text access to verify their inclusion (Figure 1).

Quality Assessment

The studies selected and included in the review were subjected to a systematic bias assessment using the Cochrane criteria, with the risk of bias being assessed as “low risk”, “high risk” or “uncertain risk” and analyzed in seven domains. Low risk indicates information reported with evidence of little or no possible bias, while high risk implies evidence of possible bias. Unclear risk denotes a paucity of information or scepticism about possible biases (38). The author's PRSA was involved in the search for scientific articles as well as the evaluation of the inclusion criteria. Authors CSS, VP and JM were

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involved in evaluating the selected manuscripts, validating and writing the first draft of the manuscript. The authors CACR and ABA were involved in reviewing the text.

Results

A total of 2,415 articles were identified in PubMed. Of these 2,232 were excluded based on the content of their titles and abstracts that did not meet the inclusion criteria defined for the present study. Then, 183 articles met the inclusion criteria and full-text were further analysed. After evaluating the full text, 170 articles were removed as they did not represent the context of the present study. In the end, 13 studies met all inclusion criteria and were selected for analysis and interpretation of the rate and determinants of ART adherence in the SSA region between 2016 and 2023. Table 1 presents the characteristics of the selected articles, which include the authors' summary, study design, population, variables of interest, country of the study, African region, location, outcome, adherence measure, time and study findings. The studies selected for this review included patients undergoing treatment in Angola, Uganda, Ethiopia, Zimbabwe, Zambia, South Africa, Nigeria, Ghana and Mozambique. Overall, ART adherence rates in different SSA regions ranged from 43% to 84%. Rates in the centre of the SSA region ranged from 58% to 80%, in the north from 50% to 83%, in the south from 77% to 84%, in the west from 43% to 60% and in the east from 69% to 73% (Table 2).

Table 1. List of scientific articles selected to analyze ART adherence in sub-Saharan countries, 2016 - 2023.

No.	Author	Study design	Population	Variables of interest	Country of study	Africa region	Local	Result	Measuring adherence	Time	Adherence results and comments
1	Tariku MK, Worede DT, Belete AH, (2023)	Transversal	Men and women	Associated factors	Ethiopia	Sub-Saharan East	Community-based	Accession	Self-report Pill Count CD4 count	1 month	Around 50% of those interviewed in the study scenarios have perfect ART adherence.
2	Ângelo AT, Alemayehu DS, (2021))	Transversal	Men and women	Associated factors	Ethiopia	Sub-Saharan East	Hospital (outpatient)	Accession	Attendance at the clinic Pill Count Self-report	1 month	Patients' adherence to ART was 83%.
3	Nyamayaro et al., (2020)	Case series	Men and women	Problem-Solving Therapeutic Intervention for Depression and Barriers to Adherence to Antiretroviral Therapy	Zimbabwe	Sub-Saharan South	Hospital (outpatient)	Accession	Self-report	6 months	Studies in the country reveal an ART adherence rate of around 80%.
4	Abdu M, Walelgn B, (2021)	Case-control	Men and women	Determinant factors	Ethiopia	Sub-Saharan East	Hospital (outpatient)	Accession	Pill Count CD4 count	1 month	Adherence to ART was 82.3% in the studied population. (29)
5	Agala et al., (2020)	Quasi-experimental	Women	Reliability, validity and measurement invariance of the Simplified Medication Adherence Questionnaire	Ethiopia	Sub-Saharan East	Hospital (outpatient)	Accession	Self-report	18 months	The ART adherence rate was 50– 77%

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6	Asrat B, Lund C, Ambaw F, Garman EC, Schneider M, (2020)	Transversal	Men and women	Major depressive disorder	Ethiopia (North)	Sub-Saharan North	Hospital	Accession	Pill Count	3 months	Membership to ART found in this study was 81.9% of the interviewees.
7	Izudi J, Okoboi S, Lwevola P, Kadengye D, Bajunirwe F, (2021)	Quasi-randomized	Men and women	Effect of disclosing HIV status	Uganda (East)	Sub-Saharan centre	Hospital outpatient	Accession	Attend the clinic on the scheduled date or within seven days before or after the scheduled date	12 months	It is estimated that the ART adherence rate is around 80%.
8	Jones et al. (2020)	Randomized clinical trial	Men and women	Stigma	Zambia and South Africa	Sub-Saharan South	Community-based	Accession	Self-report	17 months	The membership fee to ARTfee is estimated at 84.2%.
9	Safren et al., (2021)	Randomized clinical trial	Men and women	Depression treatment	South Africa	Sub-Saharan South	Hospital (outpatient)	Accession	Self-report, Wisepill, Hamilton Depression Scale, Viral load and CD4	36 months	ART adherence is estimated at 77%.
10	Eze RA, Sulaiman N, Mat DA, Babadoko A, (2023)	Transversal	Men and women	Belief in medicine	Nigeria	Sub-Saharan West	Community-based	Accession	Self-report	13 months	ART adherence is estimated at 54%.
11	Sefah IA, Mensah F, Kurdi A, Godman B., 2022)	Transversal	Men and women	Barriers and facilitators	Ghana	Sub-Saharan West	Hospital (outpatient)	Accession	Self-report	3 months	Adherence to ART among patients living with HIV was 42.9%

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12	Pires PDN, Marega A, Creagh JM (2017)	Transversal	Men and women	Clinical and Socioeconomic Factors	Mozambique	Sub-Saharan South	Hospital (outpatient)	Accession	Self-report	30 months	The ART adherence rate was 69%.
13	Baptista, MF (2016)	Transversal	Men and women	Associated factors	Angola	Sub-Saharan South	Hospital outpatient	Accession	Self-report	120 months	The fee ofAdherence toART was 58%
14	Isika et al. (2022)	Transversal	Men and women	Increased survival and quality of life of people with good adherence to ART	Nigeria	Sub-Saharan West Africa	Hospital outpatient	Accession	Respondents were recruited via a multi-stage technique. Data were obtained by a pre-tested interviewer-administered questionnaire.	6 months	The self-reported adherence rate was 60.1%.
15	Eyassu MA, Mothiba TM, Mbambo-Kekana NP, (2016)	Transversal	Men and women	Factors that hinder adherence to ART among HIV and AIDS patients at Kwa-Thema clinic. Determination of prevalence rate of ART adherence among HIV/AIDS patients at Kwa-Thema clinic.	South Africa	Southern the sub the sub-Saharan Africa	Hospital outpatient	Accession	The researchers obtained data for this study through a structured questionnaire administered with open and closed questions.	3 months	The study found that ART adherence at the Kwa-Thema clinic was suboptimal (less than 95%) at 77%.
16	Macovela, SN (2016)	Transversal	Men and women	Clinical and Socio-Econ Factorsomics	Mozambique	Sub-Saharan South	Hospital Outpatient	Accession	Self-report	30 months	The adherence rate obtained in the study was 72.6%

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Table 2. Adherence Rate to TARV by countries and region in Sub-Saharan Africa.

Countries	sub-Saharian region	ART adherence rate
Angola	Central	58%
Uganda	Central	80%
Ethiopia	North	50 – 83%
Zimbabwe	South	80%
Zambia	South	84%
South Africa	South	77%
Nigeria	West	54 – 60%
Ghana	West	43%
Mozambique	East	69 – 73%

Discussion

ART is a successful strategy in the fight against HIV. Data identifying the main reasons and associated factors causing poor ART adherence is scarce in HIV-positive patients from several African countries, where several interventions have been developed. This review allowed for exploring multiple contexts, exploring relevant information about the different approaches applied, and also enabling a critical analysis of the results obtained. There are different ways to measure adherence to ART among populations affected by HIV, highlighting self-report as the predominant measure of adherence used [7] pill counts, pharmacy refills, electronic adherence monitoring devices, plasma viral load, medication possession rate, and appointment scheduling[8–10]. On the other hand, among the many factors responsible for low adherence in African countries, we highlight stigmatization, fear of seeking and denying health care, social isolation, difficult access to health services and depression [11,12].

The lack of a "gold standard" method to measure adherence, makes the choice of evaluation method highly dependent on the economic scenario of the location where the study is taking place [13]. The association of methods such as interviews with self-report, questionnaire structured with a verbal assessment of understanding with a small group of patients (e.g.: CEAT-VIH), an electronic questionnaire with questions aimed at people living with HIV (e.g. WebAd-Q), when properly applied, can help measure adherence with more precision [14]. Although, some methods of evaluation processes consume a lot of financial resources such as MEMS (Medication Event Monitoring System), used in clinical studies and directly influencing the application of interventions.

The selection of the measure of adherence has become a major challenge in many African countries, due to the economic vulnerability of the populations. Self-reports were the method most commonly used in HIV/AIDS hospital settings, while the medication Event Monitoring system was used above all in studies intervention clinics [12,13,15]. Due to its ease of use and accessibility, self-reporting has been the most frequently used method in environments where resources are limited, such as in LMICs, consistent with data obtained from the present review, which reveals that 81% of the selected studies used self-reporting[16]. There are many advantages associated with self-reporting, making it the most commonly applied measure of adherence. In addition to being valid and easy to use, self-reporting is consistent with objective methods of measuring adherence, such as plasma viral load monitoring and the Medication Event Monitoring System. Other advantages of self-reports in resource-limited settings include accessibility and low dependence on the use of differentiated personnel; It is also considered a robust method and an adequate indicator of adherence [16,17]. However, the biggest demerit of self-report is the overestimation of adherence due to its memory bias and social desirability, which arises, in most cases, from the patient's fear of being judged by health professionals or the consequences of providing negative feedback, which forces you to inaccurate reporting of membership. Despite these, in most studies in Africa, especially in resource-limited environments such as countries Angola, Mozambique, Nigeria, Ghana, Zambia, and Ethiopia, self-reporting is observed as the most used method [17].

Scheduling appointments, considered an early warning indicator, is also considered subjective, although access to the results is possible in clinic attendance records and, therefore, enables a more

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objective analysis, being considered similar to the self-report assessment. Although the assessment clinic is prone to manipulation by clinical staff, pill counts and pharmaceutical refills remain commonly used objective measures due to their relatively inexpensive nature and ease of use. Pharmacy refills are a validated measure of adherence to ART that has the advantage of being related to viral load, which allows measuring adherence or non-adherence to medication, however, disadvantages of pharmacy refills include dumping or sharing of pills, the need for a closed pharmacy system, its dependence on accurate and reliable records, and its inability to predict or detect viral rebound in patients. The disadvantages of pill counts, also an early warning indicator, include pill procurement and limited availability. Difficulty in keeping records of pharmacy appointments and refills when patients obtain their medications from different pharmacies is another disadvantage that impacts measurement closer to reality, although most patients with limited resources return to their primary care providers for free treatment. and refills, which makes pharmacy refills a more viable adherence measure[16–18].

The real-time adherence monitoring devices that have proven viable and reliable of late are automated medication vials that have long-lasting battery half-lives capable of holding medication supplies for 30 days. Although adherence information can be examined in real-time, allowing for rapid intervention in ART adherence, an internet connection is required for this task, making this measure less feasible, especially in resource-limited settings, such as in several SSA countries. However, other disadvantages of this measure would be your inability to confirm medication intake and the lack of privacy, as patients may have to move around with the device. However, there are precise, although expensive, measurements that include direct methods such as measuring levels of the drug or its metabolite in urine or blood, detecting a biomarker added to the drug formulation, and targeting observed therapy[16,18].

Validating the measure of adherence against viral load is beneficial, and achieving undetectable viral load is also considered one of the most common measures of ART adherence. Adherence rates in SSA countries are between 43% to 84%, which may indicate that many patients do not achieve viral suppression. Indeed, a high level of ART adherence of 95% has previously been associated with undetectable viral load, equating viral suppression with adherence[19]. Currently, adherence levels between 80 and 85% are sufficient for viral suppression, making undetectable viral load an unsatisfactory intermediate method for maximum adherence. However, other supporting work has observed positive results from ART with treatment adherence levels between 80 and 95%[19,20].

Conclusions

Our review revealed that ART adherence in the sub-Saharan African region ranged from 43% to 84%. Most African countries use the self-report to assess treatment adherence, although unreliable. Complementary assessment methods, such as clinical response, monitoring of dispensing records, counting and refilling of antiretroviral tablets, as objective ways of measuring adherence without adherence, although expensive, are more reliable and should be considered in these regions of Africa in order to maximize the rate of adherence to ART, reduce new HIV infections and improve the quality of life of people living with HIV in Africa regions.

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