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Impact of depression and psychosocial management on drug adherence and viral suppression in HIV-infected patients on antiretroviral treatment in Cameroon

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Jackson Jr Nforbewing Ndenkeh

born in

Bokito, Cameroon

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Supervisors LMU:

Habilitated Supervisor	Priv. Doz. Dr. Elmar Saathoff
Direct Supervisor	Dr. Arne Kroidl
3rd LMU Supervisor	Dr. Camilla Rothe

Supervisor External:

Local Supervisor	Dr Akindeh Mbuh Nji

Reviewing Experts:

1st Reviewer	Priv. Doz. Dr. Elmar Saathoff
2nd Reviewer	Dr. Arne Kroidl
3rd Reviewer	apl. Prof. Dr. Theo Rein
4th Reviewer	apl. Prof. Dr. Susanne Lucae

Dean: Prof. Dr. med. Thomas Gudermann

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LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dean's Office
Medical Faculty

MMRS

Affidavit

Ndenkeh Nforbewing Jackson Jr

Surname, first name

Street

Zip code, town

Cameroon

Country

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Ndenkeh Nforbewing Jackson Jr

Surname, first name

Street

Zip code, town

Cameroon

Country

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Place, date

Ndenkeh Jackson Jr

Signature doctoral candidate

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Statement on own publication

I hereby declare that a considerable part of this dissertation presented with title “Impact of depression and psychosocial management on drug adherence and viral suppression in HIV-infected patients on antiretroviral treatment in Cameroon” has been published by the journal BMC Infectious Diseases as a paper entitled “Depression management and antiretroviral treatment outcome among people living with HIV in Northwest and East regions of Cameroon” with me as first and corresponding author. Both dissertation and manuscript present results from the same clinical trial thus their talking points are pretty much the same. For that reason, some sections of this dissertation will thus be presenting talking points as paraphrases of the published paper most especially at the results and discussion sections of this dissertation. Some of the tables and figures from the published paper have been naturally used for this dissertation. For any of such table(s) or figure(s) included in the result section of this dissertation, it is accompanied by an indication of its source referencing thus the published paper (Ndenkeh et al., 2022). Also, most of the text segment paraphrased from the published manuscript, is accompanied by source indication accordingly (reference #36).

I conceived this clinical trial, wrote the proposal, planned, and supervised the data and sample collection and personally built the database into which I entered the data, then cleaned with Microsoft Excel before analysis. Furthermore, I conducted the data analysis as well as drafted and revised the paper that has been published, likewise this dissertation, and this was with scientific contribution from supervisors and other co-authors. So, I have the publication rights to both the manuscript and dissertation.

Keywords

Depression, Antiretroviral treatment, Interpersonal psychotherapy, HIV treatment adherence, Viral suppression, Cameroon

Abstract

Background: The scale up of antiretroviral treatment in resource-limited settings has raised concerns regarding quality of care and treatment outcome. This study aimed to evaluate the effect of routine depression screening and management on adherence and viral suppression of people living with HIV, particularly in the rural settings of Cameroon.

Methodology: This was a cluster-randomized intervention study targeting persons aged 13 years and above who had been on antiretroviral treatment for 6-9 months. Participants were followed up for 12 months during which those in the intervention group underwent routine screening and management of depression. Treatment adherence and viral suppression were compared between both groups using the two-way ANOVA and Chi-squared test with a significance set at 5%.

Results: A total of 370 participants with a median age of 39 years (IQR: 30-49) were enrolled in this study. Of these, 10 (2.7%) were adolescents, 244 (65.9%) were females and 187 (50.7%) were married or in a union. At baseline, 42 (11.3%) were screened with moderate to severe depressive symptoms and 41 (11.1%) had poor adherence. During follow-up, there was a significant drop in depression scores in the intervention group from 3.88 (±3.76) to 2.29 (±2.39) versus 4.35 (±4.64) to 3.39 (±3.0) in controls ($p<0.001$) which was accompanied by a drop in depression prevalence in the intervention group from 9% to 0.8% ($p=0.046$). Decreased depression scores were correlated with better adherence scores with correlation coefficients of -0.191, -0.555, and -0.513 at baseline, 6 months and 12 months of follow up respectively ($p<0.001$) but there was no significant difference in adherence levels (Highly adherent: 30.6% vs 29.7%; $p=0.255$) and viral suppression (unsuppressed viral load: 11.9% vs 10.8%; $p=0.811$) between groups.

Conclusion: These findings suggest that screening and managing depression can be considered as an important part of routine HIV management, and facilitating its effective implementation at all levels of the health pyramid could lead to better treatment outcome. More large-scale and inclusive research is thus needed to identify depression management strategies that are cost-effective, take into consideration each implementation context and can bring positive impact to HIV treatment.

List of Abbreviations

ART _ Antiretroviral Therapy

CBCHS _ Cameroon Baptist Convention Health Services

CD4 _ Cluster of Differentiation 4

CHAI _ Clinton Health Access Initiative

CHAMP _ Continuum of prevention, care and treatment of HIV/AIDS with Most-at-risk Populations

CM _ Clinical Monitoring

EGPAF _ Elizabeth Glaser pediatric AIDS Foundation

HIV/AIDS _ Human Immuno-Deficiency Virus / Acquired Immuno-Deficiency Syndrome

IM _ Immunological Monitoring

IPT _ Interpersonal Therapy

NEC _ National Ethical Committee

PEPFAR _ President's Emergency Plan for AIDS Relief

PMTCT _ Prevention of Mother To Child Transmission

PHQ _ Patient Health Questionnaire

PLWHA _ Person living with HIV/AIDS

SoC _ Standard of Care

TC _ Treatment Center

UNAIDS_ Joint United Nations Programme on HIV/AIDS

VL _ Viral Load

VM _ Virological Monitoring

WHO _ World Health Organization

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1. Introduction

1.1. Background

The United Nations Organization for the fight against HIV/AIDS (UNAIDS) had set the new *95-95-95* global target for the early detection, anti-retroviral therapy (ART) coverage and viral suppression deemed reacheable by 2030 passing through the the intermediate 90-90-90 target set for 2020 (1, 2). This implies that by 2030, 95% of persons living with HIV know their serological status, 95% of those whose positive status is known be on ART and 95% of the latter successfully retained in treatment and having their viral load suppressed. Although many strategies are needed to end the HIV/AIDS epidemic, access to HIV-treatment and an effective ART constitutes the main factor for disease control (1, 3). HIV-treatment is thus one of the most important interventions of preventing and subsequently eliminating the epidemic. Subsequently, many international stakeholders, have made it a priority to ensure the treatment continuum of infected persons. According to the data from UNAIDS, there has been a 3.7-fold increase in the number of persons receiving antiretroviral treatment within the past 10 years with values moving from 7.5 million in 2010 to 28.2 million in 2021, resulting in a 47% decrease in annual HIV-related deaths since 2010 (4). This is made possible by the engagement of many countries in various parts of the world through adoption of recommended strategies like the provider initiated testing and counselling (PITC), service delivery decentralisation, test and treat strategies, and point of care testing aiming to strengthen decentralized HIV services (5). This generalised scale up of antiretroviral treatment in resource-limited settings has led to a gradual shift of focus from detection and linkage to quality of care, adherence and effective viral suppression (6).

Access to antiretroviral treatment in sub-Saharan Africa has significantly increased over the years with coverage from 24% in 2010 to 77% in 2020, which has led to a drop in deaths related to HIV/AIDS in that part of the world by 47% (4). Despite so, HIV is still a major public health problem in sub-Saharan Africa that harbours 67% of all HIV positive persons globally (4). It has been observed that South and East African countries with high burden of HIV, are on track set to achieve the 90% treatment target, include Botswana, Rwanda, Malawi, Swaziland, Lesotho and Kenya (7). It is expected that health systems in countries with lower HIV prevalence, and therefore fewer HIV positive persons to manage, ought to cope with the burden of offering lifelong treatment, but unfortunately this is not the case for West and Central African countries (7). A plausible explanation is the lack of incentive to

adapt their service delivery models, as well as insufficient resources mobilised thus suffer the effect of shortage of health workers and over-burdened health systems (6, 8).

1.2. Problem Statement

In Cameroon, treatment coverage has significantly increased across all ages from 17% in 2010 to 74% in 2020, resulting to about 370, 000 people living with HIV having access to antiretroviral treatment (9). There is however disparity in this access to antiretroviral treatment with respect to age group where children (0-14 years) have less access to treatment, with an antiretroviral treatment coverages of 35% (9). HIV-treatment follow-up parameters like CD4-count and viral loads are used to monitor treatment efficacy. The national AIDS control programme recommends that CD4-counts are monitored every 6 months while a viral load test is done after 6 months of antiretroviral treatment and then on a yearly basis (10). Despite so, follow-up monitoring is still a major challenge as many persons undergo treatment with no CD4 monitoring and barely received viral load monitoring as per the guidelines, especially in rural settings (11).

Viral suppression indicates treatment success, thus improving health and reducing subsequent transmission of virus, as well as serve as means to identify cases of HIV-treatment failure (6, 12-14). Viral load is expected to have been suppressed until it falls to undetectable levels (<50 copies per milliliters) after 6 months of effective treatment. Reaching this undetectable level is the main aim of treatment as affiliated with immune system recovery and subsequent risk reduction for opportunistic diseases. Furthermore, sustained viral suppression to undetectable levels implies the reduction of HIV-transmission to near zero as demonstrated by numerous studies (15, 16). Effective viral load suppression with a threshold of <1000 copies per millilitres as defined by WHO (17) has a similar impact (though at a lesser rate) but might expose the patient to drug resistance development caused by potential low-level viral replication (18). Notwithstanding, not much is known about viral suppression among persons receiving antiretroviral treatment in low- and middle-income contexts given that their routine viral load tests are not regularly performed yet. We witness a similar situation in Cameroon in respect to CD4-count monitoring as it is rarely performed in health facilities, while viral load testing is only offered at reference laboratories found in close by regional hospitals (19). Even when subventions and user fee elimination were implemented for the above two tests, effective use of the above monitoring methods still face a lot of structural and technical challenges notably logistics linked to sample collection and transportation, maintenance of equipment, stockout of test kits, and available human resource. This makes health

improvement and viral suppression monitoring very difficult to accomplish thus clinical monitoring becoming the most accessible method; which alone is not sufficient to quantify the level of treatment effectiveness benefited by the patients.

Recent studies in Cameroon have shown treatment failure to vary greatly from 5.45% to 27.9%, which is dependent on the time, place and target population from whom viral loads were measured resistance (11, 20-24). Most of these studies were cross sectional, performed on all persons on treatment, and two of them found alarmingly high association with drug resistance (11, 24). Viral load suppression is influenced by several factors which are treatment linked (e.g. non-adherence to treatment, poor retention in care, complexity of regimen, resistance to drug), behavioural (smoking, drinking), psychological (depression) or socioeconomic factors (stigmatisation, employment status, education) (23, 25, 26). Apart from drug resistance, which in some cases is unavoidable, most of these other factors center around treatment adherence which intend affects viral suppression. The benefit in the scale up of antiretroviral treatment depends very much on the sustainability of treatment adherence where optimal adherence is required for the effectiveness of ART in suppressing virus, reducing disease progression and preventing transmission (27-30).

Mental health problems, notably depression and anxiety, occur quite frequently in persons living with HIV/AIDS (31). Depression, which is a frequent medical condition, has been shown to be associated with medical and psychosocial wellbeing as well as socioeconomic status (31). Some studies in sub-Saharan Africa have also shown associations between depression and poor adherence to HIV treatment (32-34). The effectiveness of several interventions on mental health and wellbeing of persons living with HIV have been backed by a good number of studies even though there is still insufficient data on their effect on HIV treatment outcome (17). Furthermore, many of these demonstration studies have been conducted in high-income countries, which is home to a considerably small portion of all HIV positive persons globally (35, 36). These interventions may not have the desired outcome in low- and middle-income countries, where other socioeconomic and psychosocial factors like poverty, patterns of the burden of disease, gender norms, discrimination against specific groups etc vary greatly (36, 37). It is thus important to identify which interventions work for depression management within an African setting as well as their impact on HIV treatment outcome.

2. Literature Review

2.1. HIV Epidemic in the Cameroonian context

Despite experiencing a drop in HIV prevalence among adults from 4.1% in 2010 to 3.0% in 2020, Cameroon is still a Central African country facing a high burden of the HIV infection where 15,000 persons were newly infected and 14,000 AIDS-related deaths were recorded in 2020 (9, 38). Through the goverment-led survey called "*Cameroon population-based HIV impact assessment (CAMPHIA)*" conducted back in 2017 as shown by Figure 1, it was observed that the South region stood out in terms of HIV prevalence with 6.3% followed by the East, Centre and NorthWest regions with 5.9%, 5.8% and 5.1% respectively (39). Also, it was observed that HIV prevalence increased with age and was higher among females than among males.

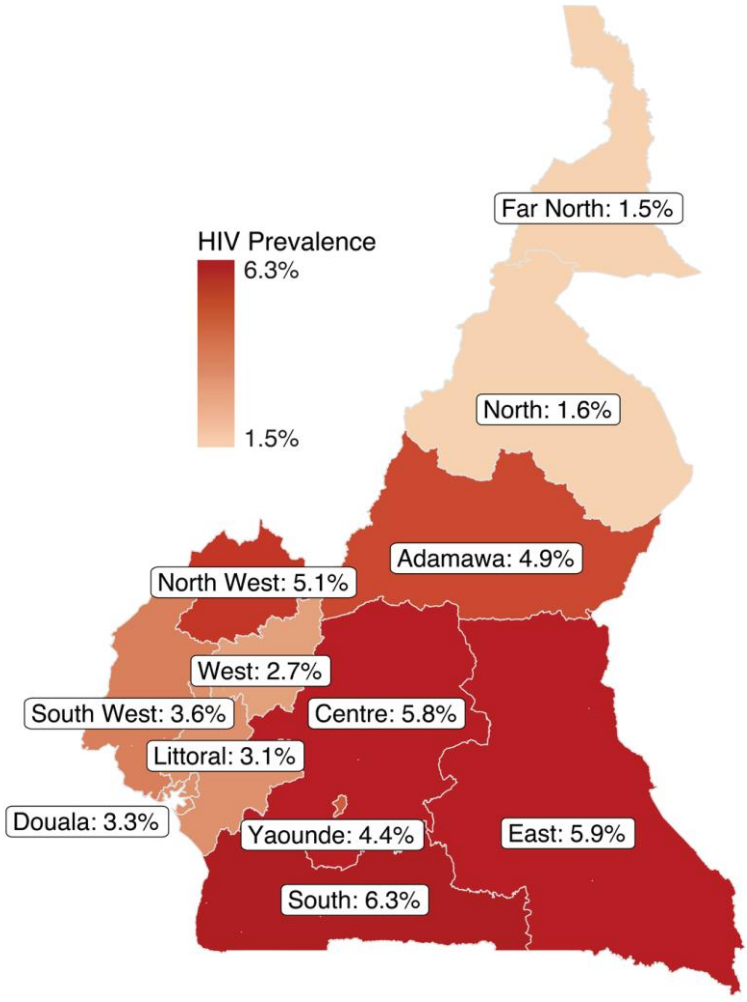


Figure 1: HIV prevalence per region in Cameroon

Source: CAMPHIA, 2018 (39)

In line with the 90-90-90 target, 78% (390,000) and 74% (370,000) of the estimated 500,000 HIV positive persons in Cameroon know their HIV status and are on ART respectively (9, 36). Furthermore, viral suppression has been shown by some recent studies to vary from 72% to 95% (21, 22, 39-41). As shown in Figure 2, the above CAMPHIA survey even went further to show viral suppression that greatly varied between the regions ranging from 62.9% in the West region to 27.6% in the North region (39). As was the case for HIV prevalence above, viral suppression greatly varied per age group and sex with younger ages and females having lower viral suppression.

In addition to the above alarming unsuppressed viral load which potentially lead to post-treatment drug resistance in a vast majority of those who stay unsuppressed (24), it is also worth noting that pre-treatment drug resistance poses a major challenge to HIV management in Cameroon. A national survey on the prevalence of pre-treatment HIV drug resistance showed that, at least 10% of patients initiating antiretroviral treatment in Cameroon already carried viruses with pre-treatment resistance thus were at risk of premature treatment failure (42). The above pre-treatment resistance prevalence which was higher in the urban setting compared to the rural setting was further concorded by another study by Fokam et al in 2020 who observed pre-treatment resistance in 9.8% of study participants (43).

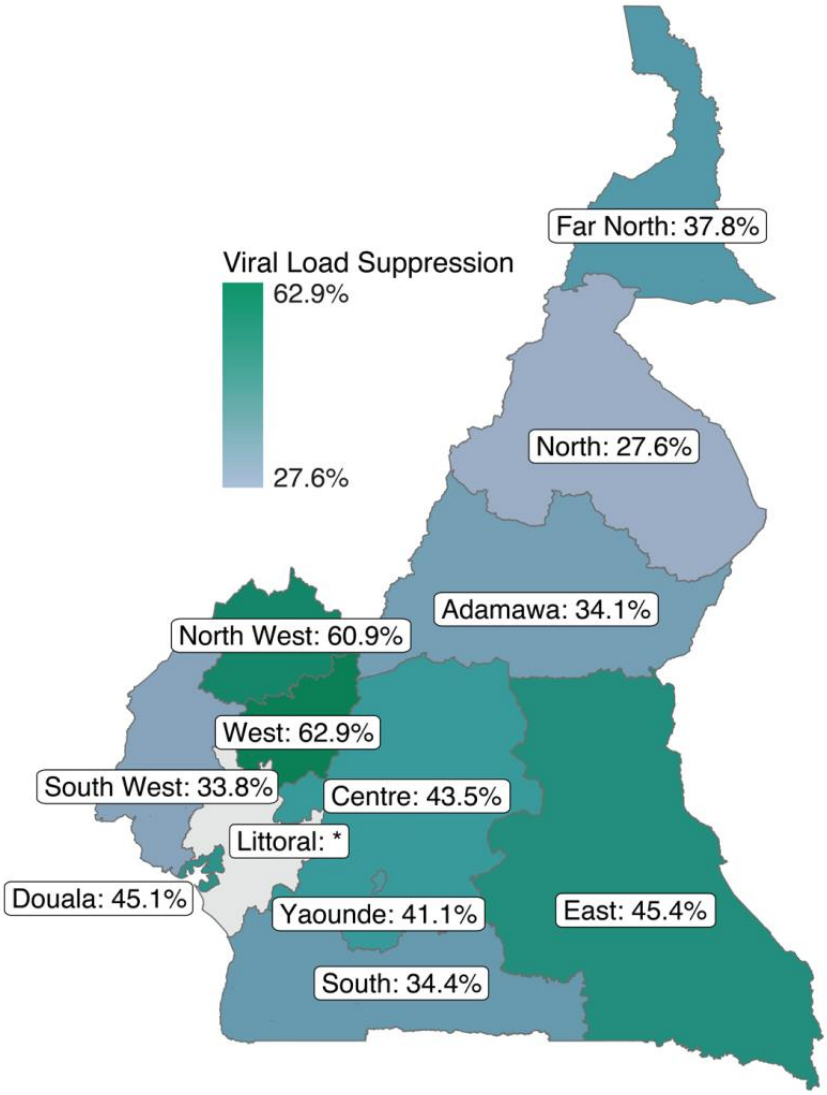


Figure 2: HIV viral suppression per region in Cameroon

Source: CAMPHIA, 2018 (39)

In Cameroon, a good number of oppotunistic infections continue to be observed in people living with HIV with the most prevalent ones being shingles and pulmonary tuberculosis. According to two studies conducted in health facilities of the major cities of Yaounde and Douala, it was observed that the above opportunistic infections were prevalent in at least 20% of the people living with HIV (44, 45). The occurrence of these opportunistic infections according to Kouanfack et al was associated elder adults (50+ years), male gender and CD4 count which were less than 200cells/mm^3 (44).

2.2. HIV Response in Cameroon

Over the years, the Cameroonian goverment with the support from other local and international stake holders has taken steps in improving HIV response within the country. In addition to receiving antiretroviral drugs for free, children below 15 years also receive HIV

testing free of charge as well as testing subvention for adults. Antiretroviral drug dispensation to people living with HIV had been decentralised to peripheral level of the health pyramid (district hospitals) since 2005 (46). As of 2016 the goverment adopted the «test and treat» strategy in HIV management which saw people newly diagnosed with HIV being put directly on antiretroviral treatment not considering their disease stage and/or level of CD4 count as was previously the case (47). Furthermore, the government had put in place subventions for HIV-associated health care services like CD4 count and viral load, all of which subsequently saw their user fees eliminated; 2019 for viral load and 2021 for all other HIV treatment linked services.

Despite the illegality of sex work and gay sex in the country, long-term projects like the "*Continuum of prevention, care and treatment of HIV/AIDS with Most-at-risk Populations (CHAMP)*" project have been allowed to run within the country for many years now (48, 49). The project sponsored by PEPFAR which has been implemmented in Cameroon since 2014, seeks to improve and expand HIV/AIDS services to key populations (female sex workers, adolescents and young women, gay men, transgenders and injectable drug users) and other vulnerable populations notably clients of female sex workers, children of female sex workers as well as adolescent girls and young women (48). It is through the above CHAMP project that HIV pre-exposure prophylaxis was introduced as complementary prevention to the use of condoms (50) as well as HIV self testing introduced to hard-to-reach female sex workers and gay men within the CHAMP project sites (51).

Another domain of HIV response in Cameroon where considerable resource mobilisation was observed is the prevention of mother to child transmission of HIV (PMTCT) program. From the early 2000s, the PMTCT program got major actors like Elizabeth Glaser Paediatric AIDS Foundation and Cameroon Baptist Convention Health Services who under the sponsorship of PEPFAR, scaled up within the country, activities and strategies that help prevented HIV infection in child transmitted from mother (52). The PMTCT program paved the way for the decentralisation of HIV linked health care services down to small clinics in remote villages and subsequently significant increase in ART coverage over the years accompanied by significant decrease in HIV prevalence in the above population group (9, 52).

2.3. The Role of Retention and Follow-up in HIV Response

The considerable increase in access to antiretroviral drugs worldwide previously mentioned has been a success story in the fight against HIV/AIDS. However, this achievement has led to

other needs and challenges in line with retention and follow up in care of all those put on treatment. Early patient losses are increasingly common especially in resource-limited countries, especially if the scaled-up programmes are accompanied with a necessary payments for all or some HIV treatment related services and serious drop in immune-potency at diagnosis (53). Some of the possible reasons to the above lost to follow up are linked to availability, accessibility and affordability of treatment and/or treatment associated health services, and these factors differ from one country/sub region to another (53). The research world has largely acknowledged the fact that an adherence rate of 90% and above is required for an individual to sufficiently suppress virus thus preventing any risk of mutation and subsequent advent of viral strains in that individual resistant to the antiretroviral drug initially used (54). On the other hand this means that poor adherence to treatment will lead to treatment failure, development of more resistant strains of the virus as well as increased costs (55, 56). This situation even worsens in those contexts where the measurement of retention in care is a real challenge, particularly in high burden countries with generalized epidemics (56). For health amelioration and viral load to be suppressed (leading thus to reduced transmissibility of the virus), adherence has to be ensured. Notwithstanding, just one-third of HIV patients vividly follow their prescription (57, 58). In Cameroon, studies have shown that HIV treatment adherence vary depending on the tool, time, place and population of research. Fonsah et al in 2017 using the "*adult AIDS Clinical Trial Group (ACTG) adherence questionnaire*" showed adherence levels to vary from 76.7% to 90.8% in men and women with association between high or detectable viral loads and lower relative adherence in the context of Cameroon (59). Another study by Roux et al showed 73% adherence in the first month which decreased to 61% in 12 months (60). Atanga et al in 2017 under the option B+ and using a composite score noted a highly adherent rate of 59.0% while observing a lost to follow up rate of 44.6% with main reasons being denial of status, stigma, religious reasons and difficulties linked to transport cost for drug refills (61).

As shown on Figure 3, antiretroviral treatment adherence is on the other hand influenced by multiple number of factors linked to regimen, medical support, experience with HIV, caregiver relationship and other factors of people living with HIV/AIDS (62).

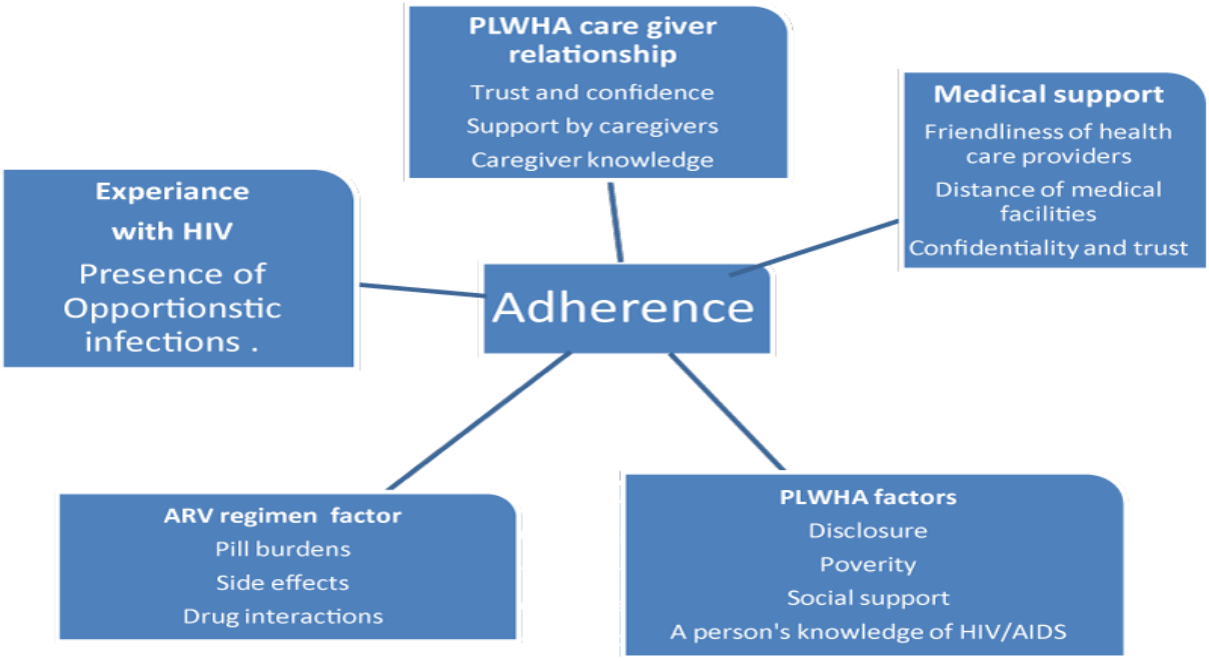


Figure 3: Conceptual Framework for the Assessment of Treatment Adherence

Source: Adopted from SAfAIDS, WHO and modified by Zegeye et al., 2015 (62)

This programmatic gap in retention can potentially facilitate viral strains resistant to drugs, transmitted to other individuals and thus reducing their possible treatment options (57). A study implemented by Billong et al in 2016 showed a retention rate of 60.4% after 12 months of ART in Cameroon; with no treatment center having an excellent adherence rate (>85%) and with only 6 sites of the 56 systematically sampled sites having an acceptable adherence rate (between 75%-85%) (63). Another study by Fokam et al in 2020 went further to show that antiretroviral treatment adherence and viral load coverage among adolescents were better in the urban settings as compared to the rural setting (64).

In addition to minimising the number of patients lost to follow up, there is an absolute need to vulgarised the monitoring of the reponse to antiretroviral treatment in the population in general and in children in particular. This can be done using the clinical monitoring, immunologic monitoring or virologic monitoring methods. Combined clinical and immunological monitoring is rather focusing on risk identification related to morbidity and mortality endpoints in resource-limited settings, whereas the use of virologic monitoring is the preferred approach to detect cases of early treatment failure or drug resistance development (65). Many low-income countries use treatment adherence monitoring methods like pharmacy refill records to monitor patients which alone is not very effective in ensuring viral suppression in patients (54). In Cameroon virologic monitoring is rarely used especially in the

rural settings of the country. This is linked to cost as well as the fact that the viral load testing is done only in reference laboratories found in the major cities of the respective regions. Some studies have been implemented to identify viral failure/drug resistance, which are mostly done in these same big cities. A study by Nlend et al in 2016 showed about 20% viral failure in children on first line ART (20). Another study by Boullé et al within the same year in the a peri urban zone close to the city of Yaounde showed unsuppressed viral loads and drug resistance rates of 23.6% and 18.2% repectively (11). On the other hand immunologic monitoring, despite its availability in most health facilities having a treatmment center, its usage is very scarce especially in the same rural zones above. This could be due to insufficience resources and trained personnel as well as problem of affordability and the non applicability by clinicians; this usually linked to the affordability setback. A study carried out by Abongwa et al in a peri urban treatment center in the North West Region of Cameroon showed its effectiveness in improving the health of children under ART though this one study is not enough to draw any generalised conclusion in that perspective in the nation (66).

2.4. COVID-19 and the Differentiated Service Delivery Model in HIV Response

The very first case of COVID-19 was confirmed as of December 2019 and from that moment has indiscriminately spread all over the globe as well as has left behind negative consequences such as unemployment, food insecurity, wider health inequality amongst others (67). Persons diagnosed with HIV are more vulnerable to this infection given their elevated risk to acquiring it due to their compromised immune systems, especially in elderly adults living with HIV. There is social stigma linked to both infections as well as an increase in the psychosocial burden coming from stress and isolation (67, 68). Despite the evolving epidemiological context where some countries were experiencing a decrease in HIV testing and positivity as they move closer towards the first 95 target, surveys from several countries have shown COVID-19 to have significantly disrupted HIV testing, HIV case finding and linkage to treatment (69, 70). These disruptions varied between the continents where HIV testing dropped by a range from 26.19% to 44.62% in Europe and Latin America and the Caribbean respectively likewise were accompanied by increase in case finding by a range from 2.2% in Africa to 43.95% in Europe (70). On the other hand, new enrolments in care dropped for countries in Africa, Asia and Latin America with rate of drop ranging from 32.05% to 56.26%, which was opposite to the increase in enrolments rather observed in European countries (70). In an attempt to curb the effect of COVID-19 on HIV response,

various context-specific resilient strategies were implemented. These resilient strategies included; online mobilisation, the scale up and promotion of the use of HIV self-testing, focused and/or index case testing, extended working hours in clinics (after-hour initiations), multi-months dispensation of antiretroviral drugs, community drug dispensation, virtual counselling and follow-up calls as well as community sample collection amongst others (69, 70).

Through the implementation of the various context-specific strategies above to reduce the effect that the COVID-19 pandemic had on HIV management, the attention received by the differentiated service delivery model only got strenthened. The World Health Organization through its 2021 consolidated guidelines promotes the above differentiated model of delivering HIV/AIDS related services which is applicable to prevention, testing, linkage to care, ART initiation amongst other aspects of HIV diagnosis and management (17, 69). The model recognizes the persons diagnosed with HIV have diversed needs and is based on four building blocks which seek to answer questions on what, who, where and when while taking into consideration specific populations and contextual settings (Figure 4).

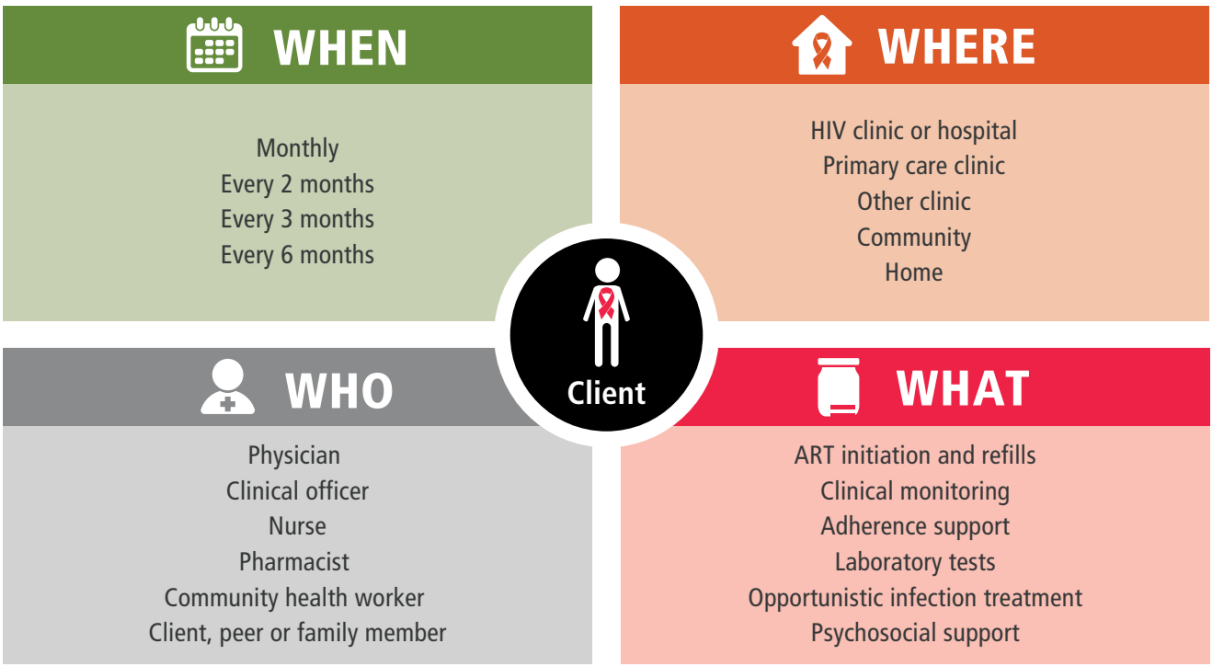


Figure 4: The core elements of the differentiated model in HIV/AIDS service delivery

Source: WHO consolidated guidelines, 2021 (17)

2.5. Depression, Screening, and Diagnosis

As defined by the World Health Organization "*depression is a common mental disorder, involving persistent sadness or loss of interest or pleasure accompanied by several of the following symptoms: disturbed sleep or appetite, feelings of guilt or low self-worth, feelings of tiredness, poor concentration, difficulties making decisions, agitation or physical restlessness, talking or moving more slowly than normal, hopelessness, and suicidal thoughts or acts*" (71). The health condition despite being one of the most common mental disorders, usually go undiagnosed and underreported in Sub Saharan African (72). The situation in Cameroon is not that different with low attention given to mental health in general and depression management in particular. However, few studies have shown alarming levels of depression in the general population and even significantly higher in persons living with HIV (PLWHIV) with range from 20-63% (73-76).

The tools used for screening and/or diagnosis of depression have been subject to a lot of debate over the years. Despite so, all are used in an attempt to identify and/or quantify severity of depressive symptoms for plausible depression diagnosis and a good number of these tools are self-reported. In a literature review conducted by Williams et al. (2002), it was observed across a total of 16 tools for depression case finding that sensitivity varied from 50%-97% and specificity from 51%-98% though these differences were not statistically significant (77). The choice of which tool to use depends on its availability, context (ie availability for in-depth interviews by mental health clinicians or the need to be short and straight forward by busy physicians or other health staff), ease with which it can be administered and of course the acceptable sensitivity by the user (78). Here below are some of the commonly used tools for depression screening and/or diagnosis as well as monitoring:

2.5.1. The Hospital Anxiety and Depression Scale (HADS): The tool is a combined auto-rating scale used to assess both the anxiety and depression levels of individuals. For each of the mental condition being assessed, the possible range of scores go from 0-21 (79). Using meta-analysis, Wu et al. (2021) showed sensitivity and specificity of 82% to screen major depression when the cut-off value of 7 or higher was used (80). Despite being widely investigated and validated for depression screening, the HADS is complex in its use by clinicians (78).

2.5.2. The Primary Care Evaluation of Mental Disorders (PRIME-MD): This tool can be used for depression diagnosis and is presented in two complementary forms as well as

administered consequentially. At first, the PRIME-MD Patient Questionnaire (PQ) which is a self-administered questionnaire consisting of 26 questions (answered either by “yes” or “no”) seeking to identify any depression symptom during the past month (78, 81). This initial screen can be further summarized by two of the questions seeking to enquire on an individual’s feelings as well as interests in routine activities. Upon screening signs of a potential depression, the individual can then undergo the PRIME-MD Clinician Evaluation Guide (CEG) which is a 5 modules interview form that permits the clinician to reach a diagnosis (81). This tool has been shown to display a good diagnostic accuracy but lacking in adequate classification of sub-thresholds thus won’t be quite reliable in following depression management outcome (82).

2.5.3. The Patient Health Questionnaire (PHQ): This tool was developed as a streamlined version of the self-report PRIME-MD which covered five most common mental issues in primary care (78). It has numerous versions, of which one was summarized to reduce the time of administration in a version called PHQ-9. Kreonke et al. were the first to validate this tool back in 2001 in the USA (36, 83), which was later validated in South Africa (84) and since then has been very much used in Sub Saharan Africa for depression screening (36). This PHQ-9 constitutes of a series of nine questions with individual and overall rating scores from 0-3 and from 0-27 respectively seeking to identify the severity of depression symptoms within a period of two weeks prior to the visits (36). The above severity score can thus be used to follow outcome (78). However, the PHQ9-questionnaire is limited in the diagnosis of dysthymia (36, 85).

2.5.4. The Hamilton Depression Rating Scale (HAM-D): This is the very first validated tool and also has many different clinician-rated and self-reported versions and widely used in clinical trials to evaluate response to treatment (78). The HAM-D contains in its original version 21-items graded on a 5 point scale each, the first 17 of which give the overall score while the remainder items used to further qualify it (86, 87). This is quite performant in depression diagnosis and most especially for monitoring response to treatment even after all these years. However, the lengthy time to administer it and the fact that there is no unique version, makes its applicability in all clinical situations somewhat difficult (86).

2.5.5. The Beck Depression Inventory (BDI): This is the second oldest validated tool and still one of the most widely used self-rating scale for depression diagnosis and treatment response monitoring. It is made up of 21-items graded on a 3 point scale each and consist of other versions notably the BDI-II with a higher cutoff point and the BDI-PC; a 7-item scale

for primary care with cutoff of 4 points (87). Despite its high performance and being the preferred tool by many clinicians, it is copy right protected and has poor discriminant validity against anxiety (78).

All in all, depression manifest itself in a set of symptoms that range from disturbed sleep and fatigue all the way to suicidal thoughts, which considerably affects the daily functioning of a person. Notwithstanding, it is of utmost importance to differentiate dysthymia and major depression and bipolar disorder which is characterized by elevation in mood and/or irritability, impulsive or reckless behaviors, as well as increased energy/activity and decreased need for sleep and potentially mania (88). The tool that was used for depression screening in this study is the PHQ-9 questionnaire (interpretation detailed under study assessments section below). This choice of screening tool was based on its simplicity in use thus could be administered by non-experts (in line with task-shifting) likewise severity score quite useful for outcome monitoring with respect to depression management done in this study.

2.6. Depression Management Interventions

In general, depression can be managed using either psychosocial interventions which seek to improve on the behavioral characteristics of an individual or using pharmacological interventions. Here below are some of the commonly used interventions for depression management:

2.6.1. Psychoeducation: This is an intervention which entails the transfer of information and knowledge on signs and symptoms, as well as treatment of an illness (in this case depression) while including motivational messages to help the affected individual to develop better coping strategies with respect to the illness (36, 89). It can be done for any individual having depression (as was the case in this study) but since it is mostly for awareness and to prepare mindset vis-à-vis depression, it is particularly helpful for those with mild symptoms of depressions. Here the individual discusses on key depression points, symptoms, perceptions and misconceptions, including regards on depression by their family and friends. The need to go for medical care is assessed as well as the choice of various depression management options that are possible (36, 88). A psychoeducation session can also serve as opportunity to put elements in place to pave the way for the implementation of a much more appropriate intervention.

2.6.2. Interpersonal Psychotherapy (IPT): This intervention is an attachment-focused psychotherapy for depression that seeks to coach individual in devising and implementing

strategies to address problems or issues that potentially linked to the onset of the depressive symptoms. It is a highly structured intervention intended to be completed within 12-16 weeks. This form of therapy was first published as a guide by Weisman et al. in 2000 for individual session therapies that can be conducted both by specialist and non-specialist staff (90). The WHO later modified the intervention in a guide published in 2016 for use in 8-session group therapies as possible first line treatment for depression (71). The IPT is implemented in three phases which seek to identify the problem area(s) causing the depression, determine the best possible strategies to handle the above problems which are adaptable while identifying and adopting (in routine life) the ones that had positive impact on the depression symptoms (36, 90). IPT intervention is one of the two used for depression management in this study and detail in its chronology of interpretation is provided under schedule of events section below. The IPT therapist plays a non-judgmental role where s/he communicates warmth and unconditional positive regards to the circumstances of the patient. The four main interpersonal problem areas explored by IPT (which could potentially be the cause of the depression symptoms, and which ought to be identified during initial phase of IPT) are:

- Role transition which is any significant change an individual's life for example change in marital or work status of an individual, diagnosis of medical illness etc.

- Grief usually happens when an individual loses a family member or friend who s/he considered to be dear thus not being able to deal with the mourning.

- Disputes with a close someone, notably spouse, another family member, coworker, or close friends.

- Interpersonal deficits when an individual seeks to be self-sufficient thus unable to properly interact with others

An example would be the case where an individual faces a problem related to role transition because of HIV infection diagnosis coupled with grief due to death of a loved one somewhat linked to the HIV infection.

2.6.3. Cognitive Behavioral Therapy (CBT): This therapy is conducted with the aim to help an individual identify and handle those behaviors that normally prevent them from self-correcting faulty beliefs, thus leading to stress management and improved mental health (91). It is conducted on the basis that an individual's way of behaving can be associated to his/her perception of events outlined at three levels; core beliefs, dysfunctional assumptions and

negative automatic thoughts (92). Core beliefs here consist of negative views about oneself (e.g. I'm worthless), about the world (e.g. everybody hates me because I'm worthless) and about the future (e.g. I'll never be good at anything as everybody hates me). These core beliefs usually lead to dysfunctional assumptions (e.g. it's better not to try than risk failing) and negative automatic thoughts most often activated involuntarily in certain circumstances (92). The CBT is considered by numerous researchers as gold standard form of psychotherapy since it's the first tested with stringent criteria of the evidence-based framework of the health field (93). Despite not showing superiority to CBT, other forms of psychotherapy like IPT above have shown comparatively to be equally effective as the previous (93, 94).

2.6.4. Pharmacological intervention (pharmacotherapy): This is a widely adopted intervention for depression management as it entails treating the depression with drugs as any other health problem. However, pharmacotherapy is most appropriate in situation where depressive symptoms are severe or are moderate but accompanied suicidal thoughts. These antidepressants act on the three neurotransmitters involved in mood regulation notably dopamine, norepinephrine and serotonin. Despite not being addictive, it is important to consider individual's age, drug side-effect profile as well as concurrent medical conditions (88). Despite the existence of numerous antidepressants for the major 5 classes, two drugs have been endorsed by WHO which are amitriptyline and fluoxetine (Table 1).

Table 1: Information on WHO endorsed antidepressants

(***Source:*** Mental health intervention guide by WHO, 2016) (88)

MEDICATION	DOSING	SIDE EFFECTS	CONTRAINDICATIONS / CAUTIONS
AMITRIPTYLINE (a tricyclic antidepressant (TCA))	**Start** 25 mg at bedtime. **Increase** by 25-50 mg per week to 100-150 mg daily (maximum 300 mg). Note: Minimum effective dose in adults is 75 mg. Sedation may be seen at lower doses. **Elderly/Medically Ill:** Start 25 mg at bedtime to 50-75 mg daily (maximum 100 mg). **Children/Adolescents:** Do not use.	**Common:** Sedation, orthostatic hypotension **(risk of fall)**, blurred vision, difficulty urinating, nausea, weight gain, sexual dysfunction. **Serious:** ECG changes (e.g. QTc prolongation), **cardiac arrhythmia, increased risk of seizure.**	Avoid in persons with **cardiac disease**, history of seizure, hyperthyroidism, urinary retention, or narrow angle-closure glaucoma, and bipolar disorder (can trigger mania in people with untreated bipolar disorder). **Overdose can lead to seizures, cardiac arrhythmias, hypotension, coma, or death.** Levels of amitriptyline may be increased by anti-malarials including quinine.
FLUOXETINE (a selective serotonin reuptake inhibitor (SSRI))	**Start** 10 mg daily for one week then 20 mg daily. If no response in 6 weeks, increase to 40 mg (maximum 80 mg). **Elderly/medically ill:** preferred choice. **Start** 10 mg daily, then increase to 20 mg (maximum 40 mg). **Adolescents** **Start** 10 mg daily. Increase to 20 mg daily if no response in 6 weeks (maximum 40 mg).	**Common:** Sedation, insomnia, headache, dizziness, gastrointestinal disturbances, changes in appetite, and sexual dysfunction. **Serious: bleeding abnormalities** in those who use aspirin or other non-steroidal anti-inflammatory drugs, low sodium levels.	**Caution in persons with history of seizure.** **Drug-Drug Interactions:** Avoid combination with **warfarin** (may increase bleeding risk). May increase levels of TCAs, antipsychotics, and beta-blockers. Caution in combination with tamoxifen, codeine, and tramadol (reduces the effect of these drugs).

Bipolar disorder should always be treated with antidepressants coupled with mood stabilizers such as carbamazepine or valproate as the former alone can lead to mania (88).

2.7. Integration of Depression in HIV Response

Studies have shown the relevance of mental health integration in HIV care in developing countries especially with respect to depression management (95). In addition to improving patients social and psychological wellbeing, it also improves their adherence to the lifetime antiretroviral treatment and subsequently their treatment outcome (95). Pharmacological management of depression could however have interactions with already taken antiretroviral drugs or have other side effects not supported by patients reason why it is proposed that a non-pharmacological approach should be given more attention (96). Many psychosocial interventions like the congitive behavioral therapy (CBT) and interpersonal therapy (individual or group IPT) mentioned above have been proposed for mild to moderate forms of depression likewise pharmacotherapy recommended especially for severe cases (97). Both psychotherapy and pharmacotherapy have shown to work in developing contexts in improving adherence to treatment underligning thus the important role in detecting and treating depression amongst people living with HIV. Despite so, mental health in Africa has not really been given the required attention especially when it come to its integration with HIV management (95, 98).

3. Research Hypotheses and Objectives

3.1. Study Hypotheses

This study was conducted with the aim to improve antiretroviral treatment outcome in study participants based on the following sequential hypotheses:

- The intervention package for depression will significantly improve the psychosocial wellbeing of the participants with respect to their randomization groups
- An improvement in the psychosocial wellbeing above will in tend significantly improve adherence to antiretroviral treatment
- The resulting improvement in treatment adherence will have a significant impact on their viral suppression status

3.2. Study Objectives

The primary study objective was to assess the impact of routine depression screening and treatment on antiretroviral treatment adherence outcome at the intermediate level and viral outcome at the final level between intervention and control study arms.

The secondary objectives were:

- To assess at baseline HIV treatment related factors associated to treatment adherence, including access to treatment facilities, drug provision stock-outs, customer satisfaction, patient's knowledge and experience with HIV, patient/caregiver relationship

- To assess at baseline patient related factors associated to treatment adherence in the study population such as depression, psychosocial wellbeing, ARV regimen, status disclosure, stigmatization and other individual or household factors of participants

- To measure and compare the psychosocial wellbeing between intervention and control arms with focus on depression

- To measure and compare treatment adherence rates between intervention and control study arms consisting of respect of drug refill appointments, pill identification, self-reported adherence, pill count and visual analogue scale

4. Materials and Methods

4.1. The Study Design

The study was conducted as a cluster-randomized, longitudinal intervention cohort study where participants were divided in two groups as thus:

4.1.1. Control arm: Participants in the control arm were put on the standard-of care (SoC) in accordance with national HIV guideline (10). This SoC comprises drug provision on monthly basis, medical consultations bi-annually as well as adherence counselling and treatment monitoring (CD4 count and viral load tests when appropriate). For treatment outcome evaluation purposes, these participants received study specific depression screening at enrolment, midway in the study and at the end of their follow up time in the study. In case of

identified depressive symptoms, controls were referred to their caregiver (usually psychosocial worker) for management in line with their psychosocial support.

4.1.2. Intervention arm: Here participants received all the above services given to the control arm though, as opposed to controls, they had to do follow up screening assessments for depression every three months and structured intervention for depression management, focusing mostly on psychoeducation and IPT. Psychoeducation only was used for participants presenting minimal symptoms of depression (5-9) while psychoeducation was given alongside IPT for participants whose symptoms were moderate (10-14), or moderately severe (15-19). Participant with severe symptoms (≥ 20) received the above indicated psychoeducation and IPT combination, and in addition an antidepressant drug (Amitriptyline) which was prescribed by a medical doctor working in the hospital. Furthermore, it was planned that participants in this study arm could facultatively receive case-to-case linkage for drug refills or multiple-months drug dispensation, but this was dependent of participants and study sites.

4.2. Study Sites

This study was implemented at two sites in Cameroon, the Abong Mbang District Hospitals in the East region and the Santa District Hospitals in the Northwest region of the country. Research sites were strategically chosen from the above regions representing the English and French speaking contexts of the country, while at the same time being amongst the highest in terms of HIV prevalence; East and Northwest regions stand 2nd and 4th with 5.9% and 5.1% respectively according to the above CAMPHIA survey conducted in 2017 (39).

4.2.1 Abong Mbang District Hospital (ADH): This hospital is found in the East region of the country serving an estimated population of 69,712 inhabitants. It is the referral health facility of the Higher Nyong Division which is semi urban and provides primary health care services including HIV/AIDS management. By the start of the study about 2,462 adult PLHIV and 79 children were on HIV treatment in ADH.

4.2.2. Santa District Hospital (SDH): This hospital is found in Mezam Division of the North-West region and serves an estimated population of 49,913 inhabitants. It has 4 medical doctors, 26 nurses and 2 laboratory technicians. By the time this study started, about 646 adult and 24 children were on HIV treatment at SDH. The hospital covers inhabitants of a savannah zone, with relatively larger rural settling communities, with support groups (relative fewer stigmas) and relative better access to service and infrastructure. It should also be noted that

this health district is one of those presently facing a sociopolitical crisis though no proof of its influence on HIV care continuum.

4.3. Study Period and Duration

This study was conducted between August 2019 and July 2021. The recruitment period lasted for 15 months (up to October 2020) then follow up for the participants continued until July 2021. Each participant was planned to be followed up for 12 months post-enrolment in the study.

4.4. Study Population and Selection Criteria

The study population here were adolescents and adults who had been enrolled and started antiretroviral treatment in the treatment centers of the above district hospitals for 6-9 months prior the start of the study. The following selection criteria were used:

4.4.1. Inclusion criteria:

1. Voluntary informed consent

2. Age ≥13 years, aware of their serological status while assenting to participate and upon co-signed consent from parent or guardian

3. Documented HIV infection

4. Patients attending their first follow-up visit after ART initiation (usually after 6-9 months)

5. Willingness to consent to active tracing including home tracing as well as comply with protocol of research, which will be well explained to him/her

4.4.2. Exclusion criteria:

1. ART naïve patients

2. Prisoners

3. Pregnant women

4. Unlikely to comply with protocol as judged by the principal investigator or his designate

4.5. Study Outcomes

4.5.1. Main outcome

- The percentage of participants with unsuppressed viral load more than or equal 1000 copies/mL at 12 months between arms

4.5.2. Secondary outcomes

- Change in adherence scores measured using self-reporting, pill count, drug refill, pill identification and visual analogue aspects between arms
- Change in depression scores measured using PHQ-9 questionnaire between arms

4.6. Study Sample Size Calculation

The formular used is that which compares proportions between two groups and the sample size was calculated based on the virological suppression proportions between the randomization groups.

$$\mathbf{N = [P_e(1-P_e)+P_c(1-P_c)/\delta^2]\ x\ f(\alpha, \beta)} \text{ ……(36, 99, 100) where}$$

$\mathbf{P_c}$=expected proportion of participants with unsuppressed viral load in control group (this value is the mean viral failure rate from 6 previous and most recent studies conducted by various authors set thus at 17.5%),

$\mathbf{P_e}$=expected proportion of participants with unsuppressed viral load in the intervention group (as we expect this proportion to be half that of the control group it was set at 8.75%),

$\boldsymbol{\delta}$=delta or the difference between both groups that we won't afford to miss (this value was set at 8.75%) and

$\mathbf{f(\alpha, \beta)}$=a constant from a function of α and β (when $\boldsymbol{\alpha}$=5% and $\boldsymbol{\beta}$=20, the constant is 7.9).

Using the above estimates in the calculation, we estimated a needed sample of 232 participants. To ensure that despite dropping out of study, that the baseline sample size would still be big enough for determining independently associated factors of poor treatment compliance and compare study outcomes, the sample was increased by 50%. Therefore, we ought to recruit for each study arm a minimum of 175 participants.

4.7. Patient Recruitment and Randomization

Every patient on ART who was coming to treatment center for their follow up visit at 6-9 months was approached by a research officer and invited to be a study participant. Upon

voluntary informed consent the participant was enrolled and attributed to an identification code which was used in subsequent visits for identification. Recruited participants from the same catchment area were considered to belong to the same cluster. An exhaustive list of mini clusters covered by each treatment center was made prior to the start of the study. From the above lists for each site, clusters were thus randomly attributed either to the intervention or control study arm. Given that the intervention package in majority is behavioral, it is important to avoid mixing that is why clusters were used. These mini clusters thus prevented bias due to influence from one participant receiving intervention on another participant living close to the former who is a control (36). Furthermore, to prevent the assignment of participants in the study arms by convenience, randomization of the above clusters was done before the start of recruitment to ensure that participants from the same area were automatically assigned to a predefined study arm. Each randomization group was assigned to 6 clusters which were equally distributed between the study sites. Even though socioeconomic and cultural characteristics of health districts harboring the treatment center are comparably different, their respective clusters have similarities thus regrouping for each site into intervention and control clusters made an overall similarity between both arms (intra site homogeneity in their inter site diversity thus bringing equal level of diversity within each randomized study arm).

4.8. Training of Public Health Care Worker

Two research officers (also serving as therapists) and a data manager were recruited and trained for this study. The research officers working one per site were nurse aids with experience in primary health care and HIV management; were recruited from the readily available nurse volunteers in the research sites as recommended by the coordinator of respective treatment sites and approved through interview by principal investigator. The data manager was someone with background knowledge on data management as well as research monitoring and evaluation with experience on HIV research an added advantage.

The recruited personnel were trained during a 5-day workshop organized by the principal investigator during which they underwent training on baseline HIV management in accordance to the national guideline, HIV research, ethics and good clinical practice and introduction to research proposal. They were also trained on data collection skills, self-monitoring and interpersonal communication skills as well as were provided detailed information on the intervention aspects through case practice. The staff were trained on how to fill the various study questionnaires and perform the interviews so as to ensure quality data.

By the end of the workshop, personnel involved had acquired knowledge on the various procedures needed for the full implementation of study in terms of data collection, intervention as well as collaboration with other hospital staff involved in the project particularly the treatment center coordinator and hospital director. Finally, they were presented their individual job description and responsibilities vis-à-vis the research implementation,

Each research officer (acting as therapist) went to the respective site with knowledge on how to conduct interpersonal psychotherapy following a guide by Weissman et al. made available as of the 2000 (90). The guide has simplified concepts practicable by non-experts of mental health which is exactly what is needed in this study as we try to set up a package that can be implemented by peripheral healthcare workers (nurses, nursing aids and psychosocial agents) with a direct impact on the community. They also went with study protocol, individual job description as well as standard operating procedures (SOPs) pulled from the above guide complemented by a mental health intervention guide by WHO (88) for future referral during activities. Of course, they were continuously supervised by the principal investigator all along the implementation period of the project using both active and passive forms of supervision.

4.9. Study Procedure and Schedule of Events

The study consists of the following periods for each participant:

i. Recruitment/inclusion visit: During this visit all the participants were recruited into the study after the participant or parent/guardian provided consent (plus assent given by the participant in the second scenario). Sociodemographic characteristics, medical history, and habits as well as their treatment linked information were collected. Participants also underwent a baseline adherence assessment using the multi method adherence measurement tool as well as depression screening using the PHQ-9 questionnaire respectively. During this visit, the research officer (serving here as therapist) identified which study arm each participant belonged to (following predefined clusters) and for the intervention study arm this visit served as the first session. Here the therapist decided on whether the participant would receive psychoeducation alone or coupled with IPT based on the depression score. It was thus the session where psychoeducation was conducted for participants with mild symptoms of depression or as prelude of IPT for participants with other more severe symptoms. We further provided information on the key problem areas that can cause

depression as well as on HIV management and the association of depression with their care. Here one or two types of interpersonal problems most related to the patient's current depression were identified from information on recent changes in the patient's life circumstances, mood, and social functioning etc. It should be noted that all psychosocial follow up visits were conducted only for participants in the intervention study arm and the control arm came back for the midpoint and endpoint visits for compliance and viral load measurements.

ii. Follow-up visits: The number of follow up visits done for the intervention arm were dependent on the assessed psychosocial health situation of the patient in question. In case of identified depression, a minimum of 5 visits was planned to include progress assessments done on a quarterly basis. During these sessions, the research officer would make the patient see the link between his or her daily problems and the occurrence of depressive symptoms and likewise encourage them in the search for solution to those problems rather than fixating on the contraction of HIV (36). Together, the participant and the research officer with participant identified some sources of stress in the patients' life for possible solutions. Patients' perceptions were challenged by reframing their illness as an opportunity to assess their present relationships and make changes to correct problems when possible. The interpersonal psychotherapy also focused on factors that hinder the patients' ability to deal with anticipatory mourning of their own death, survivor guilt over outliving others, fear of rejection by others, helping HIV patients find ways to reconcile differences, obtain alternative sources of support, and end unrewarding relationships. Finally, patients were supported in anticipating how to best deal with physicians, sexual partners, bosses, and others. In addition to the above psychosocial aspect of the intervention, case-to-case linkage or multiple months dispensations were used in the same intervention arm. In the choice of case-to-case linkage, patients living in the close neighbourhoods were grouped in 3-4 individuals, assisting each other in drug refill process. These mainly included harmonized drug refills performed by on patients for the linage group, thus reducing yearly travelling to treatment center to about 3 times for each patient (except in case of psychotherapy). In the choice of multiple months dispensation, the participants were given drug refills to cover multiple months so that they would not have to come back for drug refills on monthly basis. To follow up especially in case of patient just having an improvement in depression condition or was not able to honour interpersonal psychotherapy (IPT) appointment, the research

officer would call patient. Both research officer and patient agreed forehand on which method was to be used. It is worth noting here that only the IPT was planned for SDH since the site had already adopted as routine the multiple months dispensation approach. In ADH, both the interpersonal psychotherapy and case-to-case linkage or multiple months dispensation (MMD) were planned but the later faced some constraints linked to concerns on potential drug stockout at health facility if MMD was adopted for all study intervention cases likewise recruited participants rejected case-case linkage. However, in the advent of COVID-19 a few months later, MMD became adopted as a routine approach thus making intervention completely annulled leaving interpersonal psychotherapy as the sole intervention in both study sites.

iii. End of study visit: After every 3 months, the participant in the intervention arm would meet with the research officer for depression assessments and this was repeated until the end of study visit after 12months follow up in the study. On the other hand, the participants in the control arm only met the research officer twice; at 6months of after recruitment for their mid-study adherence and depression assessments then after 12months for the end of study adherence and depression assessments. At the end of study visit, all recruited participants (intervention and control arms), in addition to the above endpoint assessments, those who showed up had their blood samples collected for viral loads measurements.

Table 2: Chronology of study activities

Time-point	M0	M1	M2	M3	M6	M9	M12
Clinical assessments							
Study information & informed consent for all participants	*						
Demographics, HIV-status, medical and ART history, other baseline information for both arms	*						
ART adherence assessment for both arms	*				*		*
Depression assessment for both arms	*				*		*
Follow-up depression assessment for intervention arm				*		*	
Psychoeducation for intervention arm	*						
IPT alone (or with pharmacotherapy) for intervention arm		*	*	*	*	*	
Laboratory test results (where available)							
Viral load (VL) for both arms	*				*		*
CD4 count test	*				*		*
Haemoglobin level	*				*		*
White Blood Cells (WBC) count test	*				*		*
Biochemistry (ASAT, ALAT & Creat)	*				*		*

** follow-up visits*

4.10. Study Assessments

i. ***Depression assessment:*** Here the standardized PHQ-9 was used as it is usable in various contexts for depression assessment with aim early detection as well as can be used to monitor depression state when receiving a form of therapy (83, 101-103). It comprises of 9 questions summing up to 27 scoring points which will be used to classify potentially depressed participants in 4 different categories of severity as follows:

- Minimal symptoms or mild depression for participants with scores from 5-9 who were to receive psychoeducation and psychosocial support.
- Moderate symptoms of depression for participants with scores from 10-14 who were to receive psychoeducation and psychosocial support. Also, interpersonal therapy (IPT) for depression was to be started for participant if situation seemed to worsen during the next follow up visit.

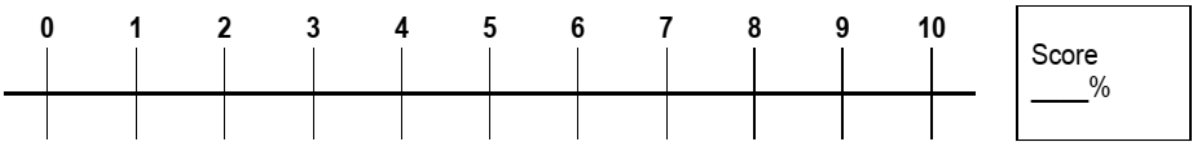
- Moderately severe symptoms of depression for participants with scores from 15-19 who were to receive psychoeducation, psychosocial support and IPT for depression. If assessed that situation is only worsening during subsequent follow up visit in spite of IPT, the participants were also to receive pharmacotherapy (amitriptyline as prescribe by a medical doctor).

- Severe symptoms of depression for participants with scores from 20 and above who were to receive psychoeducation, psychosocial support, IPT for depression and pharmacotherapy. The drugs used for the latter were to be prescribed by available clinician in site. Two anti-depressive drugs are endorsed by the WHO (fluoxetine and amitriptyline). If the situation did not improve during subsequent follow up visits, referral to a specialist or clinician more vested in the specialty was to be considered.

ii. ***Adherence assessment:*** This was done at baseline, after 6 months (midpoint) and then after 12 months (endpoint) of follow-up in the study using the multi-method adherence measurement tool developed, tested and used in South Africa (104). The initial tool constitutes of a pill identification test (PIT), 4 self-reported adherence questions, visual analogue scale (VAS) of adherence within the past five days and pill counts from the last drug refill appointment (36). Atanga et al. first used the above tool in Cameroon, adapting it such that the PIT was replaced by drug refill appointments extracted from treatment center records (23). The scores from these 5 components were interpreted as shown below and the combined scores were categorized as low, moderate and high adherence and then the overall adherence rate calculated from them:

- Self-reported adherence (SRA) constituted of four (4) Boolean questions and participant was classified as highly adherent if his/her answers to all questions were “No”, as moderately adherent if atleast one answer was “Yes” and as poorly adherent if two or more answers were “Yes”.

- Visual Analogue scale (VAS) ranged from 0-10 from which participant would choose to qualify their own adherent. The chosen point was then scaled up into percentages and interpreted. Here 95% and more was categorized as being highly adherent, 75-94% categorized as being moderately adherent and <75% categorized as being poorly adherent.



- Pill identification test (PIT) where participant's knowledge on drug, dose, time as well as other treatment instructions was assessed. Participant was categorized as being highly adherent if he/she identified drug as well as knew dose, time and drug instructions, categorized as being moderately adherent if only dose and time are known and as being poorly adherent if dose only or confused about it.

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken			Knows any additional instruction
			Morning (hour)	Evening (hour)	Judged correct (Y/N)	

- Pill count where investigator from counted number of dispensed and remainder pills would calculate (in relation to expected consumption) the participant's adherence rate expressed as a percentage. Here 95% and more was categorized as being highly adherent, 75-94% was categorized as being moderately adherent and <75% was categorized as being poorly adherent.

Calculated percentage adherence

$$\%\ \text{Adherence} = \frac{\text{Dispensed} - \text{Returned}}{\text{Expected to be taken}} \times 100 = \frac{\square - \square}{\square} \times 100 = \square\%$$

- Drug refill where the drug refill appointments respected by participant within the past 6 months of treatment were counted. Participants were classified as being highly adherent if all 6 drug refill appointments were respected, classified as being moderately adherent if one appointment was missed or classified as being poorly adherent if 2 or more appointments were missed.

- Overall adherence rate: For each of the above 5 components the highly adherent was attributed a score of 3, moderately adherent a score of 2 and poorly adherent a score of 1. For each participant, the total score was added up giving a total score of 15 considered as highly adherent in overall, a score from 10-14 considered as moderately adherent in overall and a score less than 10 (not less than 5 as its total scale was between 5-15) considered as poorly adherent (Table 3).

Table 3: HIV treatment adherence assessment guide
(***Source:*** Ndenkeh et al., 2022) (36)

Individual and overall adherence grading (scores)			
Drug refill	Had all 6 refills (3)	Missed 1 refill (2)	Missed 2 or more refills (1)
Pill Identification Test	Knows drug, dose and time (3)	Dose and time only (2)	Dose or time only or confused (1)
Self-reported	No to all 4 questions (3)	Yes to 1 question (2)	Yes to 2 or more questions (1)
Visual Analogue Scale	95% and above (3)	75-94% (2)	Less than 75% (1)
Pill count	95% and above (3)	75-94% (2)	Less than 75% (1)
Overall adherence	**Highly adherent (15)**	**Moderately adherent (10-14)**	**Poorly adherent (5-9)**

iii. ***Viral load measurement:*** Viral loads (VL) were measured at the last study visit (month 12) in values of copies per ml as the main comparable outcome in both arms. These viral loads were measured in collaboration with the closest reference laboratory (in this case reference laboratory of the regional hospital of Bamenda for samples from Santa DH and reference laboratory of Bertoua regional hospital for samples from Abong Mbang DH). VL assessments were performed based on routine Ministry of Public Health services as of January 2019, when the user fee elimination schemes for viral load testing all over the national territory were implemented. Notwithstanding, the time to reception of viral load results by these participants was dependent on transportation to the reference laboratories as well as the logistics (equipment maintenance, stock-out of viral load kits etc) of the laboratory receiving samples. For that reason, not all participants whose samples were collected received their results by the end of the study. Viral loads equal or more than 1000 copies per ml were considered as virological treatment failure, while values less than 1000 copies per ml were considered as treatment success. VL below 1000 copies/ml were further stratified

for less than 50 copies per ml (undetectable viral load), and 50-999 copies per ml (suppressed viral load with low replication).

4.11. Data Management and Analysis

This research was implemented by a staff of 3 persons in collaboration with the personnel of treatment centers: two research officers and a data manager. Each site constituted of a research officer who oversaw the smooth implementation of the study with respect to protocol and both research officers reported to the data manager who monitored research as well as oversaw data quality improvement, data entry and archiving. The data manager reported directly to the principal investigator who also reserved the right to part take in all field activities be it data collection entry, supervision etc. The data collection was done on study specific data collection forms and entered into a study tailored data entry spreadsheet in CDC Epi Info v7.2 software then was later extracted as an Excel database. To ensure data integrity and quality, the entered data in the physical forms was done in such a way that any minor change be it correction or upgrade was traceable. This database was then cleaned and validated by cross referencing the Excel database to the de-identified physical forms by the principal investigator. It is worth noting that to ensure data protection and confidentiality only pseudonymized data were used and access to the database was restricted to study staff only all of whom were under confidentiality oath.

The data collected from participants of this study was analyzed using the SPSS v23 for Windows and GraphPad Prism v9 for Windows (GraphPad Software, San Diego, California USA). We used proportions to present baseline characteristics of participants as cross tabulations with respect to the study arms and using the chi-squared test for their comparison. Correlation coefficients were calculated with the Spearman's rank correlation between depression, adherence and viral load as well as between the various individual adherence tools (36). Logistic regression was used to identify factors influencing poor adherence by adjusting for the effect of various potential covariates as well as for potential confounding factors of the association between depression and poor adherence notably study site, reported undesired drug side effects as well as Efavirenz-based regimen at start in contrast to Nevirapine and Dolutegravir-based regimens (36). The same logistic regression was used to identify factors associated to an unsuppressed VL result after 12 months of follow up while adjusting for age group, sex, study site and relationship with care provider (36). Comparisons in depression, adherence and viral suppression were done between study arms in two analysis scenarios, one of which was for all study participants ("intention to treat") while the other scenario was only

for study participant screened to present symptoms of depression thus eligible for intervention ("per protocol"). Depression and adherence score were first compared between study arms in both analysis scenarios above using the two way ANOVA and then regrouped to classes and compared with Chi-squared test with respect to study arm and period of study (36). The proportions of participants with VL equal or more than 1000 copies/mL were compared between study arms with the Chi-squared test for both analysis scenarios (36). All the above statistical tests were done with a cut-off point of significance set at 5%.

5. Results

5.1. Study Participant Flowchart and Intervention Implementation Status

Overall, 370 participants were recruited for this study, 59 from Santa District Hospital and 311 from Abong Mbang District Hospital. Of these participants, 178 (48%) constituted the intervention arm while 192 (52%) were part of the control arm. Within the first 6 months of follow up in the study, 47 and 31 participants were lost to follow up in the intervention and control arms respectively. In addition, 17 participants were lost to follow up in both arms during the last 6 months of follow up (one and six in the intervention and control arms respectively). One participant died in the control arm, and 12 participants (6 each from both arms) saw their participation in the study terminated when study ended at their 9-month follow up visit. In all, 124 and 138 participants reached the endpoint of the study in the intervention and control arms respectively, of whom 84 and 111 received their viral load results in the above arms respectively (Figure 5).

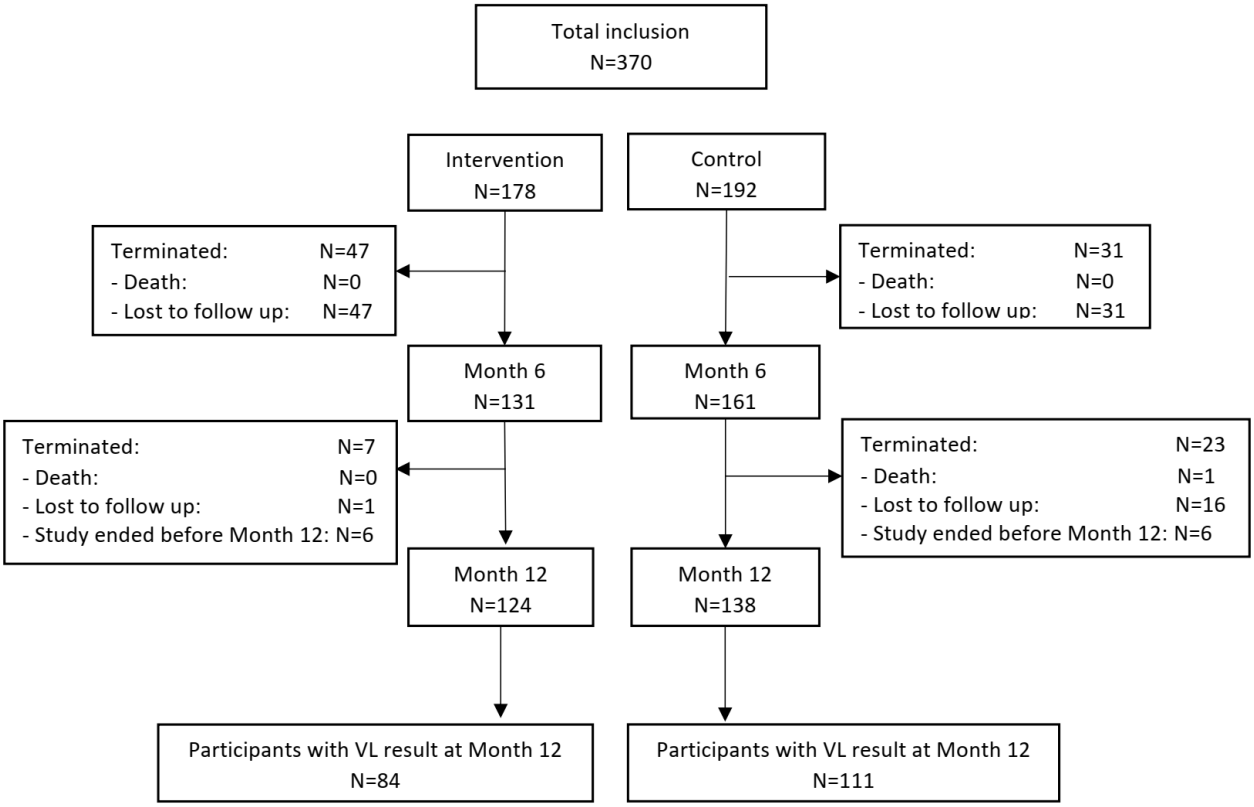


Figure 5: Enrolment and follow up flowchart of study participants

(***Source:*** Ndenkeh et al., 2022) (36)

As detailed in Table 4 below, 87 participants (all from the intervention arm) received psychoeducation while 17 of the participants received IPT. It is worth noting that all the participants who received IPT formed an integral part of the participants that received psychoeducation given that psychoeducation was the introductory mechanism to IPT proper.

Table 4: Recap on implementation of planned package for participants of the interventions arm

Intervention planned	**Site of study**	**Number of participants who received**	**Justification/comment**
Psychoeducation	Both sites	87	Participants of the intervention arm who presented at least mild symptoms of depression at any point within the study
Interpersonal psychotherapy	Both sites	17	All participants in the intervention arm who presented moderate to severe symptoms of depression at any point within the study
Pharmacotherapy	Both sites	0	Only one participant presented severe symptoms of depression but was from the control arm. We drew the attention of participant's caregiver for further action
Multi-months dispensation or case-to-case linkage	ADH (SDH was already doing multi-months dispensation)	0	All participants in ADH rejected case-to-case linkage yet would consider MMD but given that MMD could lead to imminent drug stockout, treatment centre decided not to take any risks. However, seven months later with the advent of COVID-19, the treatment centre adopted multi-months dispensation for a vast majority of its patients after receiving more stock from the government

5.2. Baseline Sociodemographic, HIV Status and Treatment linked as well as Other Psychosocial Characteristics of Participants

With respect to participants' sociodemographic characteristics as shown in Table 5, the median age of study participants was 39 years (IQR: 30-49 years) with the control arm having a slightly higher median age than the intervention arm. Also, 84.1% of study participants were from ADH, 65.9% of study participants were of the female gender, 50.7% were in a union and 83.1% had children. Furthermore, 5.2% had history of substance use and 64.2% had a habit of drinking alcohol.

Table 5: Participants' baseline socio-demographic characteristics (N=370)

(***Partial source:*** Ndenkeh et al., 2022) (36)

Variable	Total*	Randomization group		p
		Intervention, n=178	*Control, n=192*	
	N (column %)	*N (row %)*	*N (row %)*	
Age in years; median (IQR)	*39 (30-49)*	*38 (29-48)*	*40 (32-49)*	*0.057*
Age group				*0.725*
Adolescent (<20yrs)	10 (2.7)	6 (60.0)	4 (40.0)	
Adult (20-50yrs)	289 (78.1)	139 (48.1)	150 (51.9)	
Elderly adult (>50yrs)	71 (19.2)	33 (46.5)	38 (53.5)	
Sex				*0.601*
Female	244 (65.9)	115 (47.1)	129 (52.9)	
Male	126 (34.1)	63 (50.0)	63 (50.0)	
Marital status				*0.122*
Single	135 (36.6)	76 (56.3)	59 (43.7)	
Couple	187 (50.7)	83 (44.4)	104 (55.6)	
Divorced/separated	13 (3.5)	5 (38.5)	8 (61.5)	
Widow(er)	34 (9.2)	14 (41.2)	20 (58.8)	
Have children				*0.11*
No	61 (16.9)	35 (57.4)	26 (42.6)	
Yes	301 (83.1)	139 (46.2)	162 (53.8)	
Education level				*0.003*
Uneducated	16 (4.3)	10 (62.5)	6 (37.5)	
Primary education	180 (48.6)	69 (38.3)	111 (61.7)	
Secondary education	162 (43.8)	93 (57.4)	69 (42.6)	
Higher education	12 (3.2)	6 (50.0)	6 (50.0)	
Alcohol				*0.773*
No	132 (35.8)	65 (49.2)	67 (50.8)	
Yes	237 (64.2)	113 (47.7)	124 (52.3)	
History of substance use				0.42
No	343 (94.8)	166 (48.4)	177 (51.6)	
Yes	19 (5.2)	11 (57.9)	8 (42.1)	
Study site				*0.017*
ADH	311 (84.1)	158 (50.8)	153 (49.2)	
SDH	59 (15.9)	20 (33.9)	39 (66.1)	
Time to reach the treatment center				*<0.001*
Less than 30 minutes	155 (42.0)	131 (84.5)	24 (15.5)	
30 minutes to 2 hours	177 (48.0)	36 (20.3)	141 (79.7)	
More than 2 hours	37 (10.0)	11 (29.7)	26 (70.3)	

p is p-value from chi-squared test for differences between groups or from Mann Whitney test

*Due to missing data, not all totals sum up to 370

It should be noted that 15.5% of the participants in the control arm spent less than 30 minutes to reach the treatment center compared to 84.5% in the intervention arm ($p<0.001$). Furthermore, a significant difference in educational level was observed between study arms

notably with respect to participants who were uneducated and those who had primary level of education (p=0.003).

HIV status characteristics at baseline (Table 6) revealed that more than 90% of study participants started antiretroviral treatment within the same week they got diagnosed which was not different between study arms. Also, more than 80% of study participants were diagnosed at diseases stages I & II and were on Efavirenz based regimen. Only 7.6% of study participants took their antiretroviral drugs twice a day while 51.2% of them said to had experienced any form of undesired drug side effect. It is worth noting that, more 90% of these participants neither had follow up CD4 count nor VL test by the time they were enrolled in the study.

Table 6: Participants' baseline HIV status and treatment linked characteristics (N=370)

Variable	**Total***	**Randomization group** *Intervention, n=178 Control, n=192*		**p**
	N (column %)	***N (row %)***	***N (row %)***	
Started treatment within week one of diagnosis				*0.169*
No	28 (7.8)	10 (35.7)	18 (64.3)	
Yes	333 (92.2)	164 (49.2)	169 (50.8)	
CD4 count test at enrolment				0.468
<350 cells/µl	3 (0.8)	3 (100)	0 (0)	
≥350 cells/µl	7 (1.9)	1 (14.3)	6 (85.7)	
Missing CD4 count	360 (97.3)	174 (48.3)	186 (51.7)	
Viral load test at enrolment				*0.152*
<1000 copies/ml	19 (5.1)	9 (47.4)	10 (52.6)	
≥1000 copies/ml	4 (1.1)	0 (0)	4 (100)	
Missing VL	347 (93.8)	169 (48.7)	178 (51.3)	
Disease stage at start				*0.299*
Stage I & II	318 (88.6)	151 (47.5)	167 (52.5)	
Stage III & IV	41 (11.4)	23 (56.1)	18 (43.9)	
Drug at the start				*0.161*
Efavirenz-based regimen	303 (86.1)	144 (47.5)	159 (52.5)	
Nevirapine-based regimen	25 (7.1)	16 (64.0)	9 (36.0)	
Dolutegravir-based regimen	24 (6.8)	9 (37.5)	15 (62.5)	
Frequency of drug intake				*0.056*
Once per day	328 (92.4)	156 (47.6)	172 (52.4)	
Twice per day	27 (7.6)	18 (66.7)	9 (33.3)	
Any undesired drug effect				*0.018*
No	180 (48.8)	75 (41.7)	105 (58.3)	
Yes	189 (51.2)	102 (54.0)	87 (46.0)	

p is p-value from chi-squared test for differences between groups

*Due to missing data, not all totals sum up to 370

Concerning psychosocial characteristics of study participants (Table 7), 5.9% of the enrolled participants were in a support group with 71.4% of those assigned to the control arm while a considerable 23% had not informed their HIV status to any of their immediate family members on their serological status. Participant's satisfaction with services indicated that 62.2% of the study participants perceived services as satisfactory, 25.7% said services received were acceptable, while 7.8% said services received were of poor quality. When study participants were asked to provide a self-report on their HIV status knowledge level, 35.1% of them felt that they had quite considerable knowledge on HIV as a disease, their HIV treatment option and importance on their health, as well as the low risk and health-appropriate behaviours to adopt henceforth. In the same light, when asked to self-qualify their relationship with care provider, 52.2% of the study participants implied that their caregivers usually showed interest to their psychosocial wellbeing rather than just focusing on their medical needs.

Table 7: Participants' baseline psychosocial characteristics (N=370)

(***Partial source:*** Ndenkeh et al., 2022) (36)

Variable	**Total***	**Randomization group** *Intervention, n=178 Control, n=192*		**p**
	N (column %)	***N (row %)***	***N (row %)***	
Part of a support group				*0.06*
No	*332 (94.1)*	*165 (49.7)*	*167 (50.3)*	
Yes	*21 (5.9)*	*6 (28.6)*	*15 (71.4)*	
Qualify relationship with caregiver				*0.301*
More than medical	193 (52.2)	98 (50.8)	95 (49.2)	
Not only medical but not quite good	48 (13.0)	25 (52.1)	23 (47.9)	
Strictly professional/medical	129 (34.9)	55 (42.6)	74 (57.4)	
Qualify satisfaction with health services rendered				0.214
Poor	29 (7.8)	18 (62.1)	11 (37.9)	
Can't qualify	16 (4.3)	7 (43.8)	9 (56.3)	
Acceptable	95 (25.7)	39 (41.1)	56 (58.9)	
Satisfactory	230 (62.2)	114 (49.6)	116 (50.4)	
HIV status disclosure				0.588
No, to none of them	85 (23.0)	42 (49.4)	43 (50.6)	
Yes, to some of them	196 (53.1)	97 (49.5)	99 (50.5)	
Yes, to all of them	88 (23.9)	38 (43.2)	50 (56.8)	
Level of knowledge on health status				*0.206*
Basic knowledge on HIV and treatment	238 (64.9)	109 (45.8)	129 (54.2)	
Extensive knowledge on HIV and treatment	129 (35.1)	68 (52.7)	61 (47.3)	

p is p-value from chi-squared test for differences between groups *Due to missing data, not all totals sum up to 370

5.3. Depression among Participants and with respect to follow up visits

At enrolment, 42 (11.4%) of study participants presented were screened with moderate to severe symptoms of depression, 31 (8.4%), 10 (2.7%) and 1 (0.3%) of which were moderate, moderate severe and severe respectively. The depression prevalence was relatively higher among study controls arm compared to the intervention arm though not statistically significant (p=0.168). Also, 106 (28.6%) of the participants had minimal symptoms of depression which was slightly higher in the intervention arm (Table 8).

Table 8: Baseline depression status (N=370)

(***Partial source:*** Ndenkeh et al., 2022) (36)

Variable	**Total** *N (column %)*	**Intervention** *N (column %)*	**Control** *N (column %)*	**p**
Depression category				0.271
No symptom of depression	222 (60.0)	106 (59.6)	116 (60.4)	
Mild symptoms of depression	106 (28.6)	56 (31.5)	50 (26.0)	
Moderate symptoms of depression	31 (8.4)	14 (7.9)	17 (8.9)	
Moderately severe symptoms of depression	10 (2.7)	2 (1.1)	8 (4.2)	
Severe symptoms of depression	1 (0.3)	0 (0)	1 (0.5)	
Has moderate to severe depressive symptoms?				0.168
No	328 (88.6)	162 (91.0)	166 (86.5)	
Yes	42 (11.4)	16 (9.0)	26 (13.5)	

p is p-value from chi-squared test for differences between groups

The distribution of depression symptoms varied between randomization groups as well as among the nine symptoms assessed with the PHQ-9 questionnaire (Table 9). A considerable 34.3% of the participants had the feeling of hopelessness which was evenly distributed in the two study arms. The feeling of tiredness, low appetite or overeating, insomnia or oversleeping and the feeling of low esteem were all prevalent in more than 20% of study participants as well as in each case were slightly higher in the control arm. Other symptoms were less prevalent notably trouble concentrating, slow reaction or restlessness and suicidal thoughts though it should be noted that 6 (1.6%) of the participants agreed to having suicidal thoughts upon enrolment in the study.

Table 9: Depression symptoms among participants at baseline (N=370)

Depression symptoms	**Total** *N (column %)*	**Intervention** *N (column %)*	**Control** *N (column %)*
Have little or no interest in things			
No	318 (85.9)	161 (90.4)	157 (81.1)
Yes	52 (14.1)	17 (9.6)	35 (18.2)
Have the feeling of hopelessness			
No	243 (65.7)	118 (66.3)	125 (65.1)
Yes	127 (34.3)	60 (33.7)	67 (34.9)
Have trouble sleeping or oversleeping			
No	280 (75.7)	139 (78.1)	141 (73.4)
Yes	90 (24.3)	39 (21.9)	51 (26.6)
Always feeling tired			
No	273 (73.8)	135 (75.8)	138 (71.9)
Yes	97 (26.2)	43 (24.2)	54 (28.1)
Have low appetite or overeating			
No	279 (75.4)	137 (77.0)	142 (74.0)
Yes	91 (24.6)	41 (23.0)	50 (26.0)
Have low self esteem			
No	289 (78.1)	142 (79.8)	147 (76.6)
Yes	81 (21.9)	36 (20.2)	45 (23.4)
Have trouble concentrating			
No	341 (92.2)	168 (94.4)	173 (90.1)
Yes	29 (7.8)	10 (5.6)	19 (9.9)
Have slow reaction or restlessness			
No	340 (91.9)	165 (92.7)	175 (91.1)
Yes	30 (8.1)	13 (7.3)	17 (8.9)
Have suicidal thoughts			
No	364 (98.4)	176 (98.9)	188 (97.9)
Yes	6 (1.6)	2 (1.1)	4 (2.1)

NB: Any depression symptom was considered present if rated score for that symptom was ≥2/3

During conversation with participant assigned to the intervention arm in an attempt to identify main problem areas leading to the depression symptoms for appropriate IPT, it was observed that role transition seemed to be the major problem area though it was most often coupled with grief and interpersonal disputes. Participants who were part of IPT sessions were particularly affected by significant change in their lives that led to the depressive symptoms notably the pain linked to being diagnosed HIV positive as was the case with participant SNTI10 who said, "*I feel bad because I really do not know how come, I have known only one man and he does not have HIV*". Though it was a hard pill to swallow, some of the participants were working on getting over the situation notably participant SNTI14 who said, "*I am not still believing I am sick, but I take it the way it has come*". Association with grief was always within the context where a participant lost a loved one usually the

spouse which is the case with participant SNTI2 who said, "*My husband put me in to this and now he is no more. He was the one I could depend on my family does not care about me anymore*". Interpersonal disputes completed the picture within the context where the spouse's family usually held the participant responsible for their sick or dead family member as was the case with participant SNTI1 who said, *"…the loss of my husband and now his family keeps on telling me I caused his death no matter how I try to move on with my children…they keep on talking*".

For all participants, significant changes were observed in depression scores with respect to the study groups and over time (Figure 6). There was a steady drop from 3.88 (±3.76) at enrolment to 2.82 (±2.39) after six months then to 2.29 (±2.39) after 12 months among participants of the intervention group. There was rather an increase from 4.35 (±4.64) at enrolment to 4.73 (±4.01) after 6 months then dropped to 3.39 (±3.0) after 12 months among study controls. Looking only the data of participants with depression, the trends were not that different marked by steady drops from 6.58 (±3.55), to 4.26 (±2.25) then to 3.39 (±1.98) as opposed to 7.43 (±4.66), 7.48 (±3.71) and 5.44 (±2.99) at the same time periods above. These observed differences were statistically significant, irrespective of the analysis scenario ($p<0.001$ in each case). Clinical categories of depression pretty much differed with respect to study group and time where moderate to severe symptoms of depression were more prevalent among the study controls over time that is 26 (13.5%), 27 (16.8%) and 7 (5.1%) as opposed to 16 (9%), 2 (1.6%) and 1 (0.8%) (Table 16). Despite dropping for both study groups, the observed differences in depression status were significant with respect to time and randomization group (with $p<0.001$ and $p=0.046$ at month 6 and month 12 follow-up visits respectively).

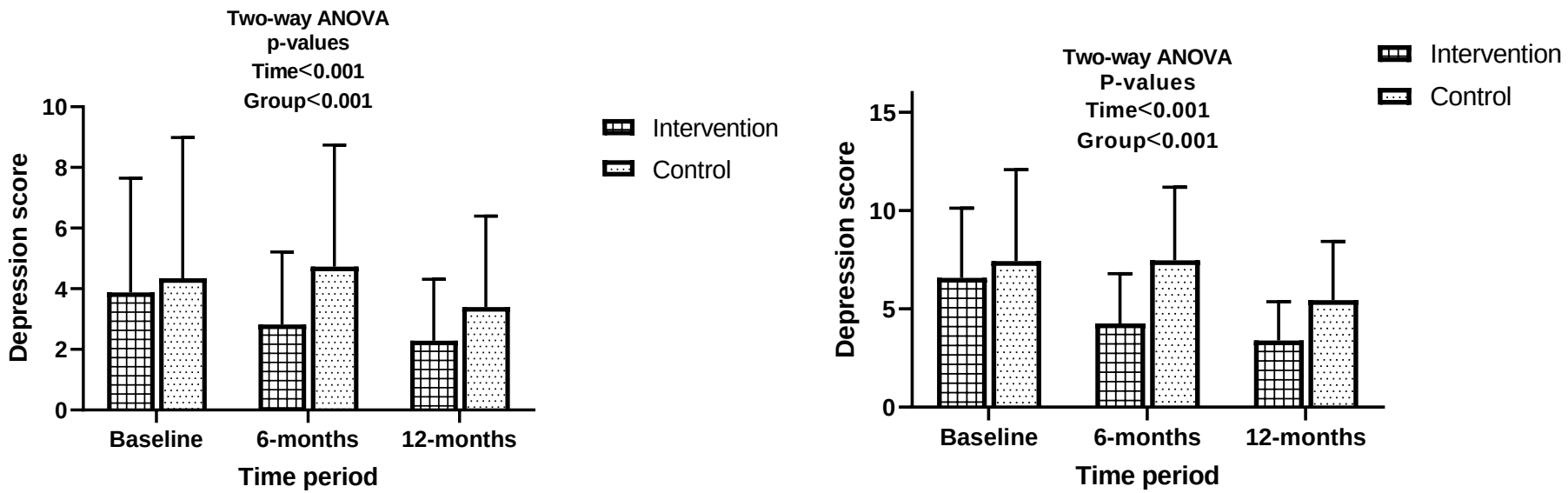


Figure 6: Effect of psychoeducation and IPT on depression with respect to time (***Left;*** all study participants, ***right;*** participants with depressive symptoms in study)

(***Source:*** Ndenkeh et al., 2022) (36)

Participants acknowledged to have benefitted in one way or another from the IPT sessions received during study. For some it helped them accept their health status notably participant SNTI3 who said, "*It helped me to understand my condition and how to live with others normally*". For others it went even further by helping them understand how to live with HIV and how to follow their treatment notably participant SNTI4 who said, "*I am happy to have been part of this and it has helped me to change positively in the way I take my treatment and how I do my things now very comfortably*".

5.4. Treatment Adherence among Participants at Baseline

At enrolment, 41 (11.1%) of the study participants were assessed to be poorly adherent to HIV treatment while 245 (66.2%) and 84 (22.7%) were assessed to be moderately and highly adherent respectively. Proportions of participants with poor or high adherence were slightly higher in the intervention arm with 11.2% and 24.7% respectively compared to 10.9% and 20.8% in the control arm (Table 10). This observed difference at baseline between the study groups was not significant (p=0.649).

Table 10: Overall adherence status at baseline (N=370)

Variable	**Total** *N (column %)*	**Intervention** *N (column %)*	**Control** *N (column %)*	**p**
Adherence category				0.649
Poorly adherent	41 (11.1)	20 (11.2)	21 (10.9)	
Moderately adherent	245 (66.2)	114 (64.0)	131 (68.2)	
Highly adherent	84 (22.7)	44 (24.7)	40 (20.8)	
Poorly adherent?				0.927
No	329 (88.9)	158 (88.8)	171 (89.1)	
Yes	41 (11.1)	20 (11.2)	21 (10.9)	

p is p-value from chi-squared test for differences between groups

When individual adherence methods were used to assess the adherence of each study participant, it was observed that the adherence levels measured varied per measurement method used (Table 11). Self-reported adherence and drug refill tool identified the highest proportion of participants who had poor adherence with 12.7% and 11.1% respectively followed by the visual analogue scale with 7%. Pill count and pill identification test (PIT) on the other hand, had the lowest proportions of participants identified to have poor adherence with 3.2% and 4.6% respectively. Despite so, it is worth noting that all the above adherence measuring methods were significantly correlated with each other (Table 12). Correlations varied widely from a Spearman's correlation coefficient of 0.165 between PIT and pill count to a coefficient of 0.74 between visual analogue scale (VAS) and self-reported adherence. All

the above correlations were statistically significant ($p<0.001$). Also, all the individual adherence measuring methods were significantly correlated to the overall adherence scores with VAS and self-reported adherence having the highest correlations with coefficients of 0.852 and 0.811 respectively.

Table 11: Adherence levels per measurement method at baseline (N=370)

Adherence measurement methods	**Total** *N (column %)*	**Intervention** *N (column %)*	**Control** *N (column %)*
Drug refill			
Poorly adherent	41 (11.1)	18 (10.1)	23 (12.0)
Moderately adherent	42 (11.4)	18 (10.1)	24 (12.5)
Highly adherent	287 (77.6)	142 (79.8)	145 (75.5)
Pill identification test			
Poorly adherent	17 (4.6)	9 (5.1)	8 (4.2)
Moderately adherent	160 (43.2)	66 (37.1)	94 (49.0)
Highly adherent	193 (52.2)	103 (57.9)	90 (46.9)
Self-reported adherence			
Poorly adherent	47 (12.7)	20 (11.2)	27 (14.1)
Moderately adherent	175 (47.3)	84 (47.2)	91 (47.4)
Highly adherent	148 (40.0)	74 (41.6)	74 (38.5)
Visual analogue scale			
Poorly adherent	26 (7.0)	12 (6.7)	14 (7.3)
Moderately adherent	161 (43.5)	72 (40.4)	89 (46.4)
Highly adherent	183 (49.5)	94 (52.8)	89 (46.4)
Pill count			
Poorly adherent	12 (3.2)	6 (3.4)	6 (3.1)
Moderately adherent	138 (37.3)	63 (35.4)	75 (39.1)
Highly adherent	220 (59.5)	109 (61.2)	111 (57.8)

Table 12: Correlation between various adherence measurement methods at baseline

		Drug refill	***PIT***	***Self-report***	***VAS***	***Pill count***	***Overall adherence***
Drug refill	***r***		0.315	0.38	0.449	0.277	0.619
	p-value	NA	<0.001	<0.001	<0.001	<0.001	<0.001
	N		370	369	370	370	369
PIT	***r***	0.315		0.207	0.27	0.165	0.556
	p-value	<0.001	NA	<0.001	<0.001	0.001	<0.001
	N	370		369	370	370	369
Self-report	***r***	0.38	0.207		0.74	0.461	0.811
	p-value	<0.001	<0.001	NA	<0.001	<0.001	<0.001
	N	369	369		369	369	368
VAS	***r***	0.449	0.27	0.74		0.642	0.852
	p-value	<0.001	<0.001	<0.001	NA	<0.001	<0.001
	N	370	370	369		370	369
Pill count	***r***	0.277	0.165	0.461	0.642		0.67
	p-value	<0.001	0.001	<0.001	<0.001	NA	<0.001
	N	370	370	369	370		369
Overall adherence	***r***	0.619	0.556	0.811	0.852	0.67	
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	NA
	N	369	369	368	369	369	

r Spearman's correlation coefficient

5.5. Viral Suppression at endpoint of study

After 12 months of follow-up in the study, 262 (70.8%) of the study participants had their blood samples collected for a viral load test. By the time study ended, 195 (74.4%) participants had received their viral load results. Of these, 22 (11.3%) of the participants had unsuppressed viral load level while 60 (30.8%) and 113 (57.9%) had suppressed viral load level with low replication and undetectable viral load level, respectively (Table 13). Proportion of participants with unsuppressed viral load level was higher in participants receiving treatment at ADH with 21 (13.2%) compared to 1 (2.8%) in participants receiving treatment at SDH. On the other hand, participants receiving treatment in SDH had higher undetectable viral load level with 29 (80.6%) compared to 84 (52.8%) in participants receiving treatment at ADH. This observed difference was statistically significant (p=0.008).

Table 13: Viral load categories after 12months of follow up (N=195)

Variable	Total *N (column %)*	ADH *N (column %)*	SDH *N (column %)*	p
Viral load category				0.008
Undetectable (<50cc/mL)	113 (57.9)	84 (52.8)	29 (80.6)	
Suppressed with low replication (50-999cc/mL)	60 (30.8)	54 (34.0)	6 (16.7)	
Unsuppressed (≥1000cc/mL)	22 (11.3)	21 (13.2)	1 (2.8)	
Viral load unsuppressed?				0.074
No	173 (88.7)	138 (86.8)	35 (97.2)	
Yes	22 (11.3)	21 (13.2)	1 (2.8)	

p is p-value from chi-squared test for differences between groups

5.6. Associations between Depression, Treatment Adherence and Viral Suppression

Depression scores and adherence scores were all significantly correlated to each other at various time points of the study with coefficients of -0.191, -0.555 and -0.513 at enrolment, after 6 months and after 12 months respectively ($p<0.001$). In all cases, any increase in depression score led to a decrease in treatment adherence score. Also, an increase in depression score was accompanied by an increase in viral load level while an increase in treatment adherence score was accompanied by a decrease in viral load level (Table 14).

Table 14: Correlations between depression scores, adherence scores and viral load levels (***Source :*** Ndenkeh et al., 2022) (36)

		Adherence at baseline	*Adherence at 6 months*	*Adherence at 12 months*	*Viral load at 12 months*
Depression score at baseline	***r***	-0.191			
	p-value	< 0.001	NA	NA	NA
	N	368			
Depression score at 6 months	***r***		-0.555		
	p-value	NA	< 0.001	NA	NA
	N		290		
Depression score at 12 months	***r***			-0.513	0.191
	p-value	NA	NA	< 0.001	0.008
	N			259	192
Viral load at 12 months	***r***	-0.12		-0.232	
	p-value	0.095	NA	0.001	NA
	N	194		195	

r Spearman's correlation coefficient

When adjusted for other covariates in a logistic model (Table 15), participants screened at baseline to present moderate to severe symptoms of depression had more chances of being poorly adherent to HIV treatment compared to those without (aOR=5.5; 95% CI=1.45-20.93;

p=0.012). On the other hand, study participants who implied that their care providers usually further showed interest to their psychosocial wellbeing had less chances of being poorly adherent to HIV treatment at baseline when compared to those whose care providers focused entirely on their medical needs. Two other variables worth noting despite not remaining significant in the multivariate model were distance to treatment center and age group. Participants living in distances less than 30 minutes or 30 minutes to two hours to the health facility (compared to those who lived more than two hours away) had less chances of being poorly adherent to HIV treatment at baseline. Adolescent participants on the other hand had more chances of being poorly adherent to HIV treatment at baseline.

Table 15: The association of depression with poor adherence at baseline (N=346) (***Source:*** Ndenkeh et al., 2022) (36)

Model covariates	**Unadjusted**		**Adjusted**	
	OR (95% CI)	**p**	**aOR (95% CI)**	**p**
Has moderate to severe depressive symptoms? *		***0.086***		***0.012***
Yes	2.1 (0.9-4.92)		5.5 (1.45-20.93)	
No	1		1	
Age group		***0.027***		***0.195***
Adolescent (<20yrs)	7.22 (1.59-32.91)	0.011	4.75 (0.67-33.54)	0.118
Adult (20-50yrs)	1.3 (0.52-3.25)	0.572	0.96 (0.32-2.92)	0.941
Elderly adult (>50yrs)	1		1	
Sex		**0.29**		0.213
Female	0.7 (0.36-1.36)		0.6 (0.27-1.34)	
Male	1		1	
Level of knowledge on health status		***0.03***		***0.966***
Basic knowledge on HIV and treatment	2.43 (1.09-5.43)		1.02 (0.38-2.77)	
Extensive knowledge on HIV and treatment	1		1	
HIV status disclosure		***0.078***		***0.452***
No, to none of them	3.79 (1.18-12.14)	0.025	2.42 (0.61-9.58)	0.208
Yes, to some of them	2.93 (0.99-8.72)	0.053	1.95 (0.53-7.13)	0.311
Yes, to all of them	1		1	
Qualify relationship with caregiver		***<0.001***		***<0.001***
More than just medical	0.14 (0.06-0.32)	<0.001	0.08 (0.02-0.28)	<0.001
Not only medical but not quite good	0.22 (0.06-0.76)	0.017	0.26 (0.06-1.08)	0.064
Strictly medical	1		1	
Time to reach treatment center		***0.008***		***0.108***
Less than 30 minutes	0.31 (0.13-0.76)	0.011	0.38 (0.13-1.11)	0.078
30 minutes to 2 hours	0.25 (0.1-0.62)	0.003	0.33 (0.11-1.01)	0.05
More than 2 hours	1		1	

* Variable of interest adjusted for other variables (Age group, Sex, Level of knowledge on health status, HIV disclosure status, Relationship with caregiver and Time to reach treatment center). The model was also adjusted for Efavirenz-based regimen at start, reported undesired drug effect and study site as all three were potential confounding factors of the observed association between depression and poor adherence

In another regression analysis (Table 16), adjusted for age group, sex, qualification of relationship with caregiver and study site, being screened to present moderate to severe symptoms of depression remained significantly associated to unsuppressed VL level after 12 months in the study while and treatment adherence level had a significance at the borderline. Those presenting the above symptoms of depression had more chances of receiving an unsuppressed VL levels when compared to those without (aOR=29.4; 95% CI=3.0-333.3; p=0.004). Also, participants who were poorly and moderately adherent to their antiretroviral

treatment at month 12 follow-up visit had higher chances of receiving viral load results with unsuppressed viral load at the same follow up time as compared to those who were highly adherent to their treatment (aOR=4.49; 95% CI=0.95-21.23; p=0.058). Another factor worth taking note of was that when adjusted for other covariates, participants from ADH had higher chances of receiving unsuppressed VL results after 12 months of follow up as compared to participants from SDH (aOR=13.25; 95% CI=0.86-203.57; p=0.064).

Table 16: The association of depression with unsuppressed VL at 12 months (N=192)

Model covariates	**Unadjusted**		**Adjusted**	
	OR (95% CI)	**p**	**aOR (95% CI)**	**p**
Moderate to severe symptoms of depression after 12months*		***0.002***		***0.004***
Yes	12.34 (2.56-58.82)		29.4 (3.0-333.3)	
No	1		1	
Treatment adherence at 12months*		***0.055***		***0.058***
Poorly/Moderately adherent	4.3 (0.97-19.06)		4.49 (0.95-21.23)	
Highly adherent	1		1	
Age group		***0.786***		***0.371***
Adolescent (<20yrs)	1.75 (0.16-18.97)	0.645	1.37 (0.12-16.2)	0.802
Adult (20-50yrs)	0.84 (0.29-2.44)	0.743	0.48 (0.15-1.57)	0.222
Elderly adult (>50yrs)	1		1	
Sex		***0.629***		***0.751***
Female	1.28 (0.47-3.44)		1.19 (0.4-3.54)	
Male	1		1	
Qualify relationship with caregiver		***0.25***		***0.932***
More than just medical	0.46 (0.18-1.19)	0.111	0.58 (0.19-1.75)	0.335
Not only medical but not quite good	0.46 (0.05-3.81)	0.47	0.82 (0.09-7.24)	0.815
Strictly medical	1		1	
Study site		***0.108***		***0.064***
ADH	5.33 (0.69-40.97)		13.25 (0.86-203.57)	
SDH	1		1	

* Variables of interest adjusted for each other and other variables (Age group, Sex, Relationship with caregiver and study site)

5.7. Effect of Depression management on Treatment Adherence

For all participants, changes were observed in adherence scores with respect to the study groups and over time (Figure 7). There was an improvement from 12.56 (±2.2) at enrolment to 13.58 (±1.26) after six months then to 13.94 (±0.99) after 12 months among participants of the intervention group. There was the same kind of improvement from 12.25 (±2.29) at enrolment to 13.33 (±1.5) after 6 months then dropped to 13.8 (±1.28) after 12 months among study controls. Looking only the data of participants with depression, the trends were not that different with both groups marked by increases from 11.78 (±2.23), to 13.08 (±1.29) then to 13.62 (±1.08) as opposed to 11.7 (±2.35), 12.62 (±1.65) and 13.29 (±1.61) at the same time periods above. These observed differences were not statistically significant, irrespective of the analysis scenario.

In the intervention arm, poor adherence dropped to 0% during months 6 and 12 follow up visits, moderate adherence increased to 71.8% at month 6 follow up visit then dropped to 69.4% at month 12 follow up visit while high adherence steadily increased to 28.2% at month 6 follow up visit then to 69.4% at month 12 follow up visit. In the control arm, same trend was observed notably the steady increase in moderate and high adherence over time except for a weaker drop in poor adherence to 2.5% at month 6 the to 2.2% at month 12 follow up visit (Table 17). Despite not being statistically significant, it should be noted that any study participant who was poorly adherent to HIV treatment within study (N=4 after 6 months and N=3 after 12 months) was a control (p=0.098 and p=0.255 at month 6 and month 12 follow up visits respectively).

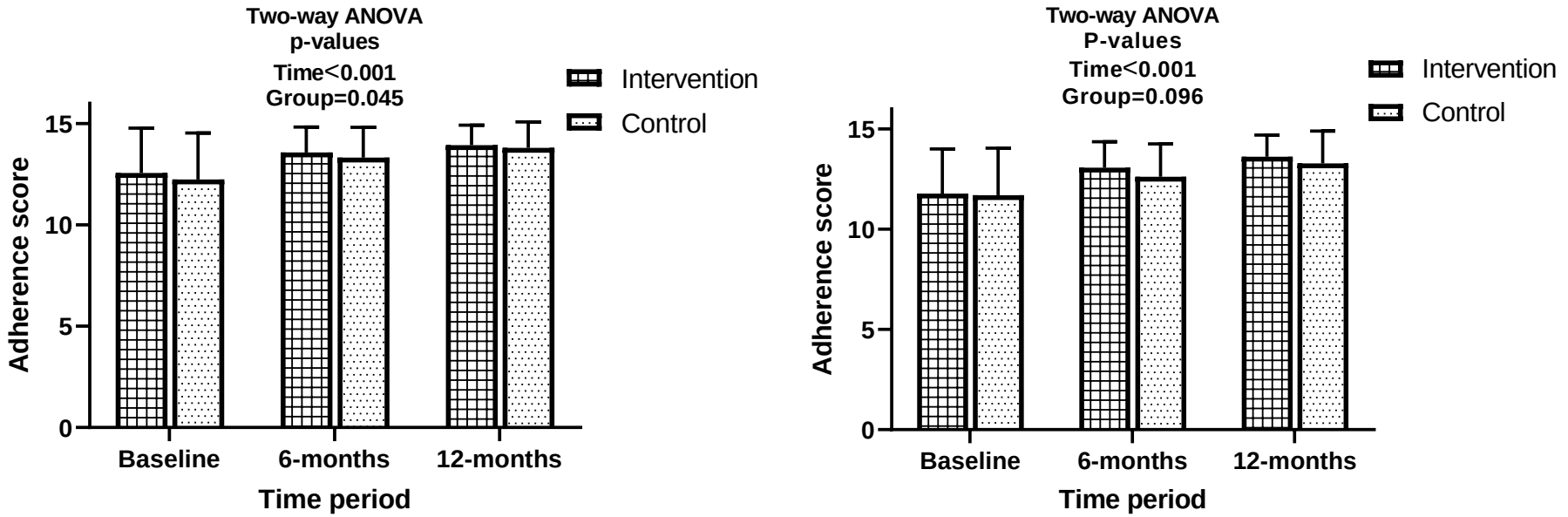


Figure 7: Effect of psychoeducation and IPT on treatment adherence with respect to time (***Left;*** all study participants, ***right;*** participants with depressive symptoms in study)

(***Source:*** Ndenkeh et al., 2022) (36)

Table 17: Depression and treatment adherence outcome

(***Source :*** Ndenkeh et al., 2022) (36)

Variable	Time period								
	Enrolment (n=370)			6 months (n=292)			12 months (n=262)		
	Intervention N (column %)	Control N (column %)	P	Intervention N (column %)	Control N (column %)	P	Intervention N (column %)	Control N (column %)	p
Depression status			0.271			<0.001			<0.001
No symptom of depression	106 (59.6)	116 (60.4)		98 (76.0)	93 (57.8)		111 (91.0)	98 (71.5)	
Mild symptoms of depression	56 (31.5)	50 (26.0)		29 (22.5)	41 (25.5)		10 (8.2)	32 (23.4)	
Moderate symptoms of depression	14 (7.9)	17 (8.9)		2 (1.6)	24 (14.9)		1 (0.8)	7 (5.1)	
Moderately severe symptoms of depression	2 (1.1)	8 (4.2)		0 (0)	3 (1.9)		0 (-)	0 (-)	
Severe symptoms of depression	0 (0)	1 (0.5)		0(-)	0 (-)		0 (-)	0 (-)	
Has moderate to severe depressive symptoms?			0.168			<0.001			0.046
No	162 (91.0)	166 (86.5)		127 (98.4)	134 (83.2)		121 (99.2)	130 (94.9)	
Yes	16 (9.0)	26 (13.5)		2 (1.6)	27 (16.8)		1 (0.8)	7 (5.1)	
Adherence status			0.649			0.098			0.255
Poorly adherent	20 (11.2)	21 (10.9)		0 (0)	4 (2.5)		0 (0)	3 (2.2)	
Moderately adherent	114 (64.0)	131 (68.2)		94 (71.8)	122 (75.8)		86 (69.4)	94 (68.1)	
Highly adherent	44 (24.7)	40 (20.8)		37 (28.2)	35 (21.7)		38 (30.6)	41 (29.7)	

p is the Chi-squared p-value for differences in outcomes between randomization groups

5.8. Effect of Intervention on Viral Suppression

The viral load suppression proportions between randomization groups did not differ significantly after 12 months of follow up in the study irrespective of analysis scenario. The proportions of study participants with VL≥1000 copies/mL were 11.9% as opposed to 10.8% (p=0.811) for all participants in intervention and control groups respectively as well as 17.4% as opposed to 20.0% (p=0.744) for depressive participants in intervention and control groups respectively. It is also worth noting though that the occurrence of unsuppressed VL was higher in participants with depressive symptoms as compared to all participants.

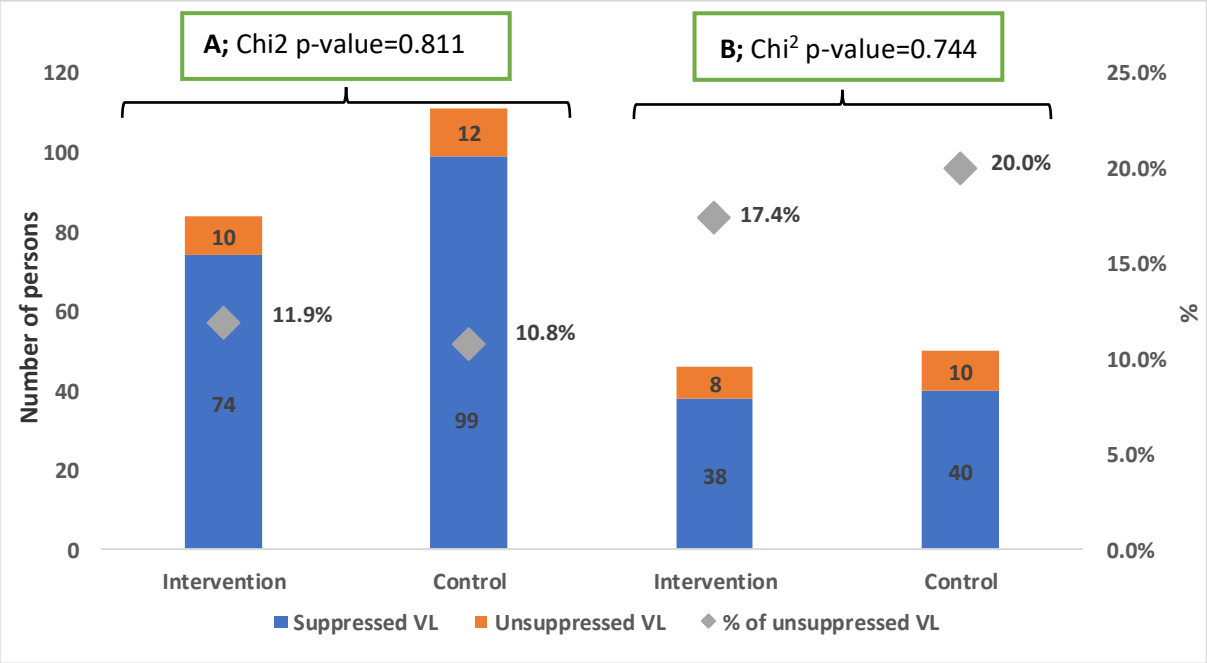


Figure 8: Effect of psychoeducation and IPT on viral load suppression after 12 months in the study (**A;** all study participants, **B;** participants with depressive symptoms in study)

(***Source:*** Ndenkeh et al., 2022) (36)

6. Discussion

It is a widely accepted fact that the level of antiretroviral treatment adherence plays an important role in HIV virological outcome where an optimal adherence level needed to ensure viral suppression. Also, literature on the role that depression management has on HIV treatment outcome in resource-limited settings is insufficient. In an attempt to shed some light on depression and HIV management integration in Cameroon and other similar contexts, this study was conducted to assess the impact of psychoeducation and IPT on depression and a potential cascade effect of the latter on treatment adherence and viral suppression.

This study showed adherence to HIV treatment to be fairly good with 11.1%, 66.2% and 22.7% of the study participants assessed to be poorly adherent, moderately adherent and highly adherent to HIV treatment respectively. The proportion of participants with poor adherence was not quite different to those from other studies conducted in Cameroon as well as other African countries notably Atanga et al. who had 9.6% (23), Afe et al. who had 8.4% (105), and Bjiker et al. who had 7.3% (106). Despite so, it is worth taking note that the latter two studies used only pill counts and visual analogue scale respectively. Also, given that the Cameroonian study was focused on adherence levels at 6 months of treatment within the PMTCT program, differences in moderate and high adherence proportions (31.4% and 59.0%) can potentially be explained by the differences in resource allocation and monitoring. More than half of our study participants had suboptimal adherence levels, which would need improvement through context-specific enhancement strategies. Despite succeeding to retain 74% of all enrolled participants throughout the study follow up time, it was not far from the 78.8% and 60.4% observed by Ajeh et al. and Billong et al. respectively in Cameroon (63, 107).

This study used composite scores to assess treatment adherence which was significantly correlated to VL results of participants with a correlation coefficient of -0.232 (p=0.001). On the other hand, 11.3% of all participants with VL results after 12 months in the study had unsuppressed viral while 30.8% and 57.9% had suppressed viral loads with low replication and undetectable viral loads respectively. Participants with low or moderate treatment adherence levels after 12 months of follow up in the study had higher chances of receiving unsuppressed viral load results which was borderline significant (aOR=4.49; 95% CI=0.95-21.23; p=0.058). Even though the measured treatment adherence scores varied per measurement method used, it should be noted that they were significantly correlated with

each other and with the overall treatment adherence scores at baseline (after 6-9 months of ART). Furthermore, VAS and self-reported adherence had the highest correlation coefficients with the overall adherence scores. This variability in treatment adherence measurement yet significant correlations between the various measurement methods concord with what was observed by Atanga et al. (2018) who went further to underline the strong correlations between VAS and self-reported scores and the composite scores (23). The above combination of multiple adherence measurement methods could prove ideal in resource-limited settings as it minimizes biases linked to each individual indirect measuring method (104). However, in contexts where its use in routine clinical practice proves not to be quite feasible, the VAS and/or self-reported adherence measurement methods could prove valuable in the follow up of patients in care (23, 108, 109).

This study also showed depression to be prevalent at 11.4% among the study participants at enrolment which in tend made them have more chances of being assessed to be poorly adherent to HIV treatment ($p=0.012$). Even though this result was close to the prevalence from other studies in the African context (34, 110), it was considerably lower than the 21%-63% prevalence range from numerous older studies in the Cameroonian context (74-76, 111-114). The possible root cause of the observed differences could be the wide cultural and socio-economic diversity in the country leading to diverse population types enrolled at different time period after initiating HIV treatment. On the other hand, many studies in SSA corroborate our finding on the fact that depression negatively impacts adherence to HIV treatment (32-34, 76, 115, 116). The WHO has thus recommended that depression screening and management be included in the routine service package of individuals on HIV treatment (17), while ensuring user friendly and acceptable as well as optimizing on any potential effect on treatment adherence and even just on the psychosocial wellbeing of the individual (117-119).

Despite the above recommendation, it should be noted that literature to help guide the choice of depression management intervention as well as their role on improving adherence to HIV treatment and/or viral suppression is insufficient especially in SSA (17, 120). Antidepressant drugs despite naturally being the potential first choice of medical staff PLHIV due to its high efficacy (112), it would have to be added to the already long term HIV treatment HIV patients are on and thus will face constraints in line with adherence as well as side effects and drug interactions to handle (121). This open thus the door to other forms of depression management notably behavioral strategies like psychoeducation and IPT both of which have

the same level of effect thus can be used separately or combined with the former for severe depression as was the case in this study (98, 121-123). The combination of psychoeducation and IPT had significant effect on depression though that effect could not proportionately be translated to HIV treatment adherence nor to viral suppression. Even so, it should be noted that depression, adherence and VL levels were all correlated to each other at various time points in the study as well as depression state being independently associated with unsuppressed VL results after 12 months of follow up. A possible insinuation from this result could be that screening and managing depression cannot be used as a "one-size fits all" all solution to enhance adherence to HIV treatment and viral outcome, given that other health, cultural, economic, and social factors could also have a role to play in the situation (36). To back up the above-mentioned assertion in the case of this study, we present the independent association of poor adherence with the quality of relationships with care providers. It is in that light that Martin et al. stipulate the value of being knowledgeable of patients as a human being by their care providers (124). This permits the care providers to better understand the core elements of the patient's life (and potentially linked to his or her adherence) which with time tends to foster the health-giving relationship as well as benefit the patient in terms of adherence and subsequently viral outcome (36, 124). Furthermore, studies have shown that social support be it from family, peers or caregivers in the form of emotional support, encouragements etc can positively influence treatment adherence mediated through positive state of mind (125, 126). This goes in line with other studies which underline the fact that ART provision should not only be about their medical needs (adherence and viral outcome) but should give some level of attention on their psychosocial wellbeing which most at times is associated to the former (127, 128).

Another reason for moderate effect of psychoeducation and IPT on depression not being translated to adherence and viral suppression could be the lack of pure controls who would neither be briefed or not treated if diagnosed diluting thus the cascade effect on HIV treatment outcome (129). That is the case of this study where participants diagnosed were referred for psychosocial support thus the logical drop in depression prevalence in study controls with respect to time in study. The time to reach health facility if longer tends to negatively impact adherence to long term treatment especially if it is marked by frequent hospital visits (130-132). Despite not being independently associated to poor adherence in this study, the time to reach health facility significantly differed between the randomization groups which could have influenced their assessed HIV treatment adherence scores. The main challenge to integrating mental health and HIV management in resource-limited settings is the insufficient

mental health labour force but this study effectively shifted the depression management task to non-expert staff in a rural resource-limited context (36). This study thus successfully illustrated the role that trained community health workers and other non-expert staff could play in depression screening and management (36), with acceptability and feasibility in concordance with studies in other contexts in SSA (112, 117, 133). It is worth noting however that, other models of task-shifting primary care already exist so doing the same thing with mental health care without a consequent increase in the current labour force will only overburden the already fragile health system in these resource-limited settings (36, 129).

This study has a good number of limitations quite detailed by Ndenkeh et al, (36) though the main ones are summarized here. The first of these limitations is number of sites used for study thus problem in generalizing observed results to a typical Cameroonian or closely related setting. It should be noted though that the study has helped in providing more literature to support integration of depression and HIV management. Secondly, the baseline association between adherence to HIV treatment and viral suppression could not be demonstrated as a vast majority of participants had not do VL test at enrolment. Similarly, the expected sample size of participants finishing study with VL results could not be reached which influenced the analysis power with respect to viral suppression comparison between study groups. However, we were still able to show interactions between depression, adherence and viral suppression at other time points in the study. Another limitation is that IPT was not performed as appropriate in terms of frequency but was dependent participant availability which could have affected its overall impact. The intention with this study though was to adopt a public health approach with task shifting to mental health non-specialists as well as accommodate sessions with the participant's routine.

7. Conclusions and Implications

In conclusion, this research study showed encouraging treatment adherence and viral suppression among people receiving antiretroviral treatment from Santa and Abong Mbang district hospitals. Unsuppressed viral load levels were higher in participants from Abong Mbang District Hospital, in participants screened with or still presenting moderate to severe depressive symptoms as well as in participants who were poorly or moderately adherent to antiretroviral treatment by the time of viral load blood sample collection. On the other hand, at baseline, poor treatment adherence was higher in participants screened to present moderate to severe symptoms of depression and lower in participants who had a better social relationship with the health personnel. Furthermore, the intervention package had moderate and significant effect on the psychosocial wellbeing of the participants, a mild yet non-significant effect on treatment adherence and no effect on the viral suppression. Despite observing that the mental health and wellbeing of the participants was closely related to their treatment adherence at baseline and all through follow up as well as to their viral suppression at the endpoint of the study, results showed that the effect of the intervention package was not strong enough to have the desired cascade effect on the treatment outcome when compared to standard of care.

These findings thus suggest that screening and managing depression can be considered as an important part of routine HIV management, facilitating its effective implementation at all levels of the health pyramid could lead to better treatment outcome. The psychosocial wellbeing of persons living with HIV should thus be given some level of priority as their medical care. However, this cannot be used as a "one-size fits all" kind of solution to achieve viral suppression as it is intertwined with other socio-economic, cultural, and medical factors. More large-scale and inclusive research is thus needed to identify depression management strategies that are cost-effective, take into consideration each implementation context and can bring positive impact to HIV treatment. Furthermore, given that the people living with HIV are already on a long-term treatment, shifting attention towards behavioral depression management interventions and task shifting to trained non-expert healthcare workers or community health workers who can be readily available and are in constant contact with these patients can prove quite valuable in this integration.

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Annex 1: Questionnaires

Enrolment Form

(Persons who started treatment 6-9 months prior start of study)

Serial No: …… Health Facility: …….. Date of recruitment in study: …../…../…….

Participant: Adult ☐ Adolescent (<20yrs) ☐ Study ID No: ……...

A. Socio-demographic information

1) Age in years: ……. 2) Sex: F ☐ M ☐

3) Marital status of participant:

Single ☐ Couple ☐ Divorced/Separated ☐ Widow(er) ☐

4) a. Have children? No ☐ Yes ☐ b. If Yes number…… c. Age of eldest…….

5) Profession of participant:

Unemployed ☐ Student ☐ Informal sector ☐ Formal sector ☐ Retired ☐

6) Religion: Catholic ☐ Protestant ☐ Pentecostal ☐ Muslim ☐ Animist ☐

7) Education level of participant:

Uneducated ☐ Primary ☐ Secondary ☐ Higher ☐

8) Smoking: Nonsmoker ☐ Former smoker ☐ Present smoker ☐

9) Alcohol: No ☐ Yes ☐ 10a) Any history of the use of substance? No ☐ Yes ☐

10b) If Yes to Question 10a, type? Cannabis ☐ Cocaine ☐ Heroin ☐ Other……....

11) Time to reach treatment center? <30mins ☐ 30mins-2hrs ☐ >2hrs ☐

12) How do you qualify your access to treatment center? Easy most of the times ☐
Difficult sometimes ☐ Difficult most of the times ☐

13) Are you part of a support group? No ☐ Yes ☐ 14) If No why? …….

15) Are you covered by a health insurance? No ☐ Yes ☐

B. Medical and HIV treatment related information

1) When you were diagnosed HIV+, did you start treatment within the week? No ☐ Yes ☐

2) If no to question 1 above reason …….

3) Did you do any of these tests before starting your treatment?(verify from book/file/register)

a) Hb level ☐; value …... b) CD4 count ☐; value …… c) WBC count ☐ ; value…….

d) ASAT ☐ ; value…… e) ALAT ☐ ; value……. Creatinine ☐; value……..

Viral load ☐ ; value ……

d) Diagnosed with any of these co-infections? TB ☐ Candidiasis ☐ Pneumonia ☐

Herpes zoster ☐ Toxoplasmosis ☐ Meningitis ☐ Others…….

4) If none or not all tests in question 3 were done reason(s) ……

……...

5) Stage of disease when starting treatment ……. (from stage I to IV)

6) a) Drug type at start? (NB: Ask to see the drug or book and tick the appropriate answer)

TDF/3TC/EFV ☐ AZT/3TC/EFV ☐ TDF/3TC/NVP ☐ AZT/3TC/NVP ☐

ABC/3TC/EFV ☐ ABC/3TC/NVP ☐ Other ☐ Precise……...

b) Date of treatment initiation? ……. c) Any switch of drug to this moment? No ☐ Yes ☐

d) If Yes switched to …… Reason for switch ……..

7) Number of takes of ART per day? Once ☐ Twice ☐

8) a) Have you done any of these follow up tests? No ☐ Yes ☐

b) Hb level ……. c) CD4 count…….. d) WBC count……. e) ASAT…….

f) ALAT……. g) Creatinine…… h) Viral load …….

i) If no to CD4/viral load follow up reason(s) ……...

……...

9) a) Since the start of your treatment have you experienced any drug stock out when you come for drug refill? No ☐ Yes ☐ b) If Yes how long did it last? .....days

10) a) Since the start of your treatment have you had any undesired effect of the drug important enough to affect your day-to-day life? No ☐ Yes ☐

b) Which of these? Vomiting ☐ Fatigue ☐ Diarrhoea ☐ Rash ☐ Neuropathy ☐ Headache ☐ Trouble sleeping/Nightmares ☐ Bleeding ☐ Weight loss/gain ☐

11) How can you qualify your relationship with your care giver(s)? Not quite good ☐ Strictly professional/medical ☐ More than just professional /medical ☐

12) a) Do you feel sometimes like you are treated differently by your caregiver(s) because of your serological status? No ☐ Yes ☐

b) If Yes to question 12a above specify how ……..

……..

13) a) In overall what is your level of satisfaction with the services rendered you? Poor ☐ Acceptable but can be ameliorated ☐ Quite satisfactory ☐ Can't qualify ☐

b) If not Quite satisfactory to question 13a above which of below aspects is/are concerned?

Poor reception ☐ Long patient waiting time ☐ Poor coordination between testing and ART services ☐ Poor flexibility in ART delivery ☐ Confidentiality concerns ☐

Other ☐, specify……

14) a) Does any immediate family member (parent/spouse/offspring) know about your serological status? No none of them ☐ Yes some of them ☐ Yes all of them ☐

b) If yes to question 14a above have you felt at anytime that they treat you differently because of your serological status? No ☐ Yes ☐

15) Did you have adequate counseling (where explanations were given about your current status and questions from you answered) before you started treatment? No ☐ Yes ☐

16) Are you frequently given the opportunity to enquire more for better understanding of your current health situation? No ☐ Yes ☐

17) Which of these categories best defines your level of knowledge of your current health situation? I just know I am sick but don't know much about it ☐ I know that I am having HIV and have base information on its transmission and consequences on my health but don't know much about the care I am receiving ☐ I can say I know almost everything as concerns my health status, pathology as well as the medical care I am receiving, its impact on my health and most appropriate behaviors to adopt ☐

Multi-method Adherence Tool

Serial No: ……..… Health Facility: …….. Date of encounter: …../…../…….

Study ID No: ……... Visit: M0 ☐ M6 ☐ M12 ☐

Participant: Adult ☐ Adolescent (<20yrs) ☐ Sex: F ☐ M ☐

A. Drug refill

1) Number of monthly drug refill appointments respected by participant within the past 6 months? _____ (0-6)

B. Pill Identification Test (PIT)

Please kindly inspect the two container and its contents pointing out which of the pills inside is yours. Please also tell me the name of the medication, number of pills to take per dose, the times he or she takes the medication, and whether there are any additional instructions.

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken			Knows any additional instruction
			Morning (hour)	Evening (hour)	Judged correct (Y/N)	

C. Self-Reporting

1) Do you sometimes find it difficult to remember to take your medicine? □ No □ Yes

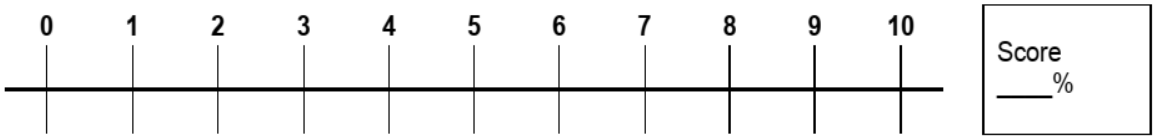
2) When you feel better, do you sometimes stop taking your medicine? □ No □ Yes

3) Thinking back over the past four days, have you missed any of your doses? □ No □ Yes

4) Sometimes do you stop when you feel worse when you take the medicine? □ No □ Yes

D. Visual Analogue Scale (VAS)

Please think back with 5 days and identify the times you missed a dose of your drug or took it at the wrong time. By taking into consideration the fact that on the grid below the point 0 (zero) means you missed all your doses and the point 1 (one) means you took all your doses, can you sincerely show me the point between the two that fairly identify your level of adherence?



E. Pill Count

1) Date of last refill _____ 2) Expected date of next appointment _____

3) Actual date of appointment _____ NB: Drugs finish after 7days of appointment

4) Number of drugs dispensed during last drug refill appointment _____

5) Number of drugs brought back during present drug refill _____

6) Within the number dispensed during drug refill, how many were expected to be taken ____

Calculated percentage adherence

$$\%\ \text{Adherence} = \frac{\text{Dispensed} - \text{Returned}}{\text{Expected to be taken}} \times 100 = \frac{\square - \square}{\square} \times 100 = \square\square\ \%$$

Assessment guide

Compliance individual and overall grading			
Drug refill	Had all 6 refills (3)	Missed 1 refill (2)	Missed 2 or more refills (1)
PIT	Dose time and instructions (3)	Dose and time only (3)	Dose or time only or confused (1)
Self-reported	No to all 4 questions (3)	Yes to 1 question (2)	Yes to 2 or more questions (1)
VAS	95% and above (3)	75-94% (2)	Less than 75% (1)
Pill count	95% and above (3)	75-94% (2)	Less than 75% (1)
Overall Compliance	**Highly compliant (15)**	**Moderately compliant (10-14)**	**Poorly Compliant (5-9)**

RESULTS

Drug Refill score _____ and category _____

PIT score _____ and category _____

Self-reported _____ and category _____

VAS _____ and category _____

Pill count _____ and category _____

Overall compliance score _____ and category _____

Patient Health Questionnaire (PHQ-9)

Serial No: ……..… Health Facility: …….. Date of encounter: …../……/……..

Study ID No: ……... Visit: M0 ☐ M3 ☐ M6 ☐ M9 ☐ M12 ☐

Participant: Adult ☐ Adolescent (<20yrs) ☐ Sex: F ☐ M ☐

Instructions for the investigator*:* The PHQ-9 can be administered in a clinical interview as so-called assisted self-report. Before starting with the questions it is necessary first to introduce the set of questions and second to explain the participant that each item refers to the time period of 2 weeks. This should be emphasized for each symptom. Use information the participant provided before and explain questions as needed to allow participant a profound understanding of each item.

	Over the past two weeks, how often have you been Bothered by any of the following problems ?	Not at all	Several days	More than half of the days	Nearly everyday
1.	Little interest or pleasure in doing things.	[0]	[1]	[2]**	[3]**
2.	Feeling down, depressed, or hopeless.	[0]	[1]	[2]**	[3]**
3.	Trouble falling or staying asleep, or sleeping too much.	[0]	[1]	[2]**	[3]**
4.	Feeling tired or having little energy.	[0]	[1]	[2]**	[3]**
5.	Poor appetite or overeating.	[0]	[1]	[2]**	[3]**
6.	Feeling bad about yourself - or that you are a failure or have left yourself or your family down.	[0]	[1]	[2]**	[3]**
7.	Trouble concentrating on things, such as reading the newspaper or watching TV	[0]	[1]	[2]**	[3]**
8.	Moving or speaking so slowly that other people could have noticed. Or the opposite –being so fidgety or restless that you have been around a lot more than usual.	[0]	[1]	[2]**	[3]**
9.	Thoughts that you would be better off dead, or of hurting yourself in some way	[0]	[1]	[2]**	[3]**

If you have checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult ☐

Is there any evidence given that a physical disorder, medication, or other drug caused the symptoms or is indicated that the symptoms were due to normal bereavement?

Oui ☐ Non ☐

Annex 2: Statement on Pre-release and Contribution

The currently dissertation presented with title “Impact of depression and psychosocial management on drug adherence and viral suppression in HIV-infected patients on antiretroviral treatment in Cameroon” is my original research conceived for the purpose of the PhD program. As previously mentioned, part of this thesis research has been published by the journal BMC Infectious Diseases as manuscript entitled “Depression management and antiretroviral treatment outcome among people living with HIV in Northwest and East regions of Cameroon”. I am still working on pulling more manuscripts from this thesis to be submitted for peer review and potential publication at a later time.

Also, an abstract from this work entitled “Determinants of Poor Treatment Adherence Among Persons Living with HIV in Rural Northwest and East Cameroon Under the Test and Treat Era” was accepted for oral presentation in the International Workshop on Healthy Living with HIV which was held virtually on 1st and 2nd of October 2021. The video recording of the presentation is available on the website of the workshop.

I conceived this study, wrote the proposal, planned and supervised the data and sample collection and personally built the database (in Epi Info v7.2) into which I entered the data, then cleaned with Microsoft Excel before analysis. The statistics presented in this thesis and affiliated manuscript was conducted by me with guidance from my local supervisor Dr Akindeh Mbuh Nji who is a senior lecturer of biostatistics in the Department of Biochemistry at the University of Yaounde I, as well as the Head of the Clinical and Laboratory Data Management Unit at the Biotechnology center of the University of Yaoundé I in Cameroon. Furthermore, I drafted the manuscript that has been published, as well as this thesis, and this was with scientific contribution from supervisors and other co-authors.

Annex 3: List of Publications

Ndenkeh, J.J.N., Nji, A.M., Yumo, H.A. et al. Depression management and antiretroviral treatment outcome among people living with HIV in Northwest and East regions of Cameroon. BMC Infect Dis 22, 732 (2022). https://doi.org/10.1186/s12879-022-07711-w

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