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Clinico-Biological and Immuno-Virological Profile of People Living with HIV Non-Adhering to HAART at the Lerato Clinic, Bertha Qxowa Hospital, Germiston, South Africa

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Abstract: *Background and objectives*: Highly active antiretroviral therapy (HAART) is a mainstay in the management of PLWHIV, improving survival. However, since its advent and its side effects, the problem of adherence to this therapy arises... The objective of this study was to investigate the impact of non-adherence to HAART on clinical, biological, immunological and virological parameters. *Methods:* The investigator conducted a cross-sectional study at the Lerato Clinic at Bertha Qxowa Hospital in Germiston, Gauteng, South Africa, from September 2019 to December 2019. Included for participation were those over 18 years of age, on HAART for at least three months, consenting to participate, and attending the clinic during this period. Non-adherence was defined as taking their medication ≤ 95% of the time. A sample of 278 participants was selected. A non-adherence threshold of >5% was considered high, with $P<0.05$ statistical significance. *Results:* A sample of 278 participants was considered. Of these, 19% (n = 52) were non-adherent to HAART. Clinico-biologically and immunobiologically, this category had high averages of Systolic blood pressure, Waist circumference (WC), Hip circumference (HC), Creatinine, Urea, Uric acid, Blood glucose, Total cholesterol, LDL Cholesterol, Triglycerides (TG), CRP and Viral load. While the mean values for diatolic blood pressure (DBP), CD4 count and body mass index (BMI) were lower. *Conclusion:* Patients receiving HAART but not adhering to it have a higher risk of diabetes mellitus, cardiovascular disease, liver disease, chronic kidney disease and opportunistic infections. Regular monitoring of patients on HAART to avoid non-compliance is imperative to detect these risk factors and allow for early initiation of treatment.

Keywords: Virological Profile, Associated Cardiometabolic Risks, Non-Adherence to HAART, HIV/AIDS

1. Introduction

HIV/AIDS is a pandemic fraught with complications related to non-adherence to antiretroviral therapy [1].

The advent of HAART has shown its effectiveness in reducing the viral load and improving the clinical and biological parameters of patients who adhere to it [2]. It is well established that the clinical effectiveness of HAART in suppressing the HIV virus towards long survival requires a non-adherence rate of less than 5% [3]. South Africa faces a high rate of HIV/AIDS where a low level of non-adherence (correct dosage, taken on time and in the right way, economic/sanitation/safety, and food security) is needed [4]. However, it is also significantly known that the level of perfect non-adherence must be ≤ 5% to minimize drug resistance and limit AIDS complications.

Thus, the present study questioned the impact of non-adherence to ART on the clinico-biological and immuno-virological parameters of PLHIV.

2. Materials and Methods

2.1. Study-Design

It was a cross-sectional study conducted from September 2019 to December 2019.

2.2. Study Setting

Lerato Clinic is an HIV clinic in Bertha Qxowa Hospital located in Germiston, Johannesburg, South Africa, and was selected as our study setting.

2.3. Study Population

All adult HIV-infected patients were on HAART for at least three months and attended during the same period and the setting management of this study.

2.3.1. Sampling

The sample size calculation used the Raosoft software:

about 150 patients are seen daily Monday to Friday. Of the patients seen daily approximately, 50 are on HAART. Over the study period, it is estimated that we need approximately 278 participants. This assumes a margin of error of 5%, a confidence level of 95%, and a response distribution of 50%.

Participants were investigated for factors that are associated with their drug non-adherence based on observing the timing of doses and keeping clinic appointments for drug refills during the period of the study.

These patients meeting the criteria for inclusion in the study were invited to participate in the study, examining potential barriers to adherence. The investigator did approach every patient during each daily interview period.

2.3.2. Criteria of Inclusion

Those being more than 18 years old, on HAART for at least three months, consenting to participate, and attending the clinic were included.

2.3.3. Criteria of Exclusion

Patients less than 18 years old, not speaking English, Tswana, or Zulu, those who are not literate, who cannot communicate in the above-selected languages, and patients on HAART with less than three months of treatment were excluded.

2.4. Data Collection

A precoded and standardized questionnaire was used for data collection. It contains five items that briefly ask for demographic (Gender: male/female, Age: ≥45 years/ <45 years, Ethnic group: Black/White/Coloured/Indian, Marital status: Single/Married/Living with life-partner/Widowed/Separated/Divorced, Level of education: Primary/High school/College/University, and status of employment: Full-time/Sessional/None) information and then put six closed-ended and a single open-ended question about potential barriers to HAART adherence that patient might identify.

That questionnaire was adapted from the one which has been used in the Botswana stud [1]. Data were not collected on Tuesdays as the day is consecrated for academic meetings. All surveys were confidential and anonymous. They were conducted in private by the principal investigator in a separate room in the clinic, where participants were filling in the questionnaire for 45 minutes. Data were collected from the consenting respondents using self-administered questionnaires with the help of an assistant for language barriers, especially for those who cannot communicate in selected languages. The key variables to examine were demographics.

The investigator used a validated questionnaire modeled after the Adult AIDS Clinical Trial Group adherence instrument that was carried out to identify missed doses over a 1-year interval. The investigator did first a pill count for all eligible patients every working day. After answering the questionnaire, the investigator collected it for analysis. The information was drawn from files and the questionnaire. The result was transferred into a data sheet.

Operational Definitions:

Good HAART adherence: Taking ≥ 95% of prescribed ART [5]. Hypertension was defined by an Blood Pressure (BP) ≥ 140/90 mmHg following measurements obtained at least 2-3 separate visits (1-4 weeks) unless BP ≥ 180/110 mmHg in the presence of cardiovascular diseases or whatever the BP, and the notion of antihypertensive treatment [7, 8]. Treated Arterial Hypertension is considered uncontrolled if: the blood pressure figures are > 140 mmHg for SBP and 90 mmHg for PAD in non-diabetic hypertensives, > 130 mmHg for SBP and 90 mmHg for PAD in diabetic hypertensive, >

130 mmHg for SBP and 90 mmHg for DBP in hypertensives with renal insufficiency, > 150 mmHg for SBP in hypertensives over 80 years old.

A Body Mass Index (BMI) ≥ 25Kg/m² and ≥ 30 Kg/m² define, respectively, overweight and obesity [8]. Diabetes Mellitus is defined by a fasting blood sugar level ≥ 126 mg/dl or, whatever the blood sugar level, with the notion of antidiabetic treatment [8]. Moderate Fasting Hyperglycemia is defined as a fasting blood glucose level between 110 and 126 mg/dl. Metabolic Syndrome is defined by the presence of at least 3 of the following criteria: BP ≥ 130/85 mm Hg, waist circumference > 102 cm (men) and > 88 cm (women), blood sugar at fasting > 110 mg/dl (5.1 mmol/l), HDL-c < 40 mg/dl (1.0 mmol/l) in men and < 50 mg/dl (1.5 mmol/l) in women, triglycerides > 150 mg/dl (1.7 mmol/l).

An increase in HDL cholesterol ≥ 75mg/dl was considered a cardiovascular risk factor [9, 10]. Non-HDL Cholesterol is the differential between total cholesterol and HDLc, it summarizes the sum of the two potentially atherogenic fractions of cholesterol, namely LDL cholesterol and VLDL cholesterol. In patients considered at high cardiovascular risk, the non-HDL cholesterol level is between 130 and 159 mg/dl. In patients considered to be at very high cardiovascular risk, this level is between 160 and 189 mg/dl. A Suppressed Viral Load was defined by a plasma HIV-RNA level ≤ 1000 copies/mL and an Undetectable Viral Load was < 50 copies/mL [10]. Increase in C-Reactive Protein (CRP) ≥ 3 mg/L [11]. A Uric Acid level > 7 mg/dl defines hyperuricaemia.

2.5. Data Analysis

The files were retrieved from the records department with the help of a clerk working in that department. The information retrieved was recorded on to excel spreadsheet. To minimize recall bias, the investigator did ask patients to indicate their non-adherence over the previous day, previous week, previous month, and previous year successively. Non-adherence was defined as taking their medication ≤ 95% of the time. If one is taking a once-daily treatment, it means missing no more than one dose per month, if it is a twice-daily treatment it means missing no more than three doses per month and if one is taking three times a day treatment it means missing no more than four doses per month.

The investigator determined the percentage of patients surveyed and met the criteria for non-adherence. The analysis was done as follows: Clinical and biological data were summarized in a table format. Statistical tests were performed to compare the characteristics of adherents and non-adherents. Quantitative variables were converted into qualitative variables that were analyzed using the chi-square test. SPSS version 23.1 software was used for all statistical analyses. Criteria for 2-sided statistical significance were defined by a P-value <0.05.

2.6. Ethical Approval and Consent to Participate

The study protocol was approved by the Human Research Ethics Committee of the University of Goma, DR Congo REF# UNIGOM/CEM/14/2022), according to the Declaration of Helsinki III recommendations (Helsinki-Declaration-1964-2015-08-20), and approved by Betha Qxowa Hospital to start the research. The researcher took into consideration the fundamental principles of ethical research.

Written informed consent was obtained from patients for participating. The investigator clearly explained to the study participants what was expected from them and what to do if they decided not to proceed with the study. Whether to participate or not from the very beginning was the decision of the study participants, and they were assured that their refusal to participate in the study would have no consequences. They were also told that they had the right to ask questions at any time and withdraw from the study under any circumstances.

Confidentiality and anonymity for participants were guaranteed as well. The completed questionnaires were kept in a locked drawer in the office of the principal investigator. Data treated were stored in a digital file of which access was only possible using the investigator´s password.

3. Results

3.1. Categorization of Participants According to Art Adherence

Of a total of 278 participants, 19% (n = 52) were found non-adherent to ART at the Lerato clinic. Regarding the Adherence category, in the study population, out of a total of 278 participants, 19% (52 participants) were non-adherent and 81 (226 participants) were adherent; but of the adherents, 63% were premature or early adherents and 18% were late adherents (Figure 1).

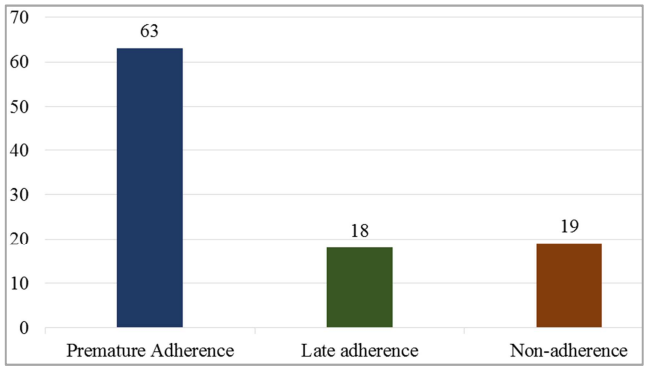

Figure 1. *Adherence category.*

3.2. Non-Adherence and Clinical Anthropometric Parameters

Regarding clinical parameters, non-adherents had disturbed clinical parameters. The average SBP in this category was higher (139 ± 8 mmHg) compared to members, while the averages of DBP, WC, HC and BMI were the lowest with respectively: 53 ± 6 mmHg; 69 ± 4 cm; 82 ± 11 cm; 25 ± 3 kg/m^2 (Table 1).

Table 1. *Adhesion category and clinical and anthropometric parameters.*

Variables	HAART Adherence		Non-Adherent	P-value
	Adherent			
	Premature	Late		
SBP (mmHg)	129±19	128±19	139±8	<0.001
DBP (mmHg)	81±11	80±9	53±6	0.001
WC (cm)	93±49	89 ± 1 0	69±4	<0.001
HC (cm)	103±13	102±9	82±11	0.445
BMI (kg/m2)	26±6	25 ± 4	25 ± 3	<0.001

Abbreviations: BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, WC: Waist Circumference, HP: Hip Circumference.

3.3. Non-Adherence and Biological and Immuno-Virological Parameters

Table 2 presents, on the one hand, the means of the biological parameters of the high participants: Creatinine 1.61 ± 0.66 mg/dL; Urea 46 ± 9 mg/dL; Uric acid 8 ± 1.99 mg/dL; Blood glucose 133.13 ± 37.66 mg/dL; Total cholesterol 219 ± 70 mg/dL; LDL cholesterol 151 ± 70 mg/dL; HDL cholesterol 30 ± 10 mg/dL; TG 114 ± 62 mg/dL; ALT 41 ± 21 IU/L; AST 34 ± 18 IU/L; CRP 19 ± 23 mg/dL; Monocytes 6.1 ± 2.1%; platelets 242736 ± 88808 thou/µL; Viral load 525 ± 383 copies/mL; and on the other, a collapse of biological parameters: GR 3.29 ± 0.62 mil/µL; Hb 11 ± 1.8 g/dL; Hct 32.25 ± 5.1%; CD4 182 ± 94 cells/mL. The WBC averages (neutrophils, lymphocytes, eosinophils, basophils) were not significant.

Table 2. *Adherence category and biological parameters.*

Variables	HAART Adherence		Non-Adherent	P-value
	Adherent			
	Premature	Late		
Creatinine (mg/dL)	0.99±0.5	0.95±0.22	1.61 ± 0.66	<0.001
Urea (mg/dL)	30±20	32±20	46±9	<0.001
Uric acid (mg/dL)	5.99±1.86	6±2.56	8±1.99	<0.001
Blood glucose (mg/dL)	102.1±59.1	133±92	133.13±37.66	0.001
Total cholesterol (mg/dL)	165±50	172±39	219±70	<0.001
LDL cholesterol (mg/dL)	105±49	104±32	151±70	<0.001
HDL cholesterol (mg/dL)	44±16	43±13	30 ± 10	<0.001
TG (mg/dL)	103±55	112±73	114±62	<0.001
ALT (IU/L)	27±14	29±29	41±21	<0.001
AST (IU/L)	23±14	28±32	34±18	0.001
CRP (mg/dL)	7±13	6±8	19±23	<0.001
White blood cells (thou/µL)	4940±1455	4957±1606	5156±2490	0.723
Neutrophils (%)	48±12	47±12	49±11	0.544
Lymphocytes (%)	41.38 ± 11.75	43.16±11.76	41.68±10.42	0.635
Monocytes (%)	7.4±2.9	7.8 ± 3.4	6.1 ± 2.1	0.005
Eosinophils (%)	3.1 ± 3.3	1.93 ± 2.3	2.53 ± 2.44	0.059
Basophils (%)	0.43±0.24	0.43 ± 0.25	0.42 ± 0.30	0.976
Red blood cells (mil/µL)	4.27±0.6	3.99±0.75	3.29±0.62	<0.001
Hgb (g/dL)	12±2	12.4±1.3	11±1.8	<0.001
Hct (%)	34.87±5.2	35.71±3.94	32.25±5.1	0.001
Platelets (thou/µL)	216626±75049	201420±66900	242736±88808	0.020
CD4 count (cells/mL)	511±311	569±325	182±94	<0.001
Viral load (copies/mL)	216.1±340	216±355	525±383	<0.001

Abbreviations: TG: Triglycerides, ALT: Aspartate aminotransferase, AST: Alanine aminotransferase, CRP: C-Reactive Protein, Hb: Hemoglobin, Hct: Hematocrit, CD4: differentiation cluster 4.

4. Discussion

It is well known that HAART therapy significantly improves the survival of people diagnosed with HIV/AIDS. In recent years, HAART has contributed to improving the quality of life of patients infected with HIV/AIDS [12]. Despite this evidence, low HAART adherence of 19% was found in the present study, a very lower rate compared to that found in a study in Latin America, which showed HAART adherence of approximately 70% [13]. These results demonstrate that it is crucial to determine and address seriously the lack of adherence to HAART in patients infected with HIV/AIDS which alters the quality of life of PLHIV.

The cardiovascular health of PLHIV has become of great concern. Cardiovascular abnormalities are increasingly common, sometimes linked to HAART, but also to non-adherence to this treatment [14].

Hypertension is very common in HIV-positive populations and may be more common than in HIV-negative populations.

Risk factors contributing to the development of hypertension in PLHIV include demographic factors, genetic predisposition, lifestyle, comorbidities such as obesity, changes in body composition related to antiretroviral therapy, and potentially also immunodeficiency, immune activation, and inflammation, as well as the effects of antiretroviral therapy itself. Clinical management of hypertension in PLHIV requires awareness of drug interactions between antiretrovirals and antihypertensives.

In the present study, means for SBPs are highest while those for DBPs are lowest in the HAART non-adherent category. Knowing that coronary and cerebrovascular mortality increases linearly with the increase in systolic blood pressure, non-adherent patients are most at risk of presenting cardiovascular events related to hypertension. On the contrary, a low DBP exposes patients to coronary pathologies [15].

Regarding the anthropometric parameters, the WC, one of the pillars of the metabolic syndrome of subcutaneous adiposity, was found in the lower averages in the participants who were not adherent to HAART compared to the participants in HAART. This can be explained by the metabolic disorders listed in several studies in PLHIV on HAART [16]. Participants who were early adherents to ART were remarkably overweight when compared to late adherents and non-adherents by BMI measurement. Non-adherent participants are in weight loss, probably related to repeated opportunistic infections. Unlike dyslipidemia associated with TG, HDL, LDL; non-adherents were the most affected.

Liver pathologies are also reported in PLHIV and responsible for 14 to 18% of deaths [17]. In HAART non-adherents, we found elevated transaminases that express hepatocyte damage. This can be explained by the occurrence of acute cytolytic hepatitis, opportunistic infections, resulting from HIV/AIDS infection [18–20]. This vulnerability is explained by the immuno-virological status of non-adherents worrying and alarming, with a very high viral load, and CD4 lymphopenia.

HAART is essential for PLHIV because it lowers the viral load, but it needs to be strictly adhered to. Good adherence produces a decrease in viral replication, which is associated with maintaining a functional immune system [13]. The present study showed a higher viral load in non-adherents to HAART than in adherents, they constitute a potentially contagious population. This constitutes an obstacle in the fight against HIV/AIDS. In addition to CD4 depletion, they are exposed to recurrence of infections.

The HIV infection can also be associated with different types of renal damages, some of which result from the direct infection of renal cells by the virus, as in HIV-associated nephropathy (HIVAN) [21]. The use of HAART significantly slows the progression of chronic kidney disease.

5. Conclusion

Adherence to antiretroviral therapy changes the lives of PLHIV. This study showed the impact of non-adherence to HAART on the clinico-biological and immuno-virological parameters of PLHIV [22]. Non-adherents were the most exposed to cardiovascular, infectious, metabolic, hepatic, and renal complications.

Immunodepression linked to CD4 depletion and contagiousness with a higher viral load found in non-adherents to HAART contributes to the deterioration of the quality of life in PLHIV.

Conflicts of Interest

The authors declare no conflict of interest.

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